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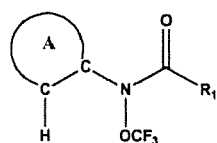
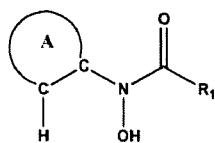
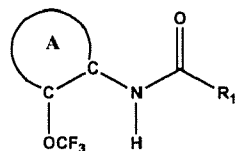
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[Continued on next page]

(54) Title: TRIFLUOROMETHOXYLATION OF ARENES VIA INTRAMOLECULAR TRIFLUOROMETHOXY GROUP MIGRATION



(57) Abstract: The present invention provides a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure: (I), wherein A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl), comprising: (a) reacting a compound having the structure: (II), with a trifluoromethylating agent in the presence of a base in a first suitable solvent under conditions to produce a compound having the structure: (III); and (b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure: (I).

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
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**TRIFLUOROMETHOXYLATION OF ARENES VIA INTRAMOLECULAR
TRIFLUOROMETHOXY GROUP MIGRATION**

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This application claims priority of U.S. Provisional Application Nos. 62/192,789, filed July 15, 2015; 62/192,462, filed July 14, 2015; 62/063,246, filed October 13, 2014; and 62/062,508, filed October 10, 2014, the contents of each of which are hereby incorporated by
10 reference.

Throughout this application various publications are referenced. The disclosures of these documents in their entireties are hereby incorporated by reference into this application in order to more
15 fully describe the state of the art to which this invention pertains.

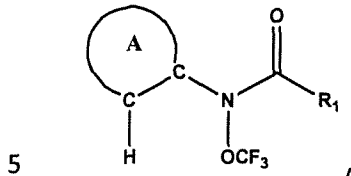
BACKGROUND OF THE INVENTION

Fluorine atoms are often introduced into organic molecules to enhance
20 their pharmacological properties such as solubility, metabolic and oxidative stability, lipophilicity, and bioavailability.^[1] Among the fluorine containing functional groups, the trifluoromethoxy group (OCF₃) is of current interest because of its unique structural and electronic properties, which can be useful in material, agricultural,
25 and pharmaceutical science.^[2] For example, one of the distinct structural features of trifluoromethoxylated arenes (Ar-OCF₃) is that the OCF₃ bond is orthogonal to the aryl ring.^[3,1b] As a result, lone pair electrons on oxygen only weakly delocalize into the ring, which renders OCF₃ an electron withdrawing group. In addition, the OCF₃
30 group has one of the highest lipophilicity values ($\pi_x = 1.04$) compared to the CF₃ ($\pi_x = 0.88$), CH₃ ($\pi_x = 0.52$), F ($\pi_x = 0.14$), and OCH₃ ($\pi_x = -0.02$) groups.^[4] Compounds with higher lipophilicity show enhancement in their *in vivo* uptake and transport in biological systems. Indeed, many OCF₃ containing pharmaceuticals and agrochemicals show enhanced
35 effectiveness often coupled with diminished side-effects (Figure 1).^[2a,2b,5]

Despite the intriguing properties of the OCF_3 group, introduction of this functional group into organic molecules remains a challenge. Only a handful of transformations have been developed over the last few decades and most of them either suffer from poor substrate scope or require the use of highly toxic and/or thermally unstable reagents. 5 A pioneering study by Yagupolskii and coworkers in 1955 led to the development of a two-step chlorination/chlorine-fluorine exchange protocol for the synthesis of simple aryl trifluoromethyl ethers.^[6] In 1964, Sheppard reported an alternative approach involving 10 reactions of aromatic or aliphatic alcohols with fluorophosgene followed by deoxyfluorination with tetrafluorosulfur (SF_4).^[7] About thirty years later, Hiyama synthesized aryl trifluoromethyl ethers via formation of dithiocarbonates followed by oxidative fluorodesulfurization.^[8] Electrophilic trifluoromethylations of 15 alcohols and phenols have also been developed. Employing thermally labile *O*-trifluoromethyldibenzyl furanium salts, Umemoto and coworkers successfully trifluoro-methylated phenols to form aryl trifluoromethyl ethers.^[9] An elegant direct trifluoromethylation of aliphatic alcohols using bench stable reagent was reported by Togni 20 and coworkers.^[10] However, poor yields were obtained for phenolic substrates due to the competing *C*-trifluoromethylation.^[11] Most recently, a direct trifluoro-methoxylation of benzene employing toxic gaseous trifluoromethyl perfluorite^[12a-b], and a transition metal-mediated trifluoro-methoxylation of aryl stannanes as well as aryl 25 boronic acids utilizing thermally labile tris(dimethylamino)sulfonium trifluoro-methoxide have been developed.^[12b] However, most of these approaches either suffer from poor substrate scope or require use of highly toxic and/or thermally labile reagents. As a result, many of OCF_3 -containing building blocks are prohibitively expensive (Figure 30 1C).

SUMMARY OF THE INVENTION

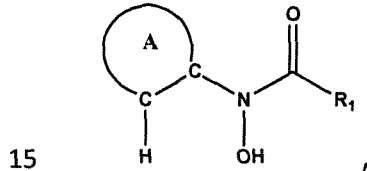
The present invention provides a process of producing a compound having the structure:



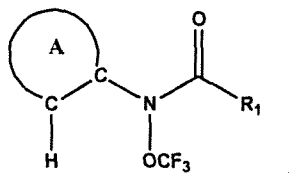
wherein

A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 10 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl), comprising:

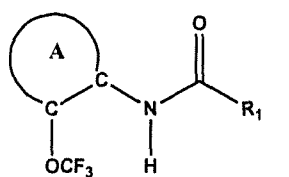
(a) reacting a compound having the structure:



with a trifluoromethylating agent in the presence of a base in a first suitable solvent under conditions sufficient to produce the compound having the structure:



The present invention also provides a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

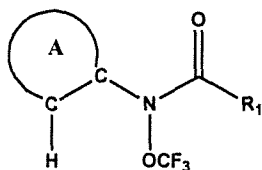


wherein

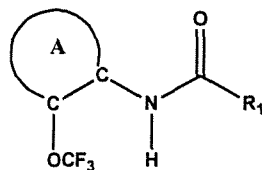
A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -

5 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl), comprising:

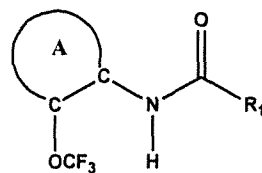
(b) maintaining the compound having the structure:



10 in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



15 The present invention further provides a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

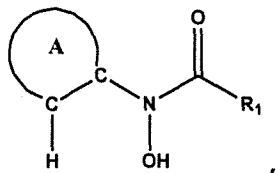


wherein

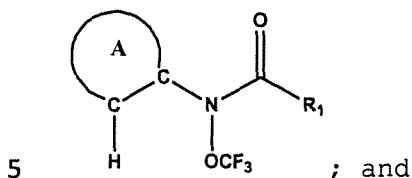
20 A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -

25 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl), comprising:

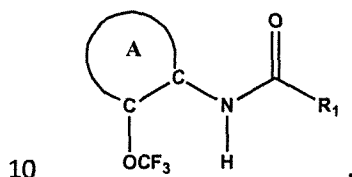
(a) reacting a compound having the structure:



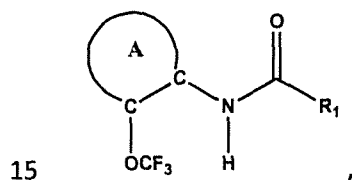
with a trifluoromethylating agent in the presence of a base in a first suitable solvent under conditions to produce a compound having the structure:



(b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



The present invention further provides a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

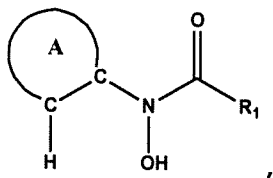


wherein

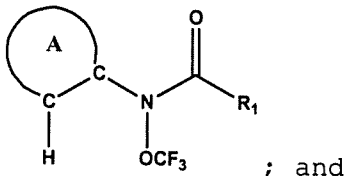
A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl), comprising:

25 (a) reacting a compound having the structure:

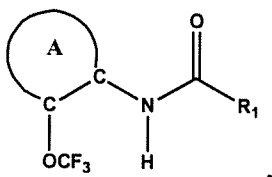
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with a trifluoromethylating agent in a first suitable solvent under conditions to produce a compound having the structure:

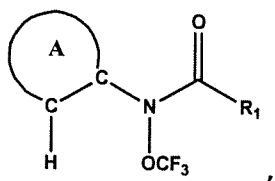


- 5 (b) maintaining the compound produced in step (a) in the first suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



10

The present invention also provides a compound having the structure:



wherein

- A is an aryl or heteroaryl, each with or without substitution; and
 15 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl).

20

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BRIEF DESCRIPTION OF THE FIGURES

Fig. 1A. Examples of OCF₃-bearing pharmaceuticals.

5 **Fig. 1B.** Examples of OCF₃-bearing agrochemicals.

Fig. 1C. Examples of OCF₃-bearing building blocks.

Fig. 2. Compounds **9a-9y**. Cited yields and isomeric ratios are of
10 isolated material by column chromatography. ^aRT → 50 °C in CH₂Cl₂. ^b4
°C in CH₂Cl₂ (0.01 M). ^cFollowing the *O*-trifluoromethylation reaction
in CH₂Cl₂ at RT, the reaction mixture was concentrated, the residue
was dissolved in MeNO₂, and the resulting mixture was heated. ^d120
°C. ^e80 °C. ^f60 °C.

15

Fig. 3. Compounds **11a-11e**. Cited yields are of isolated material by
column chromatography. ^aFollowing the *O*-trifluoromethylation reaction
in CH₂Cl₂ at RT, the reaction mixture was concentrated, the residue
was dissolved in MeNO₂, and the resulting mixture was heated at 80
20 °C. ^bCH₂Cl₂ (0.01 M). ^cRT → 50 °C in CH₂Cl₂ (0.03 M). ^dRT → 50 °C in
CH₂Cl₂.

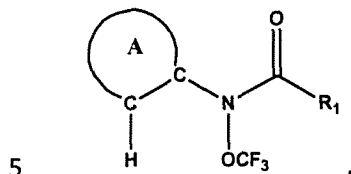
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DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process of producing a compound having the structure:



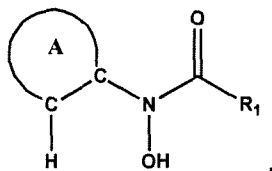
wherein

A is an aryl or heteroaryl, each with or without substitution; and
 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 10 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl),
 -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

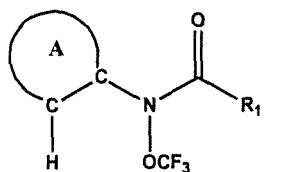
comprising:

15

(a) reacting a compound having the structure:



with a trifluoromethylating agent in the presence of a base in a
 first suitable solvent under conditions sufficient to produce the
 20 compound having the structure:



In some embodiments, the first suitable solvent is chloroform,
 dichloromethane, nitromethane, dimethylformamide, diethyl ether,
 25 tetrahydrofuran, dioxane, dichloroethane, or hexane.

In some embodiments, the first suitable solvent is degassed prior to
 use.

In some embodiments, step (a) is performed under an inert atmosphere.

In some embodiments, step (a) is carried out at room temperature.

5 In some embodiments, in step (a) the molar ratio of the compound to the trifluormethylation agent is 1:1 to 1:2.

In some embodiments, in step (a) the molar ratio of the compound to the trifluormethylation agent is 1:1.2.

10

In some embodiments, the trifluormethylating agent is Togni reagent I or Togni reagent II.

In some embodiments, the base is cesium carbonate or sodium hydride.

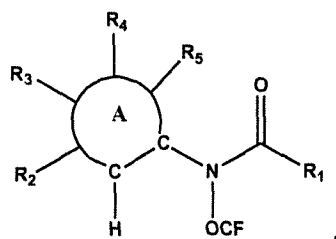
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In some embodiments, a catalytic amount of the base is used.

In some embodiments, in step (a) the compound is reacted for 5-24 hours. In some embodiments, in step (a) the compound is reacted for
20 about 15 hours.

In some embodiments of step (a), A is a phenyl or pyridine. In some
embodiments of step (a), A is a furan, thiophene, pyrrole, thiazole,
imidazole, pyrazole, isooxazole, isothiazole, naphthalene,
25 anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline,
benzofuran, benzothiophene, or quinolone.

In some embodiments, the compound produced in step (a) has the structure:



wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
-(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -

O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, - (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH- (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂- (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O- (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S- (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

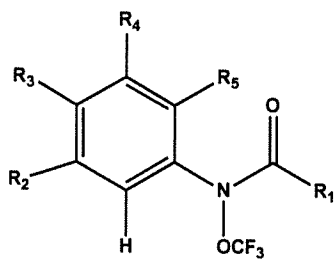
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In some embodiments of the above compound R₂, R₃, R₄ and R₅ is each, independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂- (alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH- (alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O- (alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S- (alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

30

In some embodiments of the above compound R₂, R₃, R₄ and R₅ is each, independently, -H, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

35 In some embodiments, the compound produced in step (a) has the structure:

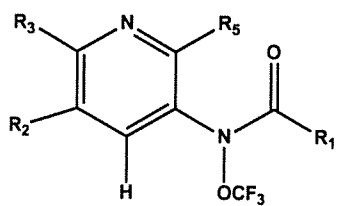


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 5 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 10 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
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 15 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
 pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
 or quinolone.

20

In some embodiments, the compound produced in step (a) has the
 structure:

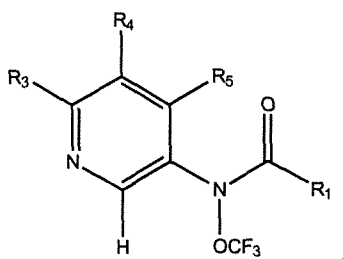


wherein

25 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 5 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 10 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

In some embodiments, the compound produced in step (a) has the
 15 structure:

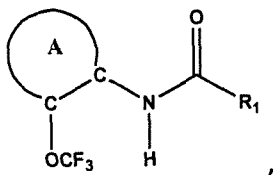


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 20 R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 25 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
 30

quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

The present invention also provides a process of producing a
5 trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having
the structure:



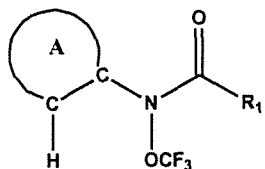
wherein

A is an aryl or heteroaryl, each with or without substitution; and
10 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
-(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

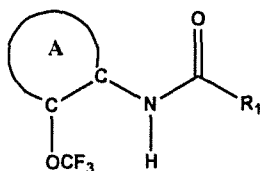
15

comprising:

(b) maintaining the compound having the structure:



20 in a second suitable solvent under conditions sufficient to produce
the trifluoromethoxylated aryl or trifluormethoxylated heteroaryl
having the structure:



25 In some embodiments, the second suitable solvent is chloroform,
dichloromethane, nitromethane, dimethylformamide, diethyl ether,
tetrahydrofuran, dioxane, dichloroethane, or hexane.

In some embodiments, the second suitable solvent is degassed prior to use.

In some embodiments, step (b) is performed under an inert atmosphere.

5

In some embodiments, step (b) is carried out at room temperature.

In some embodiments, step (b) is carried out at a temperature of 50-140 °C. In some embodiments, step (b) is carried out at a temperature of about 80 °C.

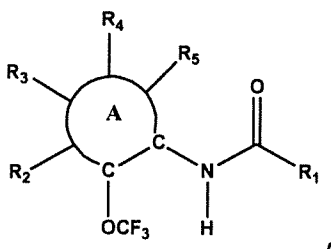
10

In some embodiments, step (b) is carried out at a temperature of about 120 °C.

In some embodiments, the compound is maintained in the second suitable solvent for 10-50 hours. In some embodiments, the compound is maintained in the second suitable solvent for about 24 hours.

In some embodiments of step (b), A is a phenyl or pyridine. In some embodiments of step (b), A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

In some embodiments of step (b), the compound produced has the structure:



wherein

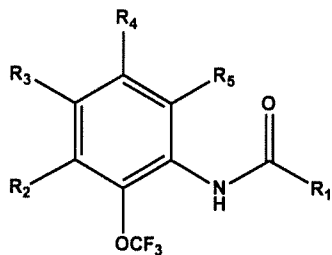
R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 30 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
-CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
5 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
-C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
10 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
or quinolone.

In some embodiments of the above compound R₂, R₃, R₄ and R₅ is each,
15 independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -
(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl),
-NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-
(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-
(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -
20 C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-
(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-
(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine,
furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole,
isothiazole, naphthalene, anthracene, pyrimidine, pyrazine,
25 pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone,
pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or
purine.

In some embodiments of the above compound R₂, R₃, R₄ and R₅ is each,
30 independently, -H, pyrazoline, triazole, benzimidazole,
benzotriazole, azaindole, or purine.

In some embodiments of step (b), the compound produced has the
35 structure:

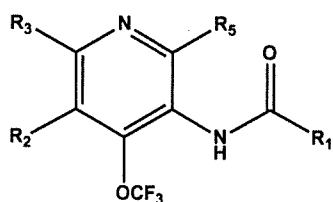


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 5 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 10 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 15 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
 pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
 or quinolone.

20

In some embodiments of step (b), the compound produced has the
 structure:

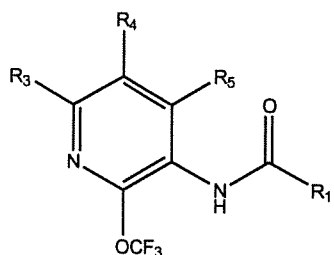


wherein

25 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 5 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 10 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
 pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
 or quinolone.

In some embodiments of step (b), the compound produced has the
 15 structure:

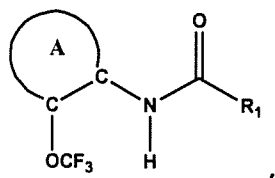


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 20 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 25 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 30 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
 pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,

quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

The present invention further provides a process of producing a
 5 trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having
 the structure:



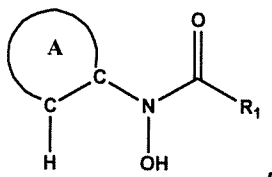
wherein

A is an aryl or heteroaryl, each with or without substitution; and
 10 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

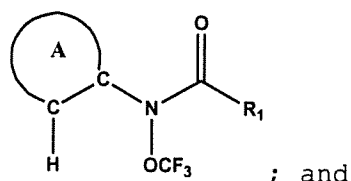
15

comprising:

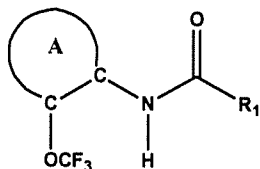
(a) reacting a compound having the structure:



20 with a trifluoromethylating agent in the presence of a base in a
 first suitable solvent under conditions to produce a compound having
 the structure:



(b) maintaining the compound produced in step (a) in a second suitable
 25 solvent under conditions sufficient to produce the
 trifluoromethoxylated aryl or trifluormethoxylated heteroaryl having
 the structure:



In some embodiments of the above process, the first suitable solvent is chloroform, dichloromethane, nitromethane, dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, dichloroethane, or hexane.

In some embodiments of the above process, the second suitable solvent is chloroform, dichloromethane, nitromethane, dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, dichloroethane, or hexane.

In some embodiments of the above process, the first suitable solvent and second suitable solvent are identical.

In some embodiments of the above process, step (a) and step (b) are performed by a sequential one-pot synthesis.

In some embodiments of the above process, step (a) and step (b) are performed by a sequential one-pot synthesis without purification or work-up in between step (a) and step (b).

In some embodiments of the above process, step (a) and step (b) are performed by a sequential two-pot synthesis.

In some embodiments of the above process, the compound produced in step (a) is subjected to a work-up prior to step (b).

In some embodiments of the above process, the compound produced in step (a) is subjected to a purification prior to step (b).

In some embodiments of the above process, the compound produced in step (a) is subjected to a work-up and purification prior to step (b).

In some embodiments of the above process, the crude compound produced in step (a) is used in step (b).

In some embodiments of the above process, the first suitable solvent is degassed prior to use.

- 5 In some embodiments of the above process, steps (a) and (b) are performed under an inert atmosphere.

In some embodiments of the above process, step (a) is carried out at room temperature.

10

In some embodiments of the above process, step (b) is carried out at room temperature.

15

In some embodiments of the above process, step (b) is carried out at a temperature of 50-140 °C.

In some embodiments of the above process, step (b) is carried out at a temperature of about 80 °C.

20

In some embodiments of the above process, step (b) is carried out at a temperature of about 120 °C.

In some embodiments of the above process, in step (a) the compound is reacted for 12-24 hours.

25

In some embodiments of the above process, in step (a) the compound is reacted for about 15 hours.

30

In some embodiments of the above process, in step (b) the compound is maintained in the second suitable solvent for 10-50 hours.

In some embodiments of the above process, in step (b) the compound is maintained in the second suitable solvent for about 24 hours.

35

In some embodiments of the above process, in step (a) the molar ratio of the compound to the trifluoromethylation agent is 1:1 to 1:2.

In some embodiments of the above process, in step (a) the molar ratio of the compound to the trifluormethylation agent is 1:1.2.

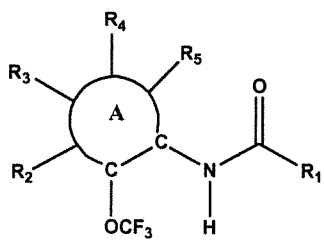
In some embodiments of the above process, the trifluormethylating agent is Togni reagent or Togni reagent II.

58 In some embodiments of the above process, the base is sodium hydride or cesium carbonate.

10 In some embodiments of the above process, A is a phenyl or pyridine. In some embodiments of the above process, A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

15

In some embodiments of the above process, the compound produced has the structure:



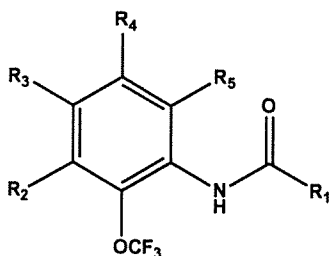
wherein

- 20 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
- 25 R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
- 30 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,

isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

- 5 In some embodiments of the above compound R_2 , R_3 , R_4 and R_5 is each, independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-
- 10 (alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole,
- 15 isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.
- 20 In some embodiments of the above compound R_2 , R_3 , R_4 and R_5 is each, independently, -H, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

- 25 In some embodiments of the above process, the compound produced has the structure:

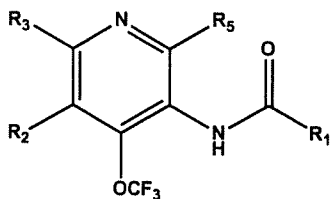


wherein

- R_1 is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
- 30 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 5 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 10 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,
 pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
 or quinolone.

In some embodiments of the above process, the compound produced has
 15 the structure:

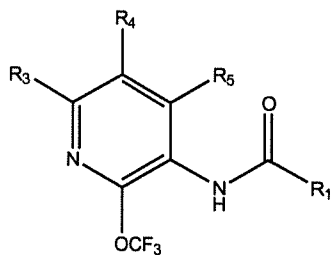


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 20 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 25 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 30 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,

pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

In some embodiments of the above process, the compound produced has
5 the structure:

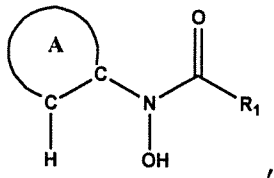


wherein

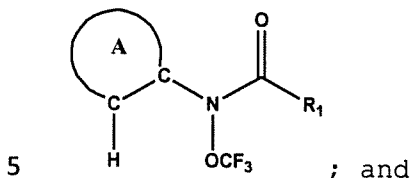
R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
10 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
15 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
20 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,
25 quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

In some embodiments, the process comprising:

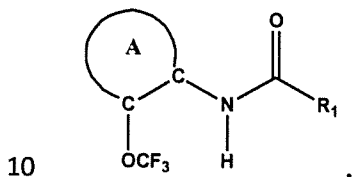
30 (a) reacting a compound having the structure:



with Togni reagent II in the presence of a base in a first suitable solvent under conditions sufficient to produce a compound having the structure:

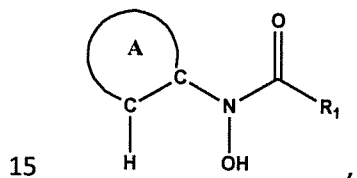


(b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

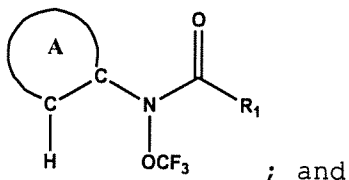


In some embodiments, the process comprising:

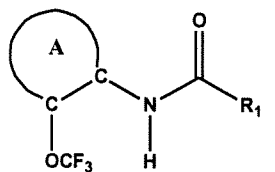
(a) reacting a compound having the structure:



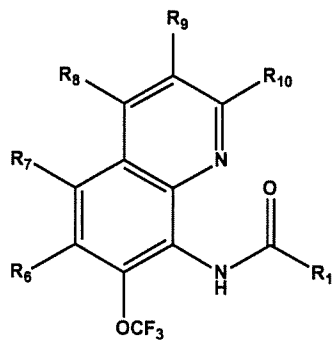
with Togni reagent II in the presence of cesium carbonate in chloroform or dichloromethane under conditions sufficient to produce a compound having the structure:



20 (b) maintaining the compound produced in step (a) in nitromethane under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

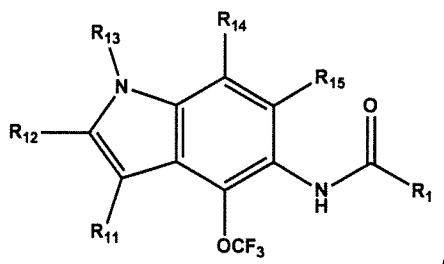


In some embodiments, the compound produced has the structure:



- 5 wherein
- R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
- 10 R₆, R₇, R₈, R₉, and R₁₀ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole,
- 15
- 20 thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

In some embodiments, the compound produced has the structure:



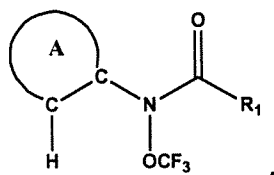
wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 5 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₁₁, R₁₂, R₁₃, R₁₄, and R₁₅ is each independently -H, halogen, -CN, -CF₃, -
 OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂,
 10 -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-
 (heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-
 (aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -
 C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -
 C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -
 15 O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -
 S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole,
 thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene,
 anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline,
 benzofuran, benzothiophene, or quinolone.

20

In some embodiments, the phenyl, pyridine, furan, thiophene, pyrrole,
 thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene,
 anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline,
 benzofuran, benzothiophene, quinolone or quinazolinone is substituted
 25 with one or more of the following: halogen, -CN, -CF₃, -OCF₃, -(alkyl),
 -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -
 NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-
 (alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 30 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), or
 an amino acid or protected amino acid.

In some embodiments, a process of producing a compound having the structure:



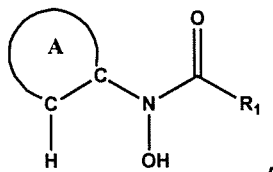
5 wherein

A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

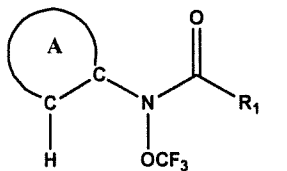
10

comprising:

15 (a) reacting a compound having the structure:

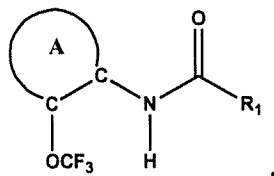


with a trifluoromethylating agent in the presence of a base in a first suitable solvent to produce the compound having the structure:



20

In some embodiments, a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

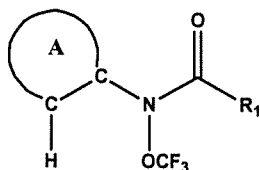


wherein

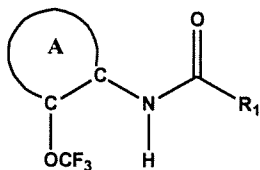
25 A is an aryl or heteroaryl, each with or without substitution; and

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 5 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),
 comprising:

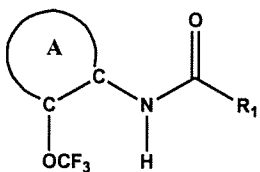
(b) maintaining the compound having the structure:



10 in a second suitable solvent to produce the trifluoromethoxylated
 aryl or trifluoromethoxylated heteroaryl having the structure:



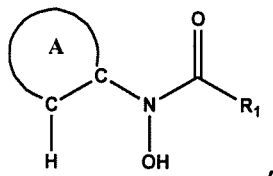
The present invention further provides a process of producing a
 15 trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having
 the structure:



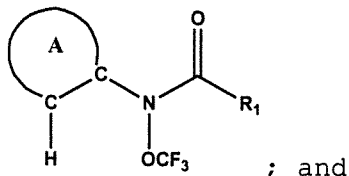
wherein

A is an aryl or heteroaryl, each with or without substitution; and
 20 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),
 25 comprising:

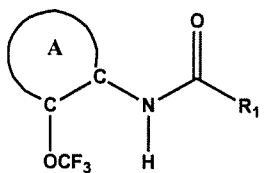
(a) reacting a compound having the structure:



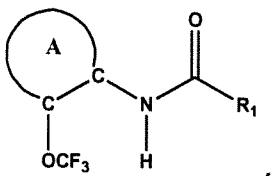
with a trifluoromethylating agent in the presence of a base in a first suitable solvent to produce a compound having the structure:



- 5 (b) maintaining the compound produced in step (a) in a second suitable solvent to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



- 10 The present invention also provides a process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

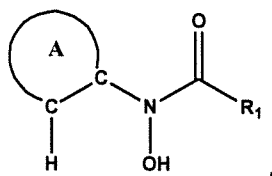


wherein

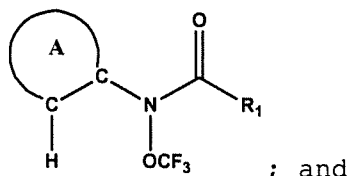
- 15 A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

comprising:

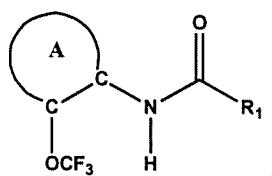
- (a) reacting a compound having the structure:



with a trifluoromethylating agent in a first suitable solvent under conditions to produce a compound having the structure:



- 5 (b) maintaining the compound produced in step (a) in the first suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

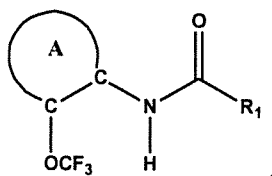


10

In some embodiments of the above process, A is a phenyl or pyridine. In some embodiments of the above process, A is pyridine.

- 15 In some embodiments of the above process, the first suitable solvent is chloroform, dichloromethane, nitromethane, dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, dichloroethane, or hexane.

- 20 In some embodiments of the above process, wherein trifluoromethylating agent is Togni reagent I or Togni reagent II. The present invention also provides a compound having the structure:



wherein

- A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 25 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-

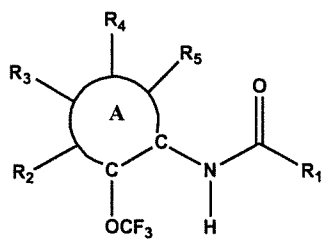
(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl).

- 5 In some embodiments of the compound, A is a phenyl or pyridine. In some embodiments of the compound, A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone,

10

or a salt or ester thereof.

In some embodiments, a compound having the structure:



- 15 wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

20 R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-

25 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),

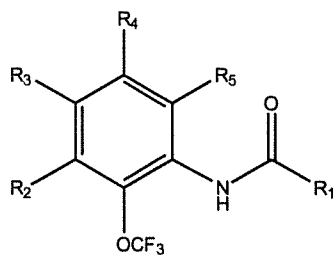
30 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

In some embodiments of the above compound R_2 , R_3 , R_4 and R_5 is each, independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

15

In some embodiments of the above compound R_2 , R_3 , R_4 and R_5 is each, independently, -H, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

20

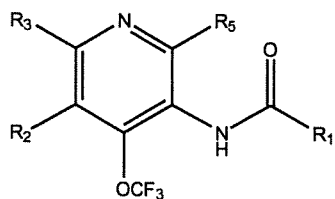


wherein

R_1 is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), or -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R_2 , R_3 , R_4 and R_5 is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-

(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

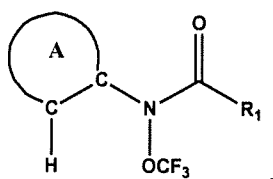
In some embodiments, a compound having the structure:



10 wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl), -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), or -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl), -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl), -CO₂-(aryl), -C(-CO₂-(heteroaryl)), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl), -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

The present invention also provides a compound having the structure:



30

wherein

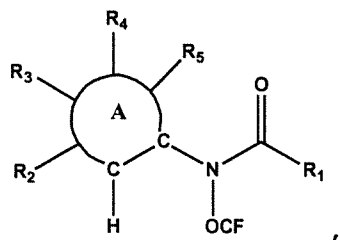
A is an aryl or heteroaryl, each with or without substitution; and
 R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 5 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

or a salt or ester thereof.

10 In some embodiments of the compound, A is a phenyl or pyridine. In
 some embodiments of the compound, A is a furan, thiophene, pyrrole,
 thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene,
 anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline,
 benzofuran, benzothiophene, or quinolone.

15

In some embodiments, a compound having the structure:

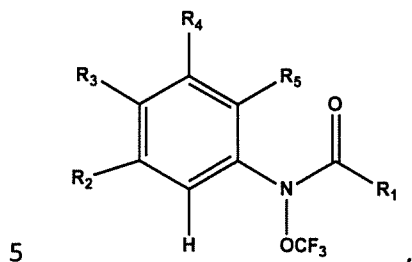


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl),
 20 -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-
 (alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -
 O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -
 S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
 R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -
 25 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-
 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),
 -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-
 (heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl)
 -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-
 30 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-
 (alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl),
 pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole,
 isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,

pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

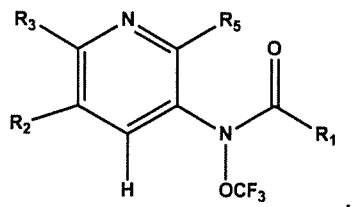
In some embodiments, a compound having the structure:



wherein

- R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), or -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and
- R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

- 25 In some embodiments, a compound having the structure:



wherein

- R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-

(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), or -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -

5 (alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-

10 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,

15 or quinolone.

In some embodiments of any of the disclosed processes or compounds, R₂, R₃, R₄ and R₅ is each, independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-

20 (alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-

25 (alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole,

30 azaindole, or purine, or any combination thereof.

In some embodiments of any of the disclosed processes or compounds, R₂, R₃, R₄ and R₅ is each, independently, -H, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine, or any

35 combination thereof.

In some embodiments of any of the disclosed processes or compounds, R₆, R₇, R₈, R₉ and R₁₀ is each, independently, -H, halogen, -CN, -CF₃, -

- OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -
- 5 C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene,
- 10 anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine, or any combination thereof.
- 15 In some embodiments of any of the disclosed processes or compounds, R₆, R₇, R₈, R₉ and R₁₀ is each, independently, -H, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine, or any combination thereof.
- 20 In some embodiments of any of the disclosed processes or compounds, R₁₁, R₁₂, R₁₃, R₁₄ and R₁₅ is each, independently, -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -
- 25 C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole,
- 30 thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine, or any combination thereof.
- 35 In some embodiments of any of the disclosed processes or compounds, R₁₁, R₁₂, R₁₃, R₁₄ and R₁₅ is each, independently, -H, pyrazoline, triazole,

benzimidazole, benzotriazole, azaindole, or purine, or any combination thereof.

In some embodiments, the compound of step (a) is purified by column
5 chromatography prior to step (b).

In some embodiments, the trifluoromethylating reagent is 1-Trifluoromethyl-1,2-benziodoxol-3-(1H)-one (Togni reagent II), which may be purchased from Sigma Aldrich, St. Louis, MO, USA (Catalog #
10 771147). In some embodiments, the trifluoromethylating reagent is 3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni reagent I), which may be purchased from Sigma Aldrich, St. Louis, MO, USA (Catalog # 696641).

15 In some embodiments, the first or second suitable solvent include, but are not limited to, inert organic solvents or mixtures thereof.

The process described herein is advantageous in that it avoids the need for highly toxic and thermally labile reagents, which is not
20 particularly desirable for industrial implementation due to the hazards associated with such reagents.

The process described herein is also advantageous in that it may be performed in one-pot. The process described herein is further
25 advantageous in that it avoids the need for highly toxic metal containing reagents.

The present reaction occurs under reaction conditions sufficient to produce the desired compound. Such conditions, e.g. temperature,
30 time, molarity, etc., may be varied by one of ordinary skill in the art based on the methods and protocols described herein.

Where a range is given in the specification it is understood that the range includes all integers and 0.1 units within that range, and any
35 sub-range thereof. For example, a range of 77 to 90% is a disclosure of 77, 78, 79, 80, and 81% etc.

As used herein, "about" with regard to a stated number encompasses a range of +one percent to -one percent of the stated value. By way of example, about 100 mg/kg therefore includes 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9, 100, 100.1, 100.2, 100.3, 100.4, 100.5, 100.6, 100.7, 100.8, 100.9 and 101 mg/kg. Accordingly, about 100 mg/kg includes, in an embodiment, 100 mg/kg.

It is understood that where a parameter range is provided, all integers within that range, and tenths thereof, are also provided by the invention. For example, "0.2-5 mg/kg/day" is a disclosure of 0.2 mg/kg/day, 0.3 mg/kg/day, 0.4 mg/kg/day, 0.5 mg/kg/day, 0.6 mg/kg/day etc. up to 5.0 mg/kg/day.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Thus, C₁-C_n as in "C₁-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement, and specifically includes methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, isopropyl, isobutyl, sec-butyl and so on. An embodiment can be C₁-C₁₂ alkyl, C₂-C₁₂ alkyl, C₃-C₁₂ alkyl, C₄-C₁₂ alkyl and so on. An embodiment can be C₁-C₈ alkyl, C₂-C₈ alkyl, C₃-C₈ alkyl, C₄-C₈ alkyl and so on. "Alkoxy" represents an alkyl group as described above attached through an oxygen bridge. The term "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present. Thus, C₂-C_n alkenyl is defined to include groups having 1, 2, ..., n-1 or n carbons. For example, "C₂-C₆ alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and at least 1 carbon-carbon double bond, and up to, for example, 3 carbon-carbon double bonds in the case of a C₆ alkenyl, respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. As described above with respect to alkyl, the straight, branched or cyclic portion of the alkenyl group may contain double bonds and may be substituted if a substituted alkenyl group is indicated. An embodiment can be C₂-C₁₂ alkenyl or C₂-C₈ alkenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present. Thus, C₂-C_n alkynyl is defined to include groups having 1, 2, . . . , n-1 or n carbons. For example, "C₂-C₆ alkynyl" means an alkynyl radical having 2 or 3 carbon atoms, and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms, and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms, and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl. As described above with respect to alkyl, the straight or branched portion of the alkynyl group may contain triple bonds and may be substituted if a substituted alkynyl group is indicated. An embodiment can be a C₂-C_n alkynyl. An embodiment can be C₂-C₁₂ alkynyl or C₃-C₈ alkynyl.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted. Examples of such aryl elements include but are not limited to: phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring. The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridazine rings that are (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O, N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl,

carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, 5 pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazoliny, quinolyl, quinoxaliny, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, aziridiny, 1,4-dioxanyl, hexahydroazepiny, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, 10 dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, 15 dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, quinoxaliny, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, 20 thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra-hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the 25 aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms, it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

30 The term "substitution", "substituted" and "substituent" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted 35 groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituent groups include the functional groups described above, and halogens

(i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino, protected amino; ester or alkyl ester; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

The starting materials used in the method of the present invention may be prepared by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art. However, these may not be the only means by which to synthesize or obtain the desired compounds.

The starting materials used in the method of the present invention may be prepared by techniques described in Vogel's Textbook of Practical Organic Chemistry, A.I. Vogel, A.R. Tatchell, B.S. Furnis, A.J. Hannaford, P.W.G. Smith, (Prentice Hall) 5th Edition (1996), March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, (Wiley-Interscience) 5th Edition (2007), and references therein, which are incorporated by reference herein. However, these may not be the only means by which to synthesize or obtain the desired compounds.

The reaction conditions used in the present invention may be varied by techniques well known in organic synthesis and familiar to a practitioner ordinarily skilled in the art to provide conditions sufficient to produce the desired product. Such techniques are described in Vogel's Textbook of Practical Organic Chemistry, A.I.

Vogel, A.R. Tatchell, B.S. Furnis, A.J. Hannaford, P.W.G. Smith, (Prentice Hall) 5th Edition (1996), March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Michael B. Smith, Jerry March, (Wiley-Interscience) 5th Edition (2007), and references
5 therein, which are incorporated by reference herein.

In the compounds in the process of the present invention, alkyl, alkenyl, alkynyl, aryl, heteroaryl groups can be further substituted by replacing one or more hydrogen atoms with alternative non-hydrogen
10 groups.

Another aspect of the invention comprises a compound used in the method of the present invention as a pharmaceutical composition.

15 In some embodiments, a pharmaceutical composition comprising the compound of the present invention and a pharmaceutically acceptable carrier.

As used herein, the term "pharmaceutically active agent" means any
20 substance or compound suitable for administration to a subject and furnishes biological activity or other direct effect in the treatment, cure, mitigation, diagnosis, or prevention of disease, or affects the structure or any function of the subject. Pharmaceutically active agents include, but are not limited to, substances and compounds
25 described in the Physicians' Desk Reference (PDR Network, LLC; 64th edition; November 15, 2009) and "Approved Drug Products with Therapeutic Equivalence Evaluations" (U.S. Department Of Health And Human Services, 30th edition, 2010), which are hereby incorporated by reference. Pharmaceutically active agents which have pendant
30 carboxylic acid groups may be modified in accordance with the present invention using standard esterification reactions and methods readily available and known to those having ordinary skill in the art of chemical synthesis. Where a pharmaceutically active agent does not possess a carboxylic acid group, the ordinarily skilled artisan will
35 be able to design and incorporate a carboxylic acid group into the pharmaceutically active agent where esterification may subsequently be carried out so long as the modification does not interfere with the pharmaceutically active agent's biological activity or effect.

The compounds used in the method of the present invention may be in a salt form. As used herein, a "salt" is a salt of the instant compounds which has been modified by making acid or base salts of the

5 compounds. In the case of compounds used to treat an infection or disease caused by a pathogen, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols.

10 The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkaline earth metal salts, sodium, potassium or lithium. The

15 term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified

20 compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate,

25 phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, *e.g.*, Berge *et al.* (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

30 The compounds of the present invention may also form salts with basic amino acids such as lysine, arginine, etc. and with basic sugars such as N-methylglucamine, 2-amino-2-deoxyglucose, etc. and any other physiologically non-toxic basic substance.

35 As used herein, "administering" an agent may be performed using any of the various methods or delivery systems well known to those skilled in the art. The administering can be performed, for example, orally, parenterally, intraperitoneally, intravenously, intraarterially,

transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, intrathecally, into a cerebral ventricle, 5 intraventricularly, intratumorally, into cerebral parenchyma or intraparenchymally.

The compounds used in the method of the present invention may be administered in various forms, including those detailed herein. The 10 treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination therapy can be sequential therapy where the patient is 15 treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more different routes of administration depending on the dosage forms employed.

20 As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, for delivering the instant compounds to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically 25 acceptable carrier as are slow-release vehicles.

The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of 30 administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with; and the desired therapeutic effect.

35 A dosage unit of the compounds used in the method of the present invention may comprise a single compound or mixtures thereof with additional antitumor agents. The compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules,

elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection, topical application, or other methods,
5 into or topically onto a site of disease or lesion, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

The compounds used in the method of the present invention can be
10 administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or in carriers such as the novel programmable sustained-release multi-compartmental nanospheres (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected with respect to the intended form of administration and as
15 consistent with conventional pharmaceutical practices. The unit will be in a form suitable for oral, nasal, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone or mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of
20 carrier is generally chosen based on the type of administration being used. The active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made
25 easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water,
30 pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for
35 example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals

and other materials to make them compatible with the type of injection or delivery system chosen.

Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern
Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979);
Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel,
Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976);
Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing
Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences
(David Ganderton, Trevor Jones, Eds., 1992); Advances in
Pharmaceutical Sciences Vol. 7. (David Ganderton, Trevor Jones, James
McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical
Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James
McGinity, Ed., 1989); Pharmaceutical Particulate Carriers:
Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol
61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal
Tract (Ellis Horwood Books in the Biological Sciences. Series in
Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson,
Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol
40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the
aforementioned publications are incorporated by reference herein.

Tablets may contain suitable binders, lubricants, disintegrating
agents, coloring agents, flavoring agents, flow-inducing agents, and
melting agents. For instance, for oral administration in the dosage
unit form of a tablet or capsule, the active drug component can be
combined with an oral, non-toxic, pharmaceutically acceptable, inert
carrier such as lactose, gelatin, agar, starch, sucrose, glucose,
methyl cellulose, magnesium stearate, dicalcium phosphate, calcium
sulfate, mannitol, sorbitol and the like. Suitable binders include
starch, gelatin, natural sugars such as glucose or beta-lactose, corn
sweeteners, natural and synthetic gums such as acacia, tragacanth,
or sodium alginate, carboxymethylcellulose, polyethylene glycol,
waxes, and the like. Lubricants used in these dosage forms include
sodium oleate, sodium stearate, magnesium stearate, sodium benzoate,
sodium acetate, sodium chloride, and the like. Disintegrators

include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds used in the method of the present invention may also
5 be administered in the form of liposome delivery systems, such as
small unilamellar vesicles, large unilamellar vesicles, and
multilamellar vesicles. Liposomes can be formed from a variety of
phospholipids such as lecithin, sphingomyelin, proteolipids, protein-
encapsulated vesicles or from cholesterol, stearylamine, or
10 phosphatidylcholines. The compounds may be administered as components
of tissue-targeted emulsions.

The compounds used in the method of the present invention may also
be coupled to soluble polymers as targetable drug carriers or as a
15 prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer,
polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylasparta-
midphenol, or polyethyleneoxide-polylysine substituted with
palmitoyl residues. Furthermore, the compounds may be coupled to a
class of biodegradable polymers useful in achieving controlled
20 release of a drug, for example, polylactic acid, polyglycolic acid,
copolymers of polylactic and polyglycolic acid, polyepsilon
caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals,
polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic
block copolymers of hydrogels.

25

Gelatin capsules may contain the active ingredient compounds and
powdered carriers, such as lactose, starch, cellulose derivatives,
magnesium stearate, stearic acid, and the like. Similar diluents can
be used to make compressed tablets. Both tablets and capsules can be
30 manufactured as immediate release products or as sustained release
products to provide for continuous release of medication over a period
of hours. Compressed tablets can be sugar-coated or film-coated to
mask any unpleasant taste and protect the tablet from the atmosphere,
or enteric coated for selective disintegration in the
35 gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug
components are combined with any oral, non-toxic, pharmaceutically

acceptable inert carrier such as ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propylparaben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

The compounds used in the method of the present invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials such as solutol and/or ethanol to make them compatible with the type of injection or delivery system chosen.

The compounds and compositions of the present invention can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by topical administration, injection or other methods, to the afflicted area, such as a wound, including ulcers of the skin, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U.S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7. (David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

35

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, powders, and chewing gum; or in liquid dosage forms, such as elixirs, syrups, and suspensions,

including, but not limited to, mouthwash and toothpaste. It can also be administered parentally, in sterile liquid dosage forms.

Solid dosage forms, such as capsules and tablets, may be enteric-coated to prevent release of the active ingredient compounds before they reach the small intestine. Materials that may be used as enteric coatings include, but are not limited to, sugars, fatty acids, proteinaceous substances such as gelatin, waxes, shellac, cellulose acetate phthalate (CAP), methyl acrylate-methacrylic acid copolymers, cellulose acetate succinate, hydroxy propyl methyl cellulose phthalate, hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), and methyl methacrylate-methacrylic acid copolymers.

The compounds and compositions of the invention can be coated onto stents for temporary or permanent implantation into the cardiovascular system of a subject.

The compounds of the present invention can be synthesized according to methods described in PCT International Publication No. WO 2010/132815 A9. Variations on those general synthetic methods will be readily apparent to those of ordinary skill in the art and are deemed to be within the scope of the present invention.

Each embodiment disclosed herein is contemplated as being applicable to each of the other disclosed embodiments. Thus, all combinations of the various elements described herein are within the scope of the invention.

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

EXPERIMENTAL DETAILS

Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using Agela Technologies TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed on SiliaFlash® Silica Gel 40-63 μm 60Å particle size using a forced flow of eluent at 0.3-0.5 bar pressure (Still, W. C. et al. *J. Org. Chem.* **1978**, 43, 2925-2927.). All air- and moisture-sensitive manipulations were performed using oven-dried glassware, including standard Schlenk and glovebox techniques under an atmosphere of nitrogen. Diethyl ether and THF were distilled from deep purple sodium benzophenone ketyl. Methylene chloride, chloroform and acetonitrile were dried over CaH_2 and distilled. Nitromethane was dried over 4Å molecular sieves. All other chemicals were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories.

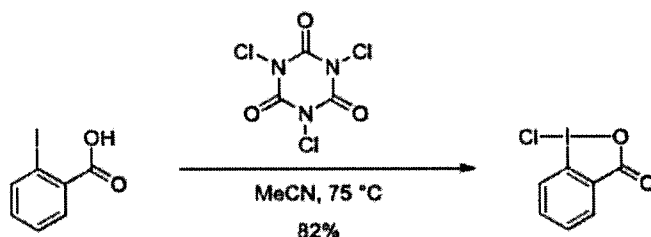
NMR spectra were recorded on either a Bruker Ascend700 spectrometer operating at 700 MHz for ^1H acquisitions and 175 MHz for ^{13}C acquisitions, a Bruker 500 Advance spectrometer operating at 500 MHz, 125 MHz, and 470 MHz for ^1H , ^{13}C , and ^{19}F acquisitions, respectively, a Bruker 400 Nanobay spectrometer operating at 400 MHz, 100 MHz, and 376 MHz for ^1H , ^{13}C , and ^{19}F acquisitions, respectively. Chemical shifts were referenced to the residual proton solvent peaks (^1H : CDCl_3 , δ 7.26; $(\text{CD}_3)_2\text{SO}$, δ 2.50; CD_3OD , δ 3.31; CD_3CN , δ 1.94), solvent ^{13}C signals (CDCl_3 , δ 77.16; $(\text{CD}_3)_2\text{SO}$, δ 39.52; CD_3OD , δ 49.00) (Fulmer, G. R. et al. *Organometallics*. **2010**, 29, 2176-2179.), dissolved or external neat PhCF_3 (^{19}F , δ -63.3 relative to CFCl_3) (Wang, X. et al. *J. Am. Chem. Soc.* **2013**, 135, 10330-10333). Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were performed at Mass Spectrometry Services at the Univ. of Illinois at Urbana-Champaign and were obtained using Waters Q-TOF Ultima ESI mass spectrometer. Concentration under

reduced pressure was performed by rotary evaporation at 25–30°C at appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure compounds.

5

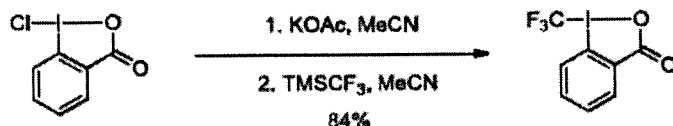
Synthesis of Togni reagent II

1-Chloro-1 λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one



The compound was prepared according to the literature procedure
 10 (Matoušek, V. et al. *J. Org. Chem.* 2013, 78, 6763–6768). A suspension
 of 2-iodobenzoic acid (30.0 g, 0.121 mmol, 1.00 equiv) in MeCN (225
 mL) was heated to 75°C. A solution of trichloroisocyanuric acid (9.46
 g, 0.0407 mol, 1.01 Cl⁺ equiv) in MeCN (45mL) was added in one portion
 and the reaction mixture was heated at 75°C for 10 min. The reaction
 15 mixture was diluted with MeCN (150 mL) and vacuum-filtered over an
 oven-preheated, sintered-glass funnel and the filter cake was rinsed
 with additional hot MeCN (150 mL). The filtrate was concentrated *in*
vacuo to near dryness and the resulting yellow solid was collected
 by filtration and washed with cold MeCN. The mother liquor from
 20 filtration was partially concentrated *in vacuo*, giving a second crop
 of crystals. The combined crops were dried under vacuum overnight to
 afford the title compound as a slightly yellow crystalline solid
 (28.0 g, 0.0991 mol, 82%). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃,
 25°C, δ): 8.27 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.22 (dd, *J* = 8.0, 0.5 Hz,
 1H), 8.00 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.80 (td, *J* = 7.4, 0.8 Hz,
 25 1H). ¹³C NMR (125 MHz, CDCl₃, 25°C, δ): 167.2, 136.8, 133.6, 132.0,
 128.8, 127.0, 117.2. These spectroscopic data correspond to
 previously reported data.

30

(1-(trifluoromethyl)-1λ3-benzo[d][1,2]iodaoxol-3(1H)-one)

Potassium acetate (10.8g, 0.110 mol, 2.00 equiv) was dried under vacuum at 150°C for 30 min and then cooled to rt. 1-chloro-1λ3-benzo[d][1,2]iodaoxol-3(1H)-one (15.6 g, 0.0551 mol, 1.00 equiv) and MeCN (155 mL) were added and the reaction mixture was stirred at 75°C for 2h. The reaction mixture was cooled to rt. TMSCF₃ (8.97 mL, 0.0607 mol, 1.10 equiv) was added in one portion and the reaction mixture was stirred at rt for 15 h. MeCN (100 mL) was then added and the brown reaction mixture was heated to 75°C and the hot reaction mixture was filtered through a pad of Celite, concentrated to about 50 mL end volume, and cooled to -20°C. The crystals were filtered off, washed with cold (-20°C) MeCN (50 mL) and dried under vacuum. The mother liquor was again concentrated to approximately 15 mL end volume and cooled to -20°C. The crystals were filtered off and washed with a cold (-20°C) MeCN (10 mL). Both crystalline fractions were dried under a high vacuum to afford the title compound as a white crystalline solid (14.6 g, 0.0463 mol, 84% yield). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25°C, δ): 8.48 (dd, *J* = 7.2, 1.7 Hz, 1H), 7.85-7.76 (m, 3H). ¹³C NMR (175 MHz, CDCl₃, 25°C, δ): 165.9, 135.9, 133.9, 132.1, 132.0, 127.3 (q, *J* = 2.5 Hz), 114.9, 107.3 (q, *J* = 378.8 Hz). ¹⁹F NMR (376 MHz, CDCl₃, 25°C, δ): -34.2 (s). These spectroscopic data correspond to previously reported data.

25 Preparation of Starting Hydroxylamines**General procedure for the synthesis of *N*-aryl-*N*-hydroxylamines**

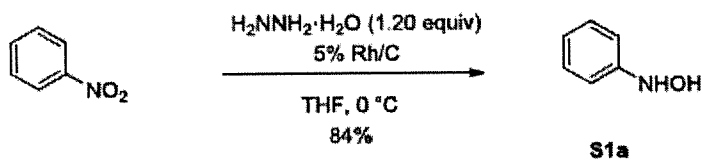
Under N₂ atmosphere, a suspension of aryl nitro compound (1.00 equiv) and Rh/C (5 mol%) in THF (0.20M) was cooled to 0°C. Hydrazine monohydrate (1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C until the TLC analysis indicated a complete consumption of the starting material. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. The residue was used

directly for the next step without further purification unless otherwise stated.

General procedure for the synthesis of protected *N*-aryl-*N*-hydroxylamines

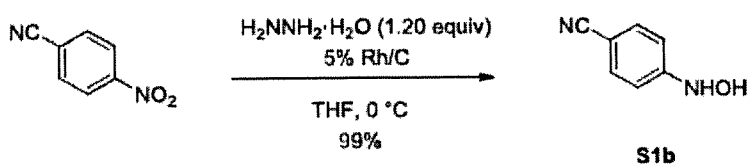
To a stirred suspension of *N*-aryl-*N*-hydroxylamine (1.00 equiv) and NaHCO₃ (1.20 equiv) in Et₂O (0.20M) at 0 °C under N₂ was slowly added a solution of protecting group precursor (1.20equiv) in Et₂O (0.24 M) via a syringe pump (at a rate of 10 mL/h). The reaction was stirred at 0°C until the TLC analysis indicated a complete consumption of the starting material. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

15 *N*-Phenyl-*N*-hydroxylamine (S1a)



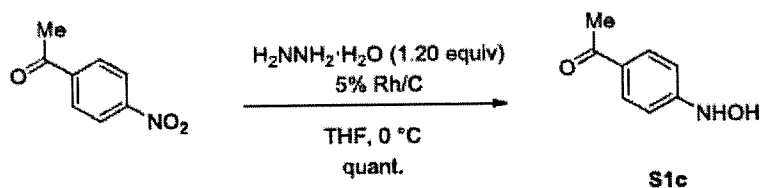
Under N₂ atmosphere, a suspension of nitrobenzene(1.00 g, 8.10 mmol, 1.00 equiv) and 5% Rh/C (40.5 mg, 0.30 mol%Rh) in THF (25.0mL, 0.324 M) was cooled to 0°C. Hydrazine monohydrate (0.487 g, 9.72 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 1 h and then slowly warmed up to rt and stirred at rt for 4h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. Recrystallization from CH₂Cl₂/hexanes at -20 °C afforded the title compound as a white solid (0.740 g, 6.78 mmol, 84% yield). R_f = 0.25 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.25(s, 1H), 8.21(s, 1H), 7.14(t, J= 7.9Hz, 2H), 6.81(d, J=7.9Hz, 2H), 6.72 (t, J= 7.9Hz, 1H). ¹³C NMR (125MHz, (CD₃)₂SO, δ): 152.1, 128.4, 119.2, 112.9.

30 4-(Hydroxyamino)benzotrile (S1b)



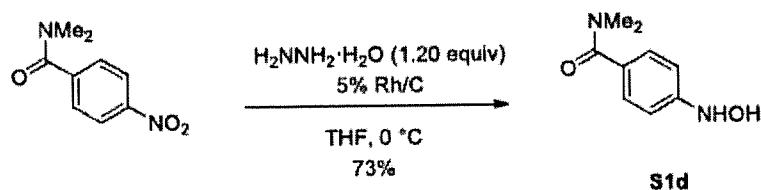
Under N₂ atmosphere, a suspension of 4-nitrobenzonitrile (2.00 g, 13.5 mmol, 1.00 equiv) and 5% Rh/C (77.6 mg, 0.30 mol%Rh) in THF (40.0mL, 0.338 M) was cooled to 0°C. Hydrazine monohydrate (0.810 g, 16.2 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 1 h and then slowly warmed up to rt and stirred at rt for 1 h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (1.80 g, 13.4 mmol, 99% yield). R_f = 0.14 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 9.10 (s, 1H), 8.76 (s, 1H), 7.57–7.52 (m, 2H), 7.85 (d, J=8.6 Hz, 2H). ¹³C NMR (100MHz, (CD₃)₂SO, δ): 155.4, 133.1, 120.1, 111.8, 90.1.

1-(4-(Hydroxyamino)phenyl)ethan-1-one (S1c)



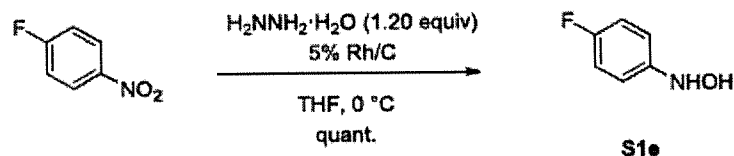
Under N₂ atmosphere, a suspension of 1-(4-nitrophenyl)ethan-1-one (3.00 g, 18.2 mmol, 1.00 equiv) and 5% Rh/C (104 mg, 0.30 mol%Rh) in THF (90.0mL, 0.202 M) was cooled to 0°C. Hydrazine monohydrate (1.09 g, 21.8mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 3.5h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (2.80 g, 18.5 mmol, quant yield). R_f = 0.27 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 8.99 (s, 1H), 8.67 (s, 1H), 7.79 (d, J= 8.7 Hz, 2H), 6.82 (d, J=8.7Hz, 2H), 2.44 (s, 3H). ¹³C NMR (100MHz, (CD₃)₂SO, δ): 195.6, 155.9, 129.8, 127.7, 110.9, 26.1.

4-(Hydroxyamino)-N,N-dimethylbenzamide (S1d)



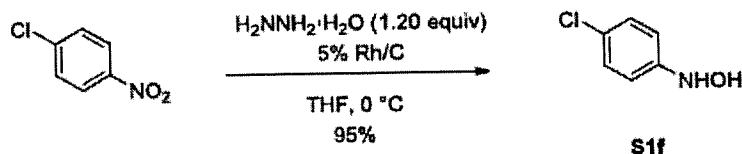
Under N₂ atmosphere, a suspension of *N,N*-dimethyl-4-nitrobenzamide (1.00 g, 6.53 mmol, 1.00equiv) and 5% Rh/C (50.0mg, 0.30 mol%Rh) in THF (25.0mL, 0.261 M) was cooled to 0°C. Hydrazine monohydrate (1.09 g, 21.8mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2h. The reaction mixture was filtered through a short pad of celite. The celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a white solid (0.860g, 4.77 mmol, 73%yield). *R_f* = 0.22 (hexanes/EtOAc 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (700MHz, CD₃OD, 25°C, δ): 7.32 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 3.06 (s, 6H). ¹³C NMR (175 MHz, CD₃OD, 25°C, δ): 174.3, 154.9, 129.4, 128.2, 113.7, 40.3, 35.9. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₁₃N₂O₂ ([M + H]⁺), 181.0977, found, 181.0982.

15 ***N*-(4-Fluorophenyl)hydroxylamine (S1e)**

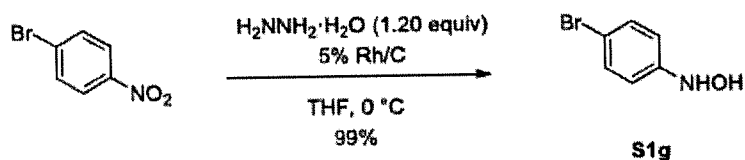


Under N₂ atmosphere, a suspension of 1-fluoro-4-nitrobenzene (2.00 g, 14.2 mmol, 1.00equiv) and 5% Rh/C (81.4 mg, 0.30 mol%Rh) in THF (40.0mL, 0.355 M) was cooled to 0 °C. Hydrazine monohydrate (0.810 g, 16.2 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2 h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (1.81 g, 14.2 mmol, quant yield). *R_f* = 0.29 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.33 (d, *J* = 2.4 Hz, 1H), 8.19 (s, 1H), 7.02–6.97 (m, 2H), 6.85–6.81 (m, 2H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 156.2 (d, *J* = 232.7 Hz), 148.5 (d, *J* = 1.5 Hz), 114.8 (d, *J* = 22.1 Hz), 114.2 (d, *J* = 7.8 Hz). ¹⁹F NMR (376 MHz, (CD₃)₂SO, 25°C, δ): -127.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₆H₇NOF ([M + H]⁺), 128.0512, found, 128.0513.

59

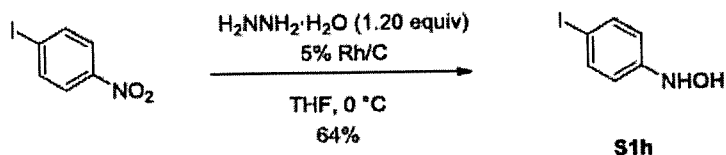
N-(4-Chlorophenyl)hydroxylamine (S1f)

Under N₂ atmosphere, a suspension of 1-chloro-4-nitrobenzene (2.00 g, 12.7 mmol, 1.00 equiv) and 5% Rh/C (72.9 mg, 0.30 mol%Rh) in THF
 5 (40.0mL, 0.318 M) was cooled to 0°C. Hydrazine monohydrate (0.762 g, 15.2mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred
 at 0°C for 2.5h. The reaction mixture was filtered through a short
 pad of celite and concentrated *in vacuo* afford the title compound
 as a yellow solid (1.72g, 12.0 mmol, 95% yield). R_f = 0.27
 10 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO,
 δ): 8.43 (d, J=2.2 Hz, 1H), 8.40 (s, 1H), 7.19(d, J=8.8 Hz, 2H), 6.87–
 6.83 (m, 2H). ¹³C NMR (125MHz, (CD₃)₂SO, δ): 151.0, 128.3, 122.6, 114.4.

N-(4-Bromophenyl)hydroxylamine (S1g)

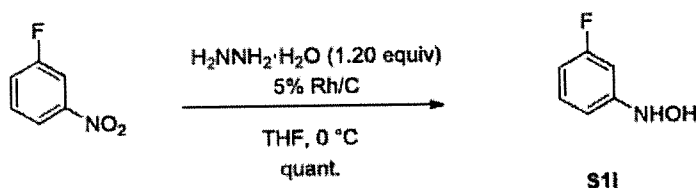
15 Under N₂ atmosphere, a suspension of 1-bromo-4-nitrobenzene (3.00 g, 14.9 mmol, 1.00equiv) and 5% Rh/C (85.3 mg, 0.30 mol%Rh) in THF (100
 mL, 0.149 M) was cooled to 0 °C. Hydrazine monohydrate (0.892 g, 16.2
 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred
 20 at 0°C for 2.5 h. The reaction mixture was filtered through a short
 pad of celite and concentrated *in vacuo* to afford the title compound
 as a brown solid (2.78 g, 14.8 mmol, 99% yield). R_f= 0.30
 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO,
 δ): 8.42 (s, 1H), 8.40 (s, 1H), 7.30 (d, J=8.8 Hz, 2H), 6.78 (d,
 25 J=8.8Hz, 2H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 151.4, 131.1, 114.8,
 110.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₆H₇NOBr ([M
 + H]⁺), 187.9711, found, 187.9714.

60

N-(4-Iodophenyl) hydroxylamine (S1h)

Under N₂ atmosphere, a suspension of 1-iodo-4-nitrobenzene (2.00 g, 8.03 mmol, 1.00 equiv) and 5% Rh/C (46.1 mg, 0.30 mol%Rh) in THF (30.0mL, 0.268 M) was cooled to 0 °C. Hydrazine monohydrate (0.482g, 9.64 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2 h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. Recrystallization from CH₂Cl₂/hexanes at -20 °C afforded the title compound as a yellow solid (1.20 g, 5.11mmol, 64% yield). R_f = 0.26 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.41 (s, 2H), 7.46 (d, J=2.7 Hz, 1H), 7.44 (d, J=2.7 Hz, 1H), 6.67 (d, J=2.6 Hz, 1H), 6.65 (d, J=2.6 Hz, 1H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 152.4, 137.3, 115.8, 81.1.

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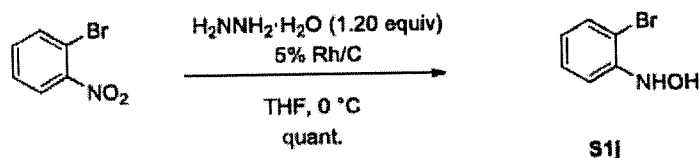
N-(3-Fluorophenyl) hydroxylamine (S1i)

Under N₂ atmosphere, a suspension of 1-fluoro-3-nitrobenzene (1.00 g, 7.09 mmol, 1.00 equiv) and 5% Rh/C (50.0 mg, 0.30 mol%Rh) in THF (25.0 mL, 0.284 M) was cooled to 0 °C. Hydrazine monohydrate (0.390 g, 7.80 mmol, 1.10 equiv) was added dropwise. The reaction mixture stirred at 0°C for 1h. The reaction mixture was filtered through a short pad of celite. The celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a white solid (0.870g, 7.12mmol, quant yield). R_f = 0.28 (hexanes/EtOAc 4:1 (v/v)). ¹H NMR (400MHz, (CD₃)₂SO, δ): 8.50 (s, 1H), 8.45 (d, J= 2.1Hz, 1H), 7.17-7.14 (m, 1H), 6.61-6.58 (m, 2H), 6.50-6.48 (m, 1H). ¹³C NMR (100MHz, (CD₃)₂SO, δ): 163.0(d, J= 238.8 Hz), 154.4(d, J= 10.2 Hz), 130.0(d, J= 9.6 Hz), 108.7(d, J= 2.3 Hz), 105.1(d, J= 21.4Hz),

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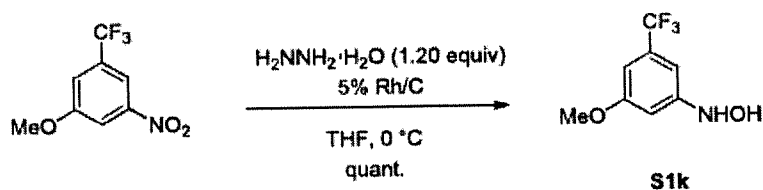
99.3(d, $J=25.5\text{Hz}$). ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C , δ): $-117.3(\text{s})$.
 Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_6\text{H}_7\text{NOF}$ ($[\text{M} + \text{H}]^+$),
 128.0512, found, 128.0513.

5 *N*-(2-Bromophenyl)hydroxylamine (S1j)



Under N_2 atmosphere, a suspension of 1-bromo-2-nitrobenzene (1.00 g,
 4.95 mmol, 1.00 equiv) and 5% Rh/C (28.4 mg, 0.30 mol% Rh) in THF
 (50.0mL, 0.0990M) was cooled to 0°C . Hydrazine monohydrate (0.297
 10 g, 5.94 mmol, 1.20 equiv) was added dropwise. The reaction mixture
 stirred at 0°C for 2.5 h. The reaction mixture was filtered through
 a short pad of celite, the celite was washed with EtOAc and the
 combined organic layers were concentrated *in vacuo* and solidified
 upon standing at -20°C to afford the title compound as a yellow
 15 solid (0.930g, 4.95 mmol, quant yield). $R_f=0.21$ (hexanes/EtOAc 1:1
 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.58 (m, 1H),
 7.98(s, 1H), 7.40(dd, $J=7.8, 0.85\text{ Hz}$, 1H), 7.28–7.24 (m, 1H), 7.18–
 7.15 (m, 1H), 6.74–6.70 (m, 1H). ^{13}C NMR (125MHz, $(\text{CD}_3)_2\text{SO}$, δ): 148.6,
 131.8, 128.2, 120.7, 114.6, 106.7. Mass Spectrometry: HRMS (ESI-TOF)
 20 (m/z): calcd for $\text{C}_6\text{H}_7\text{NOBr}$ ($[\text{M} + \text{H}]^+$), 187.9711, found, 187.9710.

N-(3-Methoxy-5-(trifluoromethyl)phenyl)hydroxylamine (S1k)

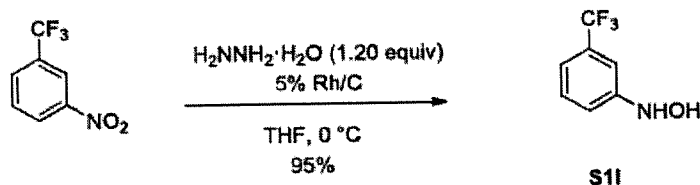


Under N_2 atmosphere, a suspension of 1-methoxy-3-nitro-5-
 25 (trifluoromethyl)benzene (1.00 g, 4.50mmol, 1.00equiv) and 5% Rh/C
 (25.9mg, 0.30 mol%Rh) in THF (15.0mL, 0.300 M) was cooled to 0°C .
 Hydrazine monohydrate (0.270g, 5.40mmol, 1.20 equiv) was added
 dropwise. The reaction mixture stirred at 0°C for 1 h and then slowly
 warmed up to rt and stirred at rt for 1 h. The reaction mixture was
 30 filtered through a short pad of celite, the celite was washed with

EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a yellow solid (0.960g, 4.60 mmol, quant yield). $R_f = 0.29$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (400MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.65(s, 1H), 8.58 (br. s, 1H), 6.68 (s, 1H), 6.61 (s, 1H), 6.57 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (100MHz, $(\text{CD}_3)_2\text{SO}$, δ): 160.3, 154.3, 130.4 (q, $J = 31.0$ Hz), 124.2 (q, $J = 271.0$ Hz), 101.6 (q, $J = 4.1$ Hz), 101.3, 101.0 (q, $J = 3.9$ Hz), 55.3. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C, δ): -63.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_9\text{NO}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 208.0585, found, 208.0579.

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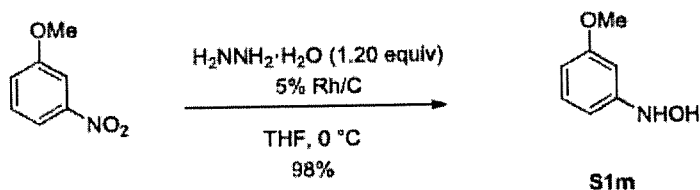
***N*- (3- (Trifluoromethyl) phenyl) hydroxylamine (S11)**



Under N_2 atmosphere, a suspension of 1-nitro-3-(trifluoromethyl)benzene (1.00 g, 5.21mmol, 1.00equiv) and 5% Rh/C (50mg, 0.30 mol%Rh) in THF (25.0mL, 0.208 M) was cooled to 0 °C. Hydrazine monohydrate (0.314g, 5.73 mmol, 1.10 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2 h. The reaction mixture was filtered through a short pad of celite, the celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a yellow solid (0.880g, 4.97 mmol, 95% yield). $R_f = 0.30$ (hexanes/EtOAc 4:1 (v/v)). ^1H NMR (400MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.66 (s, 1H), 8.58 (s, 1H), 7.37 (t, $J = 7.8$ Hz, 1H), 7.09 (s, 1H), 7.07-7.03 (m, 2H). ^{13}C NMR (175MHz, $(\text{CD}_3)_2\text{SO}$, δ): 152.7, 129.4 (q, $J = 30.6$ Hz), 124.4 (q, $J = 270.6$ Hz), 116.3, 115.2 (d, $J = 3.8$ Hz), 111.9, 108.5 (q, $J = 4.0$ Hz). ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C, δ): -63.4 (s).

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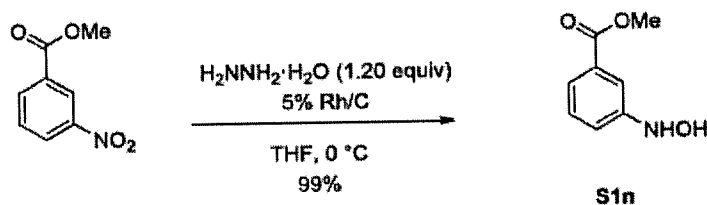
***N*- (3-Methoxyphenyl) hydroxylamine (S1m)**



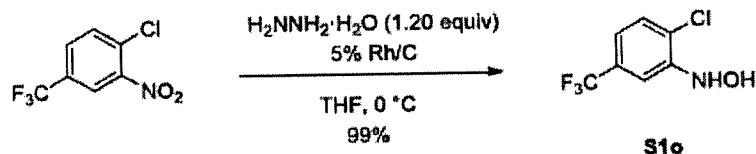
Under N₂ atmosphere, a suspension of 1-methoxy-3-nitrobenzene (1.00 g, 6.53 mmol, 1.00 equiv) and 5% Rh/C (50 mg, 0.30 mol%Rh) in THF (25.0mL, 0.261 M) was cooled to 0°C. Hydrazine monohydrate (0.360 g, 7.19 mmol, 1.10 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2 h. The reaction mixture was filtered through a short pad of celite, the celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a white solid (0.890g, 6.40 mmol, 98% yield). *R_f* = 0.47 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, 25°C, δ): 8.26 (d, *J* = 2.2 Hz, 1H), 8.23 (s, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.38–6.41 (m, 2H), 6.30 (dd, *J* = 8.0, 2.3 Hz, 1H), 3.68 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, 25°C, δ): 159.8, 153.5, 129.1, 105.5, 104.6, 98.5, 54.6. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₇H₁₀NO₂ ([M + H]⁺), 140.0712, found, 140.0714.

15

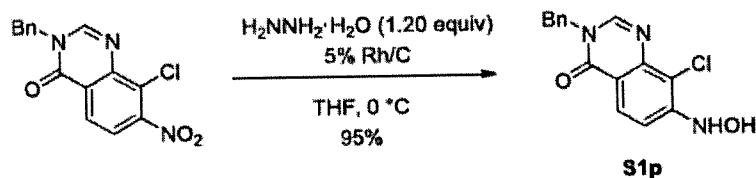
Methyl 3-(hydroxyamino)benzoate (S1n)



Under N₂ atmosphere, a suspension of methyl 3-nitrobenzoate (2.00 g, 11.0 mmol, 1.00 equiv) and 5% Rh/C (63.0mg, 0.30 mol%Rh) in THF (40.0mL, 0.275 M) was cooled to 0 °C. Hydrazine monohydrate (0.663g, 13.3mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 2.5 h. The reaction mixture was filtered through a short pad of celite, the celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a light yellow solid (1.82 g, 10.9 mmol, 99% yield). *R_f* = 0.19(hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.51 (s, 1H), 8.49 (d, *J*=2.1 Hz, 1H), 7.45 (s, 1H), 7.35–7.28 (m, 2H), 7.07–7.04 (m, 1H), 3.82 (s, 3H). ¹³C NMR (125MHz, (CD₃)₂SO, δ): 166.6, 152.4, 130.0, 128.9, 119.9, 117.5, 113.2, 52.1. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₈H₁₀NO₃ ([M + H]⁺), 168.0661, found, 168.0666.

N-(2-Chloro-5-(trifluoromethyl)phenyl)hydroxylamine (S1o)

Under N₂ atmosphere, a suspension of 1-chloro-2-nitro-4-(trifluoromethyl)benzene (1.00 g, 4.43 mmol, 1.00 equiv) and 5% Rh/C (25.5mg, 0.30 mol%Rh) in THF (45.0mL, 0.0984 M) was cooled to 0 °C. Hydrazine monohydrate (0.266g, 5.32mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 1.5 h. The reaction mixture was filtered through a short pad of celite, the celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* and solidified upon standing at -20 °C to afford the title compound as a yellow solid (0.930g, 4.40 mmol, 99% yield). R_f = 0.31 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.86 (s, 1H), 8.74 (s, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.36 (d, J=1.8 Hz, 1H), 7.10-7.08 (m, 1H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 148.4, 129.8, 128.5 (q, J= 31.6 Hz), 124.1 (q, J= 270.6 Hz), 120.7, 115.9 (m), 109.7 (m). ¹⁹F NMR (376 MHz, (CD₃)₂SO, 25°C, δ): -63.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₇H₆NOClF₃ ([M + H]⁺), 212.0090, found, 212.0092.

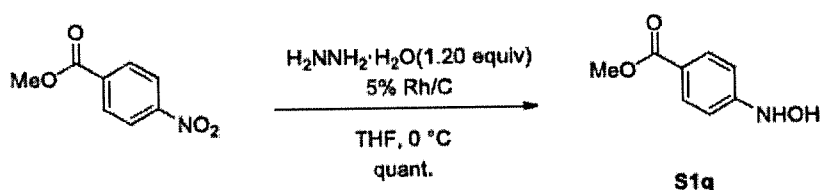
3-benzyl-8-chloro-7-(hydroxyamino)quinazolin-4(3H)-one (S1p)

Under N₂ atmosphere, a suspension of 3-benzyl-8-chloro-7-nitroquinazolin-4(3H)-one (1.05 g, 3.33 mmol, 1.00equiv) and 5% Rh/C (50.0 mg, 0.30 mol%Rh) in THF (20 mL, 0.167 M) was cooled to 0°C. Hydrazine monohydrate (0.183 g, 3.66mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 4h. The reaction mixture was filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (0.950g, 3.15mmol, 95% yield). R_f = 0.22 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700MHz, (CD₃)₂SO, δ): 8.86 (s, 1H), 8.74 (s,

65

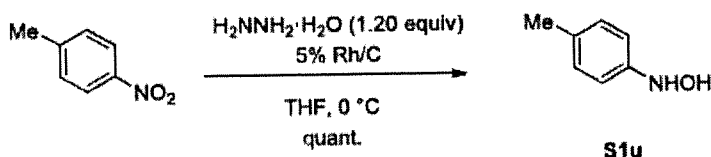
1H), 8.40 (s, 1H), 7.76 (s, 1H), 7.66 (s, 1H), 7.35–7.34 (m, 4H), 7.30–7.28 (m, 1H), 5.18 (s, 21H). ¹³C NMR (175MHz, (CD₃)₂SO, δ): 159.7, 146.9, 145.9, 141.3, 136.9, 128.6, 127.7, 127.6, 127.2, 124.8, 121.4, 108.0, 48.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₅H₁₃N₃O₂Cl ([M + H]⁺), 302.0696, found, 302.0690.

Methyl 4-(hydroxyamino)benzoate (S1q)



Under N₂ atmosphere, a suspension of methyl 4-nitrobenzoate (5.00 g, 27.6 mmol, 1.00 equiv) and 5% Rh/C (159 mg, 0.30 mol% Rh) in THF (300 mL, 0.0920 M) was cooled to 0 °C. Hydrazine monohydrate (1.52 g, 30.4 mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 5h. The reaction mixture was filtered through a short pad of celite, the celite was washed with EtOAc and the combined organic layers were concentrated *in vacuo* to afford the title compound as a yellow solid (4.62 g, 27.6 mmol, quant yield). R_f = 0.23 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 8.95 (s, 1H), 8.64 (d, J= 1.5 Hz, 1H), 7.76 (d, J=8.7 Hz, 2H), 6.82 (d, J= 8.7 Hz, 2H), 3.77 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 166.2, 156.0, 130.4, 119.1, 111.2, 51.4. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₁₀NO₃ ([M + H]⁺), 168.0661, found, 168.0667.

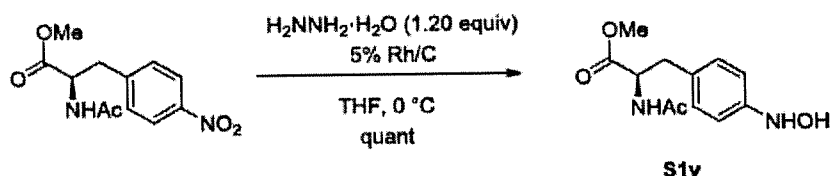
N-(p-Tolyl)hydroxylamine (S1u)



Under N₂ atmosphere, a suspension of 1-methyl-4-nitrobenzene (2.50 g, 18.3 mmol, 1.00 equiv) and 5% Rh/C (104.8 mg, 0.30 mol% Rh) in THF (91.0 mL, 0.200 M) was cooled to 0°C. Hydrazine monohydrate (1.11 g, 21.9 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 0°C for 2.5 h, filtered through a short pad of celite and

concentrated *in vacuo* to afford the title compound as a brown solid (2.25 g, 18.3 mmol, quant yield). $R_f = 0.20$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (400MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.20 (d, $J=2.3$ Hz, 1H), 8.06 (s, 1H), 6.96 (d, $J=8.2$ Hz, 2H), 6.74 (d, $J=8.2$ Hz, 2H), 2.19 (s, 1H). ^{13}C NMR (100MHz, $(\text{CD}_3)_2\text{SO}$, δ): 149.7, 128.8, 127.8, 113.3, 20.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_7\text{H}_{10}\text{NO}$ ($[\text{M} + \text{H}]^+$), 124.0762, found, 124.0761.

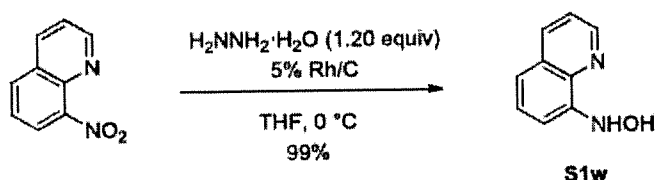
Methyl (R)-2-acetamido-3-(4-(hydroxyamino)phenyl)propanoate (S1v)



10

Under N_2 atmosphere, a suspension of methyl (R)-2-acetamido-3-(4-nitrophenyl)propanoate (1.00g, 3.76 mmol, 1.00 equiv) and 5 % Rh/C (21.6 mg, 0.30 mol%Rh) in THF (40 mL, 0.094 M) was cooled to 0°C. Hydrazine monohydrate (0.226 g, 4.51mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 8 h, filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (0.950g, 3.77 mmol, quant yield). $R_f = 0.42$ (EtOAc). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.14 (s, 1H), 8.12 (s, 1H), 8.05 (s, 1H), 7.00 (d, $J=8.3$ Hz, 2H), 6.76 (d, $J=8.3$ Hz, 2H), 4.39 (dd, $J=8.3, 14.1$ Hz, 1H), 3.58 (s, 3H), 2.89 (dd, $J=8.8, 14.1$ Hz, 1H), 2.77 (dd, $J=8.8, 14.1$ Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (125MHz, $(\text{CD}_3)_2\text{SO}$, δ): 172.1, 169.0, 150.5, 128.8, 127.6, 112.9, 53.8, 51.4, 36.2, 22.1.

25 N-(Quinolin-8-yl)hydroxylamine (S1w)

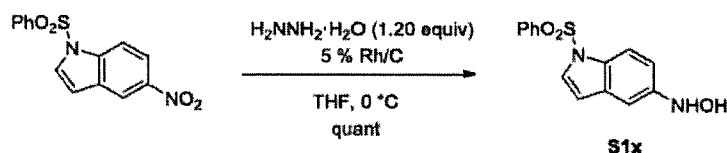


Under N_2 atmosphere, a suspension of 8-nitroquinoline (1.00 g, 5.74 mmol, 1.00 equiv) and 5%Rh/C (32.9 mg, 0.30 mol%Rh) in THF (60mL, 0.096 M) was cooled to 0°C. Hydrazine monohydrate (0.345 g, 6.89mmol,

67

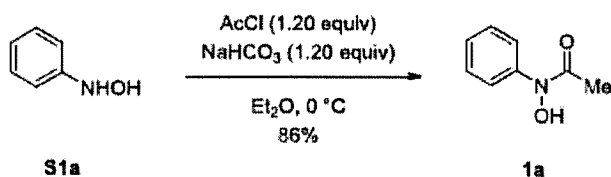
1.20 equiv) was added dropwise. The reaction mixture was stirred at 0°C for 4h, filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a brown solid (0.910g, 5.68 mmol, 99% yield). $R_f = 0.50$ (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.78–8.75 (m, 2H), 8.68 (s, 1H), 8.26 (d, $J=8.2$ Hz, 1H), 7.51 (dd, $J=4.1, 8.2$ Hz, 1H), 7.47 (t, $J=7.9$ Hz, 1H), 7.30 (d, $J=8.2$ Hz, 1H), 7.22 (d, $J=7.9$ Hz, 1H). ^{13}C NMR (125MHz, $(\text{CD}_3)_2\text{SO}$, δ): 147.7, 147.3, 137.1, 135.9, 127.7, 127.3, 121.6, 117.2, 109.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_9\text{N}_2\text{O}$ ($[\text{M} + \text{H}]^+$), 161.0715, found, 161.0721.

***N*-(1-(phenylsulfonyl)-1*H*-indol-5-yl)hydroxylamine (S1x)**



Under N_2 atmosphere, a suspension of 5-nitro-1-(phenylsulfonyl)-1*H*-indole (1.00 g, 3.31 mmol, 1.00 equiv) and 5 % Rh/C (19.0 mg, 0.30mol%Rh) in THF (35 mL, 0.094 M) was cooled to 0°C. Hydrazine monohydrate (0.199 g, 3.97mmol, 1.20 equiv) was added dropwise. The reaction mixture stirred at 0°C for 1h, filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a yellow solid (0.950g, 3.29 mmol, quant yield). $R_f = 0.27$ (hexanes/EtOAc 2:1 (v/v)). ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 8.33 (d, $J=2.1$ Hz, 1H), 8.25 (s, 1H), 7.92 (s, 1H), 7.90 (s, 1H), 7.74 (d, $J=8.9$ Hz, 1H), 7.67–7.63 (m, 2H), 7.58–7.54 (m, 2H), 7.02 (d, $J=1.5$ Hz, 1H), 6.85 (dd, $J=1.9, 8.9$ Hz, 1H), 6.72 (d, $J=3.6$ Hz, 1H). ^{13}C NMR (125MHz, $(\text{CD}_3)_2\text{SO}$, δ): 148.8, 137.1, 134.4, 131.2, 129.8, 128.6, 127.1, 126.5, 113.2, 112.2, 110.0, 104.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_3\text{S}$ ($[\text{M} + \text{H}]^+$), 289.0647, found, 289.0645.

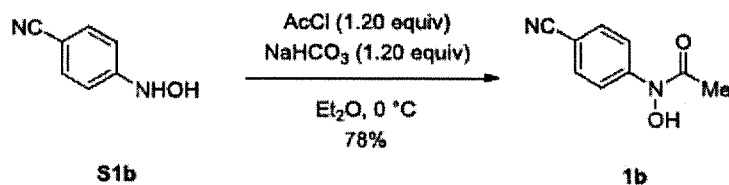
***N*-Hydroxy-*N*-phenylacetamide (1a)**



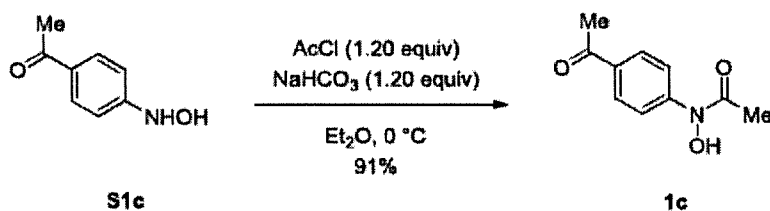
30

To a stirred suspension of *N*-phenylhydroxylamine (0.500g, 4.58 mmol, 1.00 equiv) and NaHCO₃ (0.462 g, 5.50 mmol, 1.20 equiv) in Et₂O (15.0mL, 0.305 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.432 g, 5.50 mmol, 1.20equiv) in Et₂O (15.0mL, 0.367 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The combined organic layers were washed with water, dried with MgSO₄, filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a white solid (0.590g, 3.90 mmol, 86% yield). R_f = 0.27 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 10.61 (s, 1H), 7.59 (d, *J*=6.0Hz, 2H), 7.35 (t, *J*= 6.0 Hz, 2H), 7.13 (t, *J*= 6.0 Hz, 1H), 2.18 (s, 3H). ¹³C NMR (125MHz, (CD₃)₂SO, δ): 169.9, 141.7, 128.4, 124.7, 120.3, 22.5.

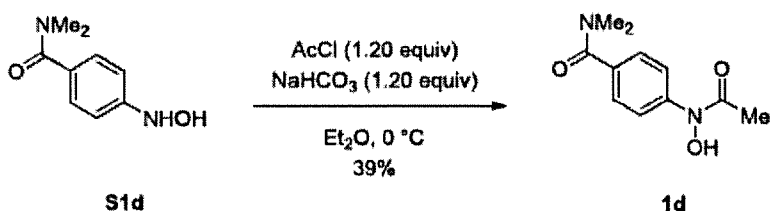
***N*-(4-Cyanophenyl)-*N*-hydroxyacetamide (1b)**



To a stirred suspension of 4-(hydroxyamino)benzonitrile (0.500g, 3.73 mmol, 1.00 equiv) and NaHCO₃ (0.380 g, 4.47 mmol, 1.20 equiv) in Et₂O (25.0mL, 0.149 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.350 g, 4.47 mmol, 1.20 equiv) in Et₂O (10.0mL, 0.447 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined, concentrated *in vacuo*. Recrystallization from Et₂O/hexanes afforded the title compound as a light pink solid (0.510g, 2.89 mmol, 78% yield). R_f = 0.32 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.92 (s, 1H), 7.88 (d, *J*=9.0 Hz, 2H), 7.82 (d, *J*= 9.0 Hz, 2H), 2.27 (s, 3H). ¹³C NMR (100MHz, (CD₃)₂SO, δ): 171.1, 145.1, 132.9, 118.9, 118.8, 105.7, 22.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₉N₂O₂ ([M + H]⁺), 177.0664, found, 177.0665.

***N*-(4-Acetylphenyl)-*N*-hydroxyacetamide (1c)**

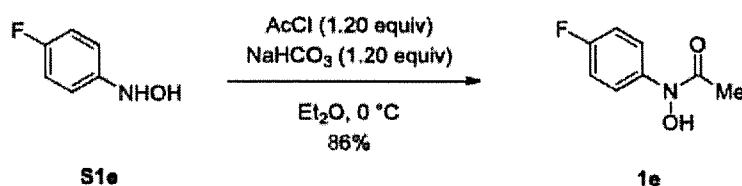
To a stirred suspension of 1-(4-(hydroxyamino)phenyl)ethan-1-one (**S1c**) (0.200g, 1.32 mmol, 1.00 equiv) and NaHCO₃ (0.130 g, 1.59 mmol, 1.20 equiv) in Et₂O (10.0mL, 0.132 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.130 g, 1.59 mmol, 1.20equiv) in Et₂O (5.00mL, 0.318 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:1 to 1:1 (v/v)), to afford the title compound as a white solid (0.230g, 1.19 mmol, 91% yield). R_f = 0.13 (hexanes/EtOAc 2:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.84 (s, 1H), 7.96 (d, J=8.9 Hz, 2H), 7.82 (d, J=8.9 Hz, 2H), 2.54 (s, 3H), 2.27 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 196.6, 170.8, 145.3, 132.2, 128.9, 118.3, 26.5, 22.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₁₂NO₃ ([M + H]⁺), 194.0817, found, 194.0820.

4-(*N*-Hydroxyacetamido)-*N,N*-dimethylbenzamide (1d)

To a stirred suspension of 4-(hydroxyamino)-*N,N*-dimethylbenzamide (**S1d**) (0.800g, 3.93 mmol, 1.00 equiv) and NaHCO₃ (0.400 g, 4.72 mmol, 1.20 equiv) in Et₂O (15.0 mL, 0.262 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.370 g, 4.72 mmol, 1.20 equiv) in Et₂O (20.0mL, 0.236 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, water was added, and the reaction mixture was filtered. The solid was washed with Et₂O, dried under vacuum at 40 °C for 2h to afford the title compound as a yellow solid

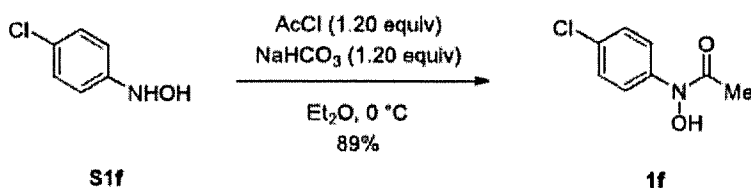
(0.570g, 2.56 mmol, 39% yield). $R_f = 0.11$ (hexanes/EtOAc 2:1 (v/v)). ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.71 (s, 1H), 7.70 (d, $J=7.5\text{Hz}$, 2H), 7.41 (d, $J=7.5\text{Hz}$, 2H), 2.94 (s, 6H), 2.24 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 170.2, 169.7, 142.3, 132.0, 127.5, 118.9, 34.9, 22.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{15}\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 223.1083, found, 223.1084.

***N*-(4-Fluorophenyl)-*N*-hydroxyacetamide (1e)**



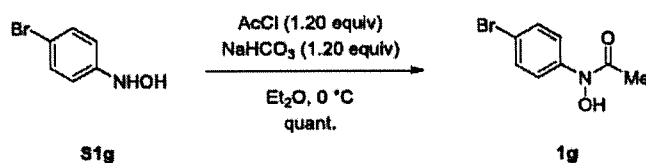
10 To a stirred suspension of *N*-(4-fluorophenyl)hydroxylamine (**S1e**) (0.500 g, 3.93 mmol, 1.00 equiv) and NaHCO_3 (0.400 g, 4.72 mmol, 1.20 equiv) in Et_2O (15.0mL, 0.262 M) at 0 °C under N_2 was slowly added a solution of acetyl chloride (0.370 g, 4.72 mmol, 1.20equiv) in Et_2O (20.0 mL, 0.236 M) via a syringe pump (at a rate of 10.0mL/h). After
 15 the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a
 20 yellow solid (0.570g, 3.37 mmol, 86% yield). $R_f = 0.10$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (400MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.66 (s, 1H), 7.66–7.60 (m, 2H), 7.23–7.16 (m, 2H), 2.19 (s, 3H). ^{13}C NMR (100 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 169.7, 158.9 (d, $J= 240.2\text{Hz}$), 138.1 (d, $J= 2.6\text{ Hz}$), 122.5, 115.0 5 (d, $J= 22.3\text{ Hz}$), 22.2. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C,
 25 δ): -120.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_9\text{NO}_2\text{F}$ ($[\text{M} + \text{H}]^+$), 170.0617, found, 170.0620.

***N*-(4-Chlorophenyl)-*N*-hydroxyacetamide (1f)**



To a stirred suspension of *N*-(4-chlorophenyl)hydroxylamine (**1f**) (1.00g, 6.97 mmol, 1.00equiv) and NaHCO₃ (0.700 g, 8.36 mmol, 1.20 equiv) in Et₂O (20.0mL, 0.349 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.660 g, 8.36 mmol, 1.20 equiv) in Et₂O (20.0 mL, 0.418 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. Recrystallization from Et₂O/hexanes afforded the title compound as a yellow solid (1.15 g, 6.20 mmol, 89% yield). R_f = 0.13 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.72 (s, 1H), 7.67 (d, J=8.9 Hz, 2H), 7.44–7.38 (m, 2H), 2.21 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.1, 140.5, 128.3, 128.1, 121.4, 22.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₉NO₂Cl ([M + H]⁺), 186.0322, found, 186.0321.

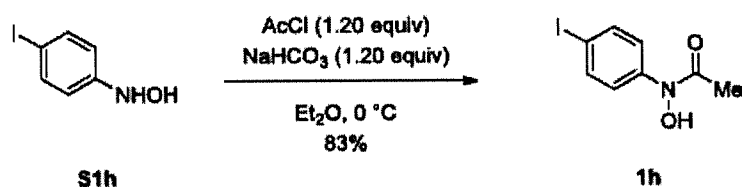
***N*-(4-Bromophenyl)-*N*-hydroxyacetamide (1g)**



To a stirred suspension of *N*-(4-bromophenyl)hydroxylamine (**1g**) (1.00g, 5.32 mmol, 1.00equiv) and NaHCO₃ (0.540 g, 6.38 mmol, 1.20 equiv) in Et₂O (25.0 mL, 0.213 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.500 g, 6.38 mmol, 1.20equiv) in Et₂O (30.0 mL, 0.213 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo* to afford the title compound as a brown solid (1.23 g, 5.34 mmol, quant yield). R_f = 0.14 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.72 (s, 1H), 7.61 (d, J=9.0Hz, 2H), 7.54 (d, J=9.0 Hz, 2H), 2.21 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.2, 140.9, 131.2, 121.6, 116.2, 22.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₉NO₂Br ([M + H]⁺), 229.9817, found, 229.9818.

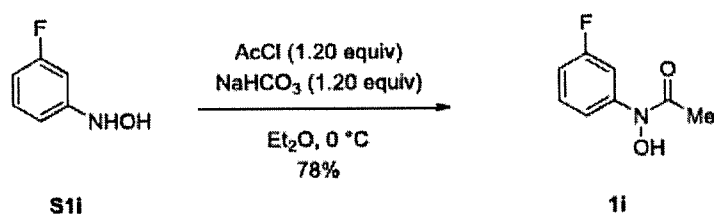
***N*-Hydroxy-*N*-(4-iodophenyl)acetamide (1h)**

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To a stirred suspension of *N*-(4-iodophenyl)hydroxylamine (**S1h**) (1.00g, 4.25 mmol, 1.00 equiv) and NaHCO₃ (0.430 g, 5.11 mmol, 1.20 equiv) in Et₂O (30.0mL, 0.412 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.400 g, 5.11 mmol, 1.20equiv) in Et₂O (20.0mL, 0.256 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, water was added. The aqueous layer was extracted with EtOAc (4 15 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated *in vacuo*. Recrystallization from Et₂O/hexanes afforded the title compound as light brown solid (0.980 g, 3.54 mmol, 83% yield). *R_f* = 0.18 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.69 (s, 1H), 7.72–7.67 (m, 2H), 7.48 (d, *J*=8.5Hz, 2H), 2.21 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.1, 141.4, 137.0, 121.8, 88.4, 22.6. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₈H₉NO₂I ([M + H]⁺), 277.9678, found, 277.9684.

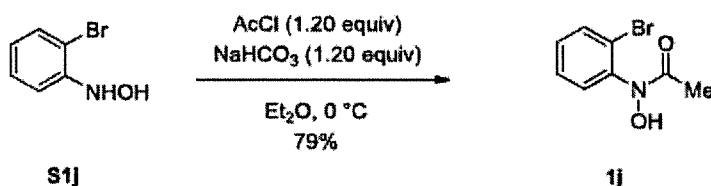
N-(3-Fluorophenyl)-*N*-hydroxyacetamide (**1i**)



To a stirred suspension of *N*-(3-fluorophenyl)hydroxylamine (**S1i**) (0.800g, 6.29 mmol, 1.00equiv) and NaHCO₃ (0.634 g, 7.55 mmol, 1.20 equiv) in Et₂O (35.0mL, 0.180 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.593 g, 7.55 mmol, 1.20 equiv) in Et₂O (30.0mL, 0.252 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a

yellow liquid(0.830 g, 4.91 mmol, 78% yield). $R_f = 0.52$ (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.77 (s, 1H), 7.54–7.50 (m, 2H), 7.50–7.37 (m, 1H), 7.00–7.6.94 (m, 1H), 2.23 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 170.4, 161.80 (d, $J = 240.2$ Hz), 143.1 (d, $J = 10.7$ Hz), 130.1 (d, $J = 9.2$ Hz), 115.0, 110.7 (d, $J = 20.9$ Hz), 106.3 (d, $J = 27.7$ Hz), 22.7. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C, δ): -114.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_9\text{NO}_2\text{F}$ ($[\text{M} + \text{H}]^+$), 170.0617, found, 170.0617.

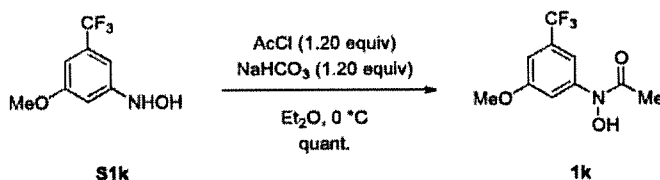
10 ***N*-(2-Bromophenyl)-*N*-hydroxyacetamide (1j)**



To a stirred suspension of *N*-(2-bromophenyl)hydroxylamine (**S1j**) (0.820g, 4.36mmol, 1.00 equiv) and NaHCO₃ (0.430g, 5.23mmol, 1.20 equiv) in Et₂O (20.0mL, 0.218 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.410g, 5.23mmol, 1.20equiv) in Et₂O (25.0mL, 0.209 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 (v/v)), to afford the title compound as a brown solid (0.790 g, 3.43 mmol, 79% yield). $R_f = 0.21$ (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.65 (s, 1H), 7.71–7.70 (m, 1H), 7.45–7.44 (m, 1H), 7.31–7.30 (m, 1H), 3.34 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 170.5, 141.0, 133.0, 129.9, 128.6, 122.1, 21.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_9\text{NO}_2\text{Br}$ ($[\text{M} + \text{H}]^+$), 229.9817, found, 229.9820.

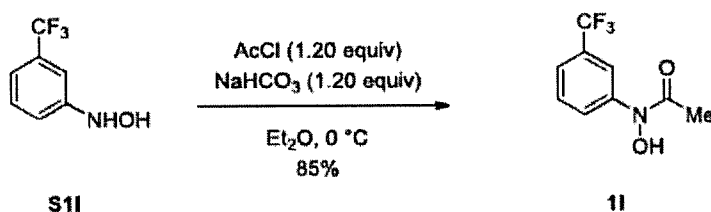
***N*-Hydroxy-*N*-(3-methoxy-5-(trifluoromethyl)phenyl)acetamide (1k)**

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To a stirred suspension of *N*-(3-methoxy-5-(trifluoromethyl)phenyl) hydroxylamine (**S1k**) (0.720g, 3.48 mmol, 1.00 equiv) and NaHCO₃ (0.350 g, 4.17 mmol, 1.20 equiv) in Et₂O (15.0 mL, 0.232 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.330 g, 4.17 mmol, 1.20equiv) in Et₂O (20.0mL, 0.209 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo* to afford the title compound as a yellow solid (0.870 g, 3.49 mmol, quant yield). *R_f* = 0.18 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.87 (s, 1H), 7.64 (s, 1H), 7.53 (s, 1H), 7.01 (s, 1H), 3.83 (s, 3H), 2.25 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.8, 159.8, 143.4, 130.2 (q, *J* = 31.4 Hz), 123.9 (q, *J* = 270.9 Hz), 108.6, 107.9, 105.8, 55.7, 22.8. ¹⁹F NMR (376 MHz, (CD₃)₂SO, 25 °C, δ): -63.3 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₀H₁₁NO₃F₃ ([M + H]⁺), 250.0691, found, 250.0696.

***N*-Hydroxy-*N*-(3-(trifluoromethyl)phenyl)acetamide (11)**



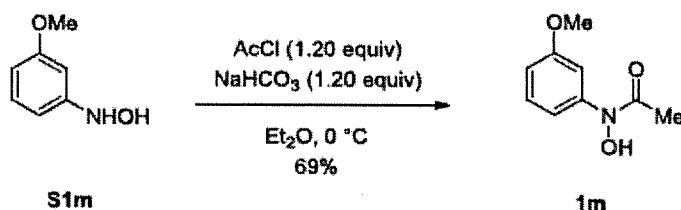
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To a stirred suspension of *N*-(3-(trifluoromethyl)phenyl)hydroxylamine (**S11**) (0.720g, 4.06mmol, 1.00 equiv) and NaHCO₃ (0.410g, 4.88mmol, 1.20 equiv) in Et₂O (20.0mL, 0.203 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.380g, 4.88mmol, 1.20equiv) in Et₂O (25.0mL, 0.192 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with

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hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (0.760 g, 3.47 mmol, 85% yield). $R_f = 0.19$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.88 (s, 1H), 8.03 (s, 1H), 7.94 (d, $J = 8.0\text{Hz}$, 1H), 7.61 (t, $J = 8.0\text{Hz}$, 1H), 7.48 (d, $J = 8.0\text{Hz}$, 1H), 2.08 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 170.7, 142.2, 129.8, 129.1 (q, $J = 31.6\text{ Hz}$), 126.2 (d, $J = 270.9\text{Hz}$), 122.9 (d, $J = 9.6\text{Hz}$), 120.6 (d, $J = 29.7\text{Hz}$), 115.5, 22.6. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C, δ): -63.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_9\text{NO}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 220.0585, found, 220.0589.

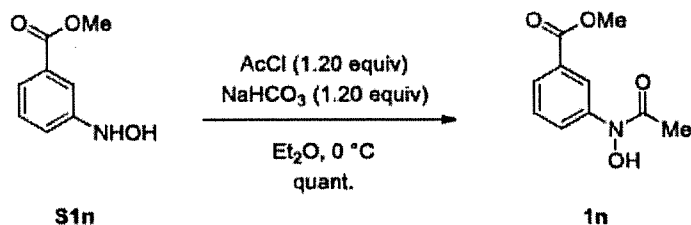
10

***N*-Hydroxy-*N*-(3-methoxyphenyl)acetamide (1m)**

To a stirred suspension of *N*-(3-methoxyphenyl)hydroxylamine (**S1m**) (0.900 g, 6.47 mmol, 1.00 equiv) and NaHCO₃ (0.650g, 7.76mmol, 1.20 equiv) in Et₂O (30.0mL, 0.216 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.610g, 7.76mmol, 1.20equiv) in Et₂O (30.0mL, 0.259 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 4:1 (v/v)), to afford the title compound as a brown liquid (0.810 g, 4.47 mmol, 69% yield). $R_f = 0.26$ (hexanes/EtOAc 5:1 (v/v)). ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.61 (s, 1H), 7.30–7.20 (m, 3H), 6.74–6.71 (m, 1H), 3.74 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 169.9, 159.2, 142.8, 129.2, 112.3, 109.8, 106.0, 55.1, 22.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_{12}\text{NO}_3$ ($[\text{M} + \text{H}]^+$), 182.0817, found, 182.0816.

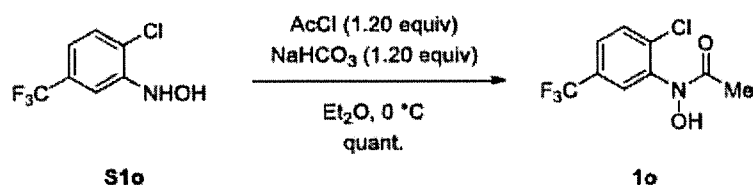
30 Methyl 3-(*N*-hydroxyacetamido)benzoate (1n)

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To a stirred suspension of methyl 3-(hydroxyamino)benzoate (**S1n**) (1.00g, 5.98 mmol, 1.00equiv) and NaHCO₃ (0.600 g, 7.18 mmol, 1.20 equiv) in Et₂O (30.0mL, 0.199 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.560 g, 7.18 mmol, 1.20equiv) in Et₂O (30.0mL, 0.239 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo* to afford the title compound as a yellow solid (1.25 g, 5.98 mmol, quant yield). R_f = 0.10 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.80 (s, 1H), 8.26 (s, 1H), 7.95–7.90 (m, 1H), 7.72 (d, J=7.6 Hz, 1H), 7.51 (t, J=7.9 Hz, 1H), 3.86 (s, 3H), 2.24 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.4, 166.0, 141.9, 129.8, 128.9, 124.9, 124.2, 120.1, 52.3, 22.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₁₂NO₄ ([M + H]⁺), 210.0766, found, 210.0764.

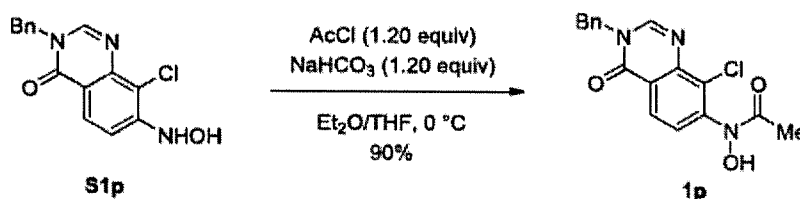
***N*-(2-Chloro-5-(trifluoromethyl)phenyl)-*N*-hydroxyacetamide (**1o**)**



To a stirred suspension of *N*-(2-chloro-5-(trifluoromethyl)phenyl)hydroxylamine (**S1o**) (0.930g, 4.43 mmol, 1.00 equiv) and NaHCO₃ (0.447 g, 5.32 mmol, 1.20 equiv) in Et₂O (25.0mL, 0.177 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.417 g, 5.32 mmol, 1.20equiv) in Et₂O (20.0mL, 0.266 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with

hexanes:EtOAc (4:1 to 2:1 (v/v)), to afford title compound as a yellow liquid (1.11 g, 4.38 mmol, quant yield). $R_f = 0.39$ (hexanes/EtOAc 2:1 (v/v)). $^1\text{H NMR}$ (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.87 (s, 1H), 7.84–7.75 (m, 3H), 2.19 (s, 3H). $^{13}\text{C NMR}$ (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 170.7, 140.3, 135.7, 131.3, 128.6 (q, $J = 32.5$ Hz), 126.3 (m), 125.9 (m), 123.3 (q, $J = 270.8$ Hz), 20.8. $^{19}\text{F NMR}$ (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25°C, δ): -63.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{ClF}_3$ ($[\text{M} + \text{H}]^+$), 254.0196, found, 254.0194.

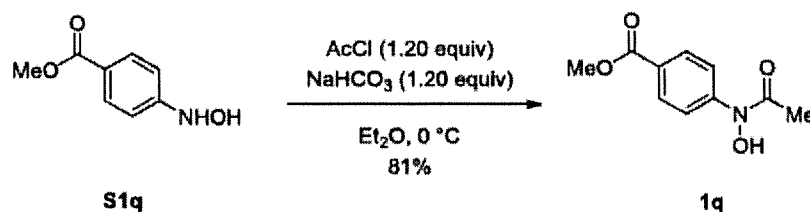
10 ***N*-(3-Benzyl-8-chloro-4-oxo-3,4-dihydroquinazolin-7-yl)-*N*-hydroxyacetamide (1p)**



To a stirred suspension of methyl 3-benzyl-8-chloro-7-(hydroxyamino)quinazolin-4(3H)-one (**S1p**) (0.700 g, 2.32 mmol, 1.00 equiv) and NaHCO_3 (0.234 g, 2.78 mmol, 1.20 equiv) in $\text{Et}_2\text{O/THF}$ 1:1 (v/v) (10 mL, 0.232 M) at 0 °C under N_2 was slowly added a solution of acetyl chloride (0.219 g, 2.78 mmol, 1.20 equiv) in Et_2O (15.0 mL, 0.185M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction was quenched with water, filtered and the solid was washed with Et_2O , dried at r.t. for 24 h to afford the title compound as a yellow solid (0.720 g, 2.09 mmol, 90% yield). $R_f = 0.14$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: $^1\text{H NMR}$ (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.83(s, 1H), 8.65 (s, 2H), 8.15(s, 1H), 7.91(s, 1H), 7.25–7.40 (m, 5H), 5.20 (s, 2H), 2.19 (s, 3H). $^{13}\text{C NMR}$ (125MHz, $(\text{CD}_3)_2\text{SO}$, δ): 159.3, 150.0, 148.1, 138.1, 137.7, 136.5, 128.7, 128.2, 127.8, 127.6, 126.7, 121.3, 49.1, 20.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_3\text{Cl}$ ($[\text{M} + \text{H}]^+$), 344.0802, found, 344.0808.

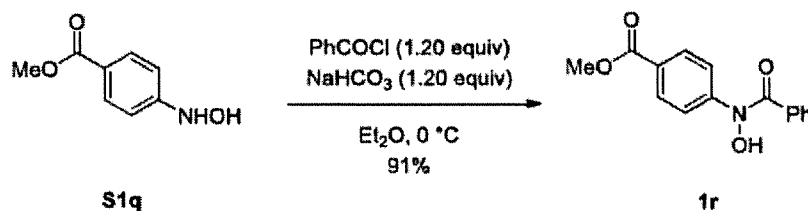
25 **Methyl 4-(*N*-hydroxyacetamido)benzoate (1q)**

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To a stirred suspension of methyl 4-(hydroxyamino)benzoate (**S1q**) (0.900 g, 5.38 mmol, 1.00 equiv) and NaHCO₃ (0.540 g, 6.46 mmol, 1.20 equiv) in Et₂O (30.0 mL, 0.179 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.510 g, 6.46 mmol, 1.20 equiv) in Et₂O (30.0 mL, 0.215 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a light yellow solid (0.910 g, 4.35 mmol, 81% yield). R_f = 0.13 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, (CD₃)₂SO, δ): 10.83 (s, 1H), 7.96 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H), 2.26 (s, 3H). ¹³C NMR (100 MHz, (CD₃)₂SO, δ): 170.8, 165.7, 145.4, 129.8, 124.6, 118.4, 52.0, 22.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₁₂NO₄ ([M + H]⁺), 210.0766, found, 210.0766.

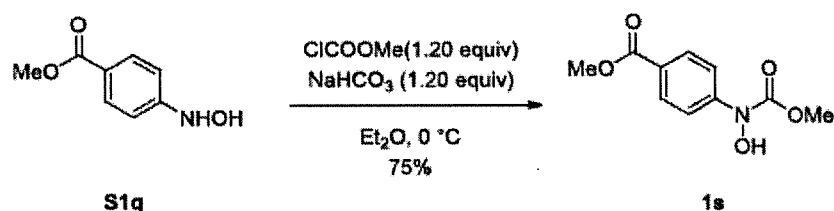
20 Methyl 4-(N-hydroxybenzamido)benzoate (1r)



To a stirred suspension of methyl 4-(hydroxyamino)benzoate (**S1q**) (1.00 g, 5.98 mmol, 1.00 equiv) and NaHCO₃ (0.603 g, 7.18 mmol, 1.20 equiv) in Et₂O (30.0 mL, 0.199 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (1.01 g, 7.18 mmol, 1.20 equiv) in Et₂O (30.0 mL, 0.239 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The

organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 (v/v)), to afford the title compound as a light yellow solid (1.47 g, 5.42 mmol, 91% yield). $R_f = 0.20$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.93 (s, 1H), 8.00 (d, $J = 8.8$ Hz, 2H), 7.81 (d, $J = 8.8$ Hz, 2H), 7.69 (d, $J = 7.4$ Hz, 2H), 7.52–7.44 (m, 3 H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 168.6, 165.7, 145.9, 135.2, 130.6, 129.8, 128.4, 127.9, 125.5, 120.0, 52.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{15}\text{H}_{14}\text{NO}_4$ ($[\text{M} + \text{H}]^+$), 272.0923, found, 272.0925.

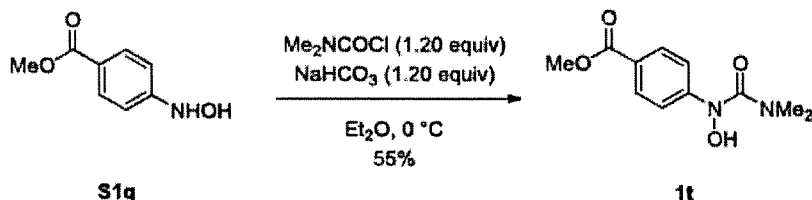
Methyl 4-(hydroxy(methoxycarbonyl)amino)benzoate (1s)



To a stirred suspension of methyl 4-(hydroxyamino)benzoate (**S1q**) (0.800g, 4.84 mmol, 1.00equiv) and NaHCO_3 (0.554 g, 6.55 mmol, 1.35 equiv) in Et_2O (15.0mL, 0.323 M) at 0 °C under N_2 was slowly added a solution of methyl chloroformate (0.490 g, 5.50 mmol, 1.10equiv) in Et_2O (15.0mL, 0.367 M) via a syringe pump (at a rate of 7.50mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2 /hexanes to afford the title compound as a light yellow solid (0.830 g, 3.69mmol, 75% yield). $R_f = 0.34$ (hexanes/EtOAc 3:2 (v/v)). ^1H NMR (400MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.63 (s, 1H), 7.94 (d, $J = 9.0$ Hz, 2H), 7.70 (d, $J = 9.0$ Hz, 2H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 165.7, 154.3, 146.1, 129.8, 124.3, 118.1, 53.2, 52.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_{12}\text{NO}_5$ ($[\text{M} + \text{H}]^+$), 226.0715, found, 226.0714.

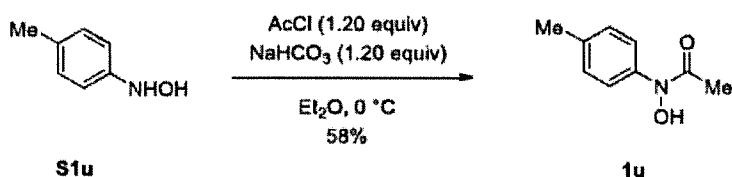
Methyl 4-(1-hydroxy-3,3-dimethylureido)benzoate (1t)

80



To a stirred suspension of methyl 4-(hydroxyamino)benzoate (**S1q**) (1.00g, 5.98 mmol, 1.00equiv) and NaHCO₃ (0.603 g, 7.18 mmol, 1.20 equiv) in Et₂O (30.0mL, 0.199 M) at 0 °C under N₂ was slowly added a solution of dimethylcarbamoyl chloride (0.772 g, 7.18 mmol, 1.2 equiv) in Et₂O (30.0mL, 0.239 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction was quenched by water and extracted with EtOAc (20mL×4). The combined organic layers were dried with MgSO₄, filtered, and concentrated *in vacuo*. The residue was recrystallized from Et₂O/hexane to afford title compound as a yellow solid (0.780 g, 3.27 mmol, 55% yield). R_f = 0.25 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 10.14 (s, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.23 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.95 (s, 6H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 166.0, 159.0, 149.4, 129.6, 122.7, 117.0, 51.8, 37.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₁H₁₅N₂O₄ ([M + H]⁺), 239.1032, found, 239.1033.

***N*-Hydroxy-*N*-(*p*-tolyl)acetamide (**1u**)**

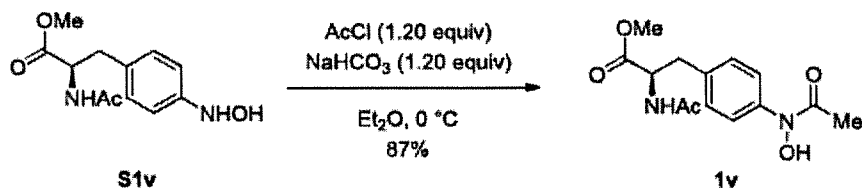


To a stirred suspension of *N*-(*p*-tolyl)hydroxylamine (**S1u**) (0.200g, 1.62 mmol, 1.00 equiv) and NaHCO₃ (164 mg, 1.95 mmol, 1.20 equiv) in Et₂O (10.0 mL, 0.162 M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (153 mg, 1.95 mmol, 1.20 equiv) in Et₂O (5.00 mL, 0.390 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 2:1 (v/v)), to afford the title compound as a yellow solid (0.156 g, 0.944 mmol, 58% yield). R_f = 0.27 (hexanes/EtOAc 2:1 (v/v)). NMR Spectroscopy: ¹H NMR (400MHz, (CD₃)₂SO, δ): 10.51 (s, 1H), 7.47

(d, $J=8.2$ Hz, 2H), 7.15 (d, $J=8.2$ Hz, 2H), 2.28 (s, 3H), 2.16 (s, 3H).
 ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 169.5, 139.3, 133.8, 128.8, 120.3, 22.3, 20.4. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_{12}\text{NO}_2$ ($[\text{M} + \text{H}]^+$), 166.0868, found, 166.0867.

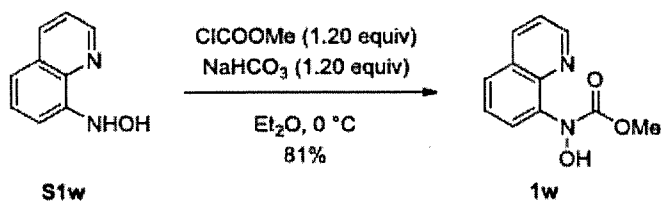
5

Methyl (R)-2-acetamido-3-(4-(N-hydroxyacetamido)phenyl)propanoate (1v)



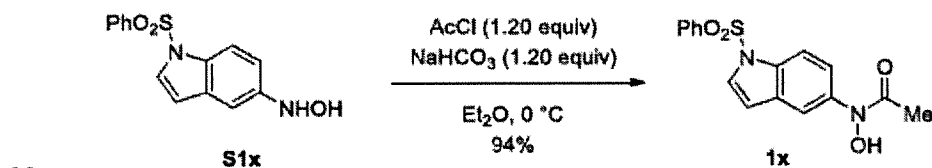
To a stirred suspension of methyl (R)-2-acetamido-3-(4-
 10 (hydroxyamino)phenyl)propanoate (**S1v**) (0.910g, 3.61 mmol, 1.00 equiv) and NaHCO_3 (0.364 g, 4.33 mmol, 1.20 equiv) in Et_2O (20.0mL, 0.185 M) at 0 °C under N_2 was slowly added a solution of acetyl chloride (0.340 g, 4.33 mmol, 1.20equiv) in Et_2O (20.0 mL, 0.217 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the
 15 reaction mixture was slowly warmed up to rt. The reaction mixture was then quenched with water and the solid was collected by filtration and dried under vacuum overnight at 40 °C. The procedure afforded the title compound as a yellow solid (0.920 g, 3.13 mmol, 87% yield). NMR Spectroscopy: ^1H NMR (500MHz, $(\text{CD}_3)_2\text{SO}$, δ): 10.57 (s, 1H), 8.32 (d,
 20 $J=7.2$ Hz, 1H), 7.52 (d, $J=7.7$ Hz, 2H), 7.19 (d, $J=7.7$ Hz, 2H), 4.43 (d, $J=5.9$ Hz, 1H), 3.60 (s, 3H), 2.98 (dd, $J=5.9, 13.6$ Hz, 1H), 2.85 (dd, $J=5.9, 13.6$ Hz, 1H), 2.18 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, δ): 172.2, 169.7, 169.3, 140.2, 133.5, 129.0, 120.0, 53.6, 51.8, 36.2, 22.4, 22.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd
 25 for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_5$ ($[\text{M} + \text{H}]^+$), 295.1294, found, 295.1296.

Methyl hydroxy(quinolin-8-yl)carbamate (1w)



To a stirred suspension of *N*-(quinolin-8-yl)hydroxylamine (**S1w**) (0.50g, 3.12 mmol, 1.00 equiv) and NaHCO₃ (0.315 g, 3.75 mmol, 1.20 equiv) in Et₂O (15.0mL, 0.208 M) at 0 °C under N₂ was slowly added a solution of methyl chloroformate (0.325 g, 3.75 mmol, 1.20equiv) in Et₂O (16.0mL, 0.234 M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was warmed up to rt and stirred for another 4 h. The reaction mixture was quenched with water and the solid was collected by filtration and dried under vacuum overnight. The procedure afforded the title compound as a dark brown solid (0.550 g, 2.52 mmol, 81% yield). *R_f* = 0.23 (hexanes/EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 10.19 (s, 1H), 8.93 (dd, *J*=1.7, 4.2 Hz, 1H), 8.43 (dd, *J*=1.7, 8.3 Hz, 1H), 8.00 (dd, *J*=1.3, 8.3 Hz, 1H), 7.76 (d, *J*=7.6 Hz, 1H), 7.64 (dd, *J*=7.6, 8.3 Hz, 1H), 7.59 (dd, *J*=4.2, 8.3 Hz, 1H), 3.57 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 157.2, 150.5, 143.0, 139.7, 136.4, 128.8, 128.66, 128.65, 126.4, 121.9, 52.6. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₁H₁₁N₂O₃ ([M + H]⁺), 219.0770, found, 219.0773.

***N*-hydroxy-*N*-(1-(phenylsulfonyl)-1*H*-indol-5-yl)acetamide (**1x**)**



To a stirred suspension of *N*-(1-(phenylsulfonyl)-1*H*-indol-5-yl)hydroxylamine (**S1x**) (0.950g, 3.31 mmol, 1.00 equiv) and NaHCO₃ (0.333 g, 3.97 mmol, 1.20 equiv) in Et₂O (25.0 mL, 0.132M) at 0 °C under N₂ was slowly added a solution of acetyl chloride (0.311 g, 3.97 mmol, 1.20equiv) in Et₂O (20.0 mL, 0.199M) via a syringe pump (at a rate of 10.0mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a white solid (1.02 g, 3.09 mmol, 94% yield). *R_f* = 0.19 (hexanes/EtOAc 2:1 (v/v)). NMR Spectroscopy: ¹H NMR (500MHz, (CD₃)₂SO, δ): 10.63 (s, 1H), 7.97 (d, *J*=8.1 Hz, 2H), 7.92 (d, *J*=9.1 Hz, 1H), 7.82 (d, *J*=3.6 Hz, 1H), 7.79 (s, 1 H), 7.70-7.66 (m, 1H), 7.61-7.56 (m, 3H), 6.87 (d, *J*=3.6 Hz, 1H), 2.18 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 169.7,

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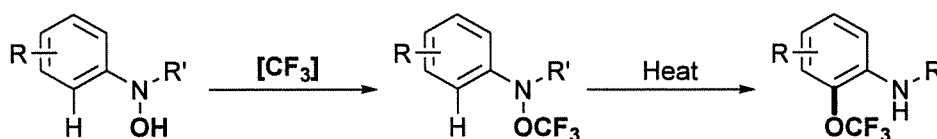
137.8, 136.9, 134.7, 131.3, 130.4, 129.8, 127.9, 126.6, 118.5, 113.7, 112.9, 109.9, 22.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₆H₁₅N₂O₄S ([M + H]⁺), 331.0753, found, 331.0759.

5 **Example 1. General Method for O-trifluoromethylation/ OCF₃-migration**

Herein is described the first synthesis, isolation, and characterization of protected N-aryl-N-(trifluoromethoxy)amines and their application in the synthesis of *ortho*-OCF₃ aniline derivatives (Scheme 1).

10

Scheme 1. General synthetic sequence



15 **Standard procedure for O-trifluoromethylation of protected N-aryl-N-hydroxylamines**

Under N₂ atmosphere, to a mixture of protected N-aryl-N-hydroxylamine (1.00 equiv) and Cs₂CO₃ (10 mol%) in CHCl₃ (0.100 M) was added Togni reagent II (1.20 equiv) and the reaction mixture was stirred at rt for 14–23h. The reaction mixture was then washed with sat. aq. NaHCO₃* and the organic layer was collected, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

20

*The wash with sat. aq. NaHCO₃ was not necessary in case of compounds of low polarity, which could be easily separated from 2-iodobenzoic acid by means column chromatography.

25

Standard procedure for the synthesis of ortho-OCF₃ aniline derivatives via OCF₃-migration

30 A solution of protected N-aryl-N-(trifluoromethoxy)amine (0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at an appropriate temperature (e.g., 50 °C, 80 °C, 120 °C or 140 °C) under N₂ atmosphere for 11–48h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

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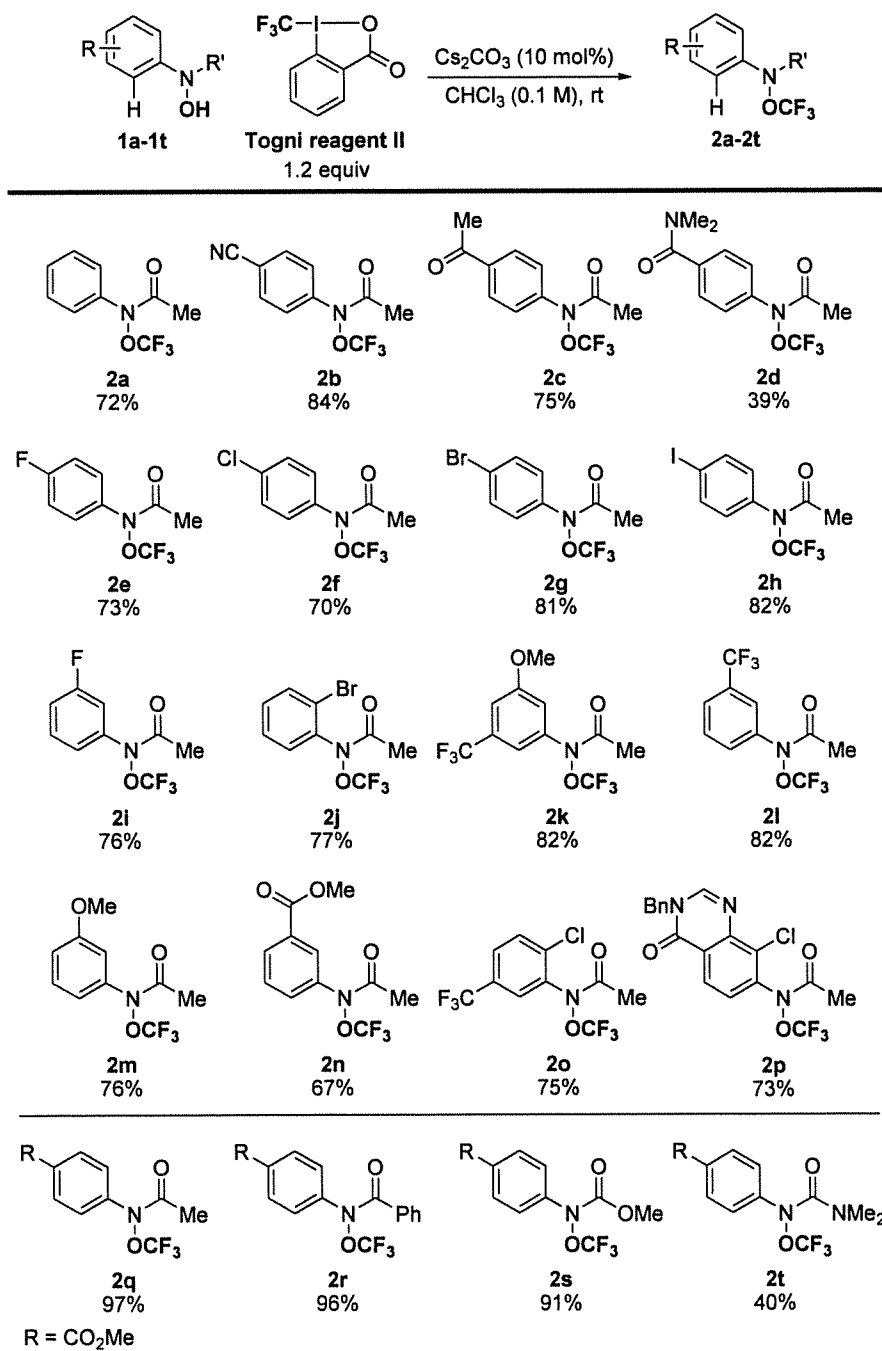
Example 2. Synthesis of N-OCF₃ Compounds

Although synthesis and applications of N-SCF₃ compounds are known,^[15] direct synthesis of the analogous N-OCF₃ compounds from protected *N*-aryl-*N*-hydroxylamines has not been reported.^[14] It is known that sodium 2,6,6-tetramethylpiperidin-1-oxide (TEMPO_{Na}) reacts with 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni reagent II)^[16] to form TEMPO-CF₃.^[17] Based on this reactivity, Togni and co-workers developed *O*-trifluoromethylation of *N,N*-dialkylhydroxylamines using 3,3-Dimethyl-1-(trifluoromethyl)-1,2-benziodoxole (Togni reagent I).^[14b] Therefore, it was envisioned that protected *N*-aryl-*N*-hydroxylamines could react with Togni reagents to provide the desired products of *O*-trifluoromethylation. Indeed, treatment of *N*-phenyl-*N*-hydroxamic acid (**1a**) with 1.2 equiv of Togni reagent II in the presence of 10 mol% Cs₂CO₃ in CHCl₃ (0.1 M) at room temperature furnished the desired product **2a** in 72% yield (Scheme 2). Addition of a stoichiometric amount of radical trap, 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), diminished the product yield. Moreover, this reaction is oxygen sensitive, so strictly degassed chloroform is required for high yield. These observations are consistent with a radical reaction mechanism.^[14b,17]

Under the optimized reaction conditions, various protected *N*-aryl-*N*-hydroxylamines (**1a-1t**, Scheme 2) were surveyed to determine the scope and limitations of this reaction. The reaction tolerated a wide range of functional groups including nitrile (**2b**), ketone (**2c**), amide (**2d**), halogens (**2e-2j**, **2o**, **2p**), CF₃ group (**2k**, **2l**, **2o**), ether (**2k**, **2m**), ester (**2n**, **2q-2t**), and heterocycle substituent (**2p**). Examination of different nitrogen protecting groups revealed that acetyl-, benzoyl-, and methoxycarbonyl-protected *N*-[(4-methoxycarbonyl)phenyl] hydroxylamines showed excellent and comparable reactivities (**2q-2s**), while dimethylcarbamoyl-protected *N*-[(4-methoxycarbonyl)phenyl] hydroxylamine was found to react sluggishly (**2t**). Substrates bearing a dimethylcarbamoyl group (**2d**, **2t**) afforded the corresponding products in lower yields. This is probably due to decomposition of the dimethylcarbamoyl group resulting from a hydrogen atom abstraction of N-CH₃ by a *N*-hydroxyl radical.^[18] It is noteworthy that this class of the OCF₃ compounds (**2a-2t**) shows the most shielded

chemical shift (~ -65 ppm) in ^{19}F -NMR compared to other OCF_3 containing compounds such as TEMPO- CF_3 (-55.7 ppm),^[19] Ph- OCF_3 (-58 ppm),^[20] and $n\text{-C}_{10}\text{H}_{21}\text{-OCF}_3$ (-61.3 ppm).^[21]

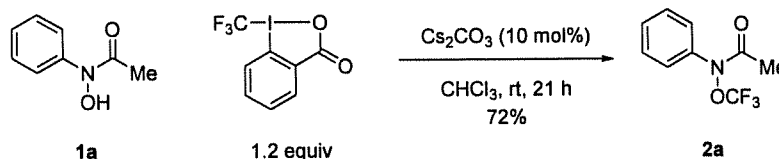
5 **Scheme 2.** Selected examples of O-trifluoromethylation of protected N-aryl-N-hydroxylamines.^a



^aReaction time: 14-23 hours. Cited yields are for isolated material following chromatography.

Procedures for O-trifluoromethylation of protected N-aryl-N-hydroxylamines

N-Phenyl-N-(trifluoromethoxy)acetamide (2a)

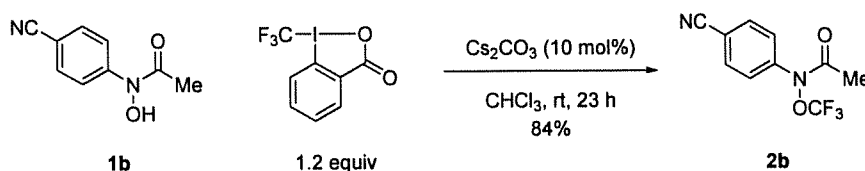


5

Under N₂ atmosphere, to a mixture of *N*-hydroxy-*N*-phenylacetamide (**1a**) (400 mg, 2.65 mmol, 1.00 equiv) and Cs₂CO₃ (86.2 mg, 0.265 mmol, 10 mol%) in CHCl₃ (26.5 mL, 0.100 M) was added Togni reagent II (1.00 g, 3.18 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 21 h. The reaction mixture concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (19:1 to 9:1 (v/v)), to afford the title compound as a slightly yellow oil (420 mg, 1.92 mmol, 72% yield). R_f = 0.63 (hexanes/EtOAc 9:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 7.49–7.41 (m, 2H), 7.41–7.31 (m, 3H), 2.22 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 172.4, 140.4, 129.5, 129.4, 126.3, 122.9 (q, *J* = 263.0 Hz), 22.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.8 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₉NO₂F₃ ([M + H]⁺), 220.0585, found, 220.0580.

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N-(4-Cyanophenyl)-N-(trifluoromethoxy)acetamide (2b)

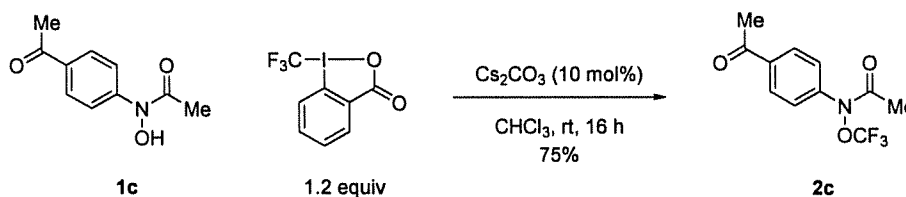


Under N₂ atmosphere, to a mixture of *N*-(4-cyanophenyl)-*N*-hydroxyacetamide (**1b**) (200 mg, 1.14 mmol, 1.00 equiv) and Cs₂CO₃ (37.0 mg, 0.114 mmol, 10 mol%) in CHCl₃ (11.4 mL, 0.100 M) was added Togni reagent II (432 mg, 1.37 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 23 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:2 to 0:1 (v/v)), to afford the title compound as an off-white solid (234 mg, 0.958 mmol, 84% yield). R_f = 0.66 (CH₂Cl₂). NMR Spectroscopy: ¹H

30

NMR (700 MHz, CDCl₃, 25 °C, δ): 7.74–7.70 (m, 2H), 7.55–7.51 (m, 2H), 2.38 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.4, 143.6, 133.1, 123.8, 122.7 (q, *J* = 265.2 Hz), 118.1, 111.6, 21.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -65.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*):
 5 calcd for C₁₀H₈N₂O₂F₃ ([M + H]⁺), 245.0538, found, 245.0541.

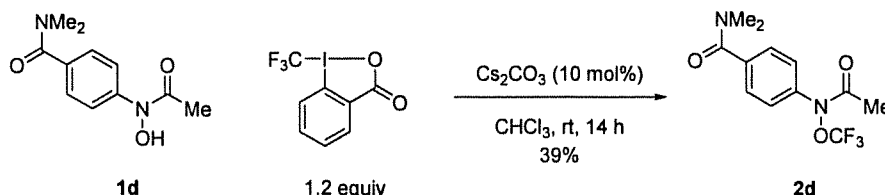
***N*-(4-Acetylphenyl)-*N*-(trifluoromethoxy)acetamide (2c)**



Under N₂ atmosphere, to a mixture of methyl *N*-(4-acetylphenyl)-*N*-
 10 hydroxyacetamide (**1c**) (309 mg, 1.60 mmol, 1.00 equiv) and Cs₂CO₃
 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added
 Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction
 mixture was stirred at rt for 16 h. The reaction mixture was then
 washed with sat. aq. NaHCO₃ (30 mL) and the layers were separated.
 15 The organic layer was dried (MgSO₄), filtered, and concentrated *in*
vacuo. The residue was purified by chromatography on silica gel,
 eluting with hexanes:EtOAc (9:1 to 7:3 (v/v)), to afford the title
 compound as a slightly yellow oil (314 mg, 1.20 mmol, 75% yield). *R*_f
 = 0.62 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz,
 20 CDCl₃, 25 °C, δ): 8.03–8.00 (m, 2H), 7.50–7.48 (m, 2H), 2.61 (s, 3H),
 2.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 196.9, 172.3, 143.9,
 136.5, 129.3, 124.0, 122.7 (q, *J* = 264.2 Hz), 26.8, 21.9. ¹⁹F NMR (376
 MHz, CDCl₃, 25 °C, δ): -65.00 (s). Mass Spectrometry: HRMS (ESI-TOF)
 (*m/z*): calcd for C₁₁H₁₁NO₃F₃ ([M + H]⁺), 262.0691, found, 262.0691.

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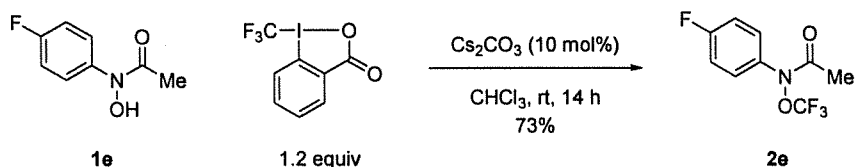
***N,N*-Dimethyl-4-(*N*-(trifluoromethoxy)acetamido)benzamide (2d)**



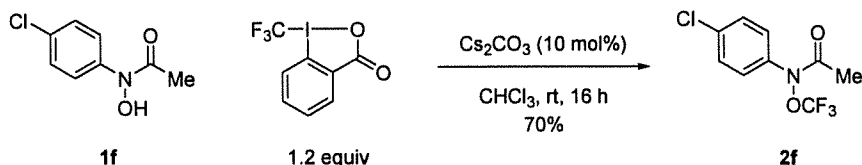
Under N₂ atmosphere, to a mixture of 4-(*N*-hydroxyacetamido)-*N,N*-
 30 dimethylbenzamide (**1d**) (192 mg, 0.864 mmol, 1.00 equiv) and Cs₂CO₃
 (28.2 mg, 0.0864 mmol, 10 mol%) in CHCl₃ (8.64 mL, 0.100 M) was added

Togni reagent II (329 mg, 1.04 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 14 h. The reaction mixture was then washed with sat. aq. NaHCO₃ (30 mL) and the layers were separated. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development (prep TLC was developed four times). The purification afforded the title compound as a pink oil (98.4 mg, 0.339 mmol, 39% yield). R_f = 0.30 (hexanes/EtOAc 2:3 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.49 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 3.12 (br. s, 3H), 2.99 (br. s, 3H), 2.27 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.4, 170.5, 141.1, 136.8, 128.2, 125.2, 122.8 (q, J = 263.8 Hz), 39.7, 35.5, 21.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₂H₁₄N₂O₃F₃ ([M + H]⁺), 291.0957, found, 291.0958.

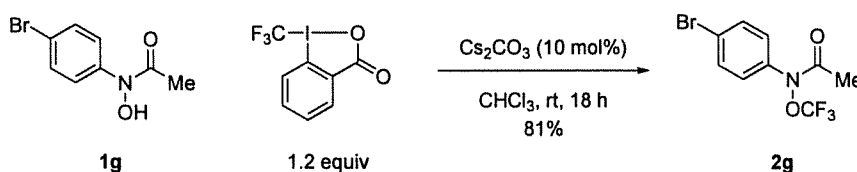
***N*-(4-Fluorophenyl)-*N*-(trifluoromethoxy)acetamide (2e)**



Under N₂ atmosphere, to a mixture of *N*-(4-fluorophenyl)-*N*-hydroxyacetamide (**1e**) (200 mg, 1.18 mmol, 1.00 equiv) and Cs₂CO₃ (38.5 mg, 0.118 mmol, 10 mol%) in CHCl₃ (11.8 mL, 0.100 M) was added Togni reagent II (447 mg, 1.42 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 14 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:1 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (206 mg, 0.868 mmol, 73% yield). R_f = 0.42 (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.39–7.34 (m, 2H), 7.16–7.11 (m, 2H), 2.24 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.7, 162.7 (d, J = 249.0 Hz), 136.4 (d, J = 2.6 Hz), 128.5, 122.9 (q, J = 263.1 Hz), 116.6 (d, J = 22.9 Hz), 21.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.8 (s), -111.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₈NO₂F₄ ([M + H]⁺), 238.0491, found, 238.0493.

***N*-(4-Chlorophenyl)-*N*-(trifluoromethoxy)acetamide (2f)**

Under N_2 atmosphere, to a mixture of *N*-(4-chlorophenyl)-*N*-hydroxyacetamide (**1f**) (297 mg, 1.60 mmol, 1.00 equiv) and Cs_2CO_3 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl_3 (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (7:3 to 1:1 (v/v)), to afford the title compound a slightly yellow oil (284 mg, 1.12 mmol, 70% yield). $R_f = 0.59$ (hexanes/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 7.42 (d, $J = 8.6$ Hz, 2H), 7.32 (d, $J = 8.6$ Hz, 2H), 2.26 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 172.6, 138.8, 135.0, 129.7, 127.1, 122.8 (q, $J = 263.7$ Hz), 21.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -64.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_3\text{Cl}$ ($[\text{M} + \text{H}]^+$), 254.0196, found, 254.0198.

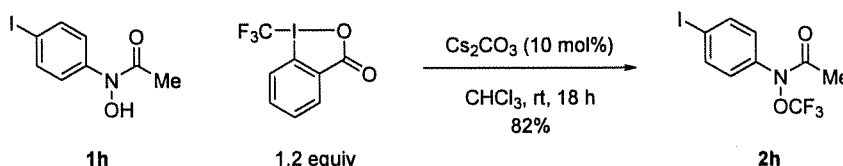
***N*-(4-Bromophenyl)-*N*-(trifluoromethoxy)acetamide (2g)**

Under N_2 atmosphere, to a mixture of *N*-(4-bromophenyl)-*N*-hydroxyacetamide (**1g**) (368 mg, 1.60 mmol, 1.00 equiv) and Cs_2CO_3 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl_3 (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (1:1 to 1:3 (v/v)), to afford the title compound as a slightly yellow oil (384 mg, 1.29 mmol, 81% yield). $R_f = 0.47$ (hexanes/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 7.59–7.55 (m, 2H), 7.23–7.28 (m, 2H), 2.26 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C,

δ): 172.5, 139.3, 132.6, 127.2, 122.9, 122.8 (q, $J = 263.3$ Hz), 21.8. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -64.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_3\text{Br}$ ($[\text{M} + \text{H}]^+$), 297.9690, found, 297.9694.

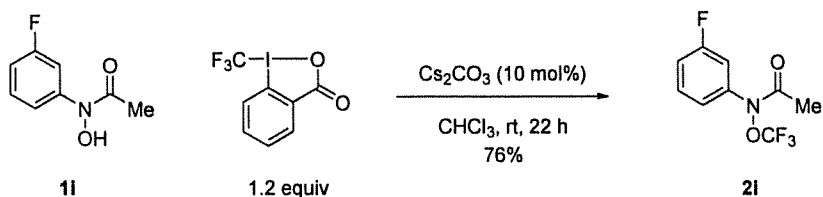
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***N*-(4-Iodophenyl)-*N*-(trifluoromethoxy)acetamide (2h)**



Under N_2 atmosphere, to a mixture of *N*-hydroxy-*N*-(4-iodophenyl)acetamide (**1h**) (200 mg, 0.722 mmol, 1.00 equiv) and Cs_2CO_3 (23.5 mg, 0.0720 mmol, 10 mol%) in CHCl_3 (7.20 mL, 0.100 M) was added Togni reagent II (274 mg, 0.867 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (1:1 (v/v)), to afford the title compound as a slightly yellow oil (205 mg, 0.594 mmol, 82% yield). $R_f = 0.48$ (hexanes/ CH_2Cl_2 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 7.79–7.76 (m, 2H), 7.14–7.11 (m, 2H), 2.27 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 172.5, 140.1, 138.6, 127.2, 122.8 (q, $J = 263.5$ Hz), 94.4, 21.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -64.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_3\text{I}$ ($[\text{M} + \text{H}]^+$), 345.9552, found, 345.9549.

***N*-(3-Fluorophenyl)-*N*-(trifluoromethoxy)acetamide (2i)**



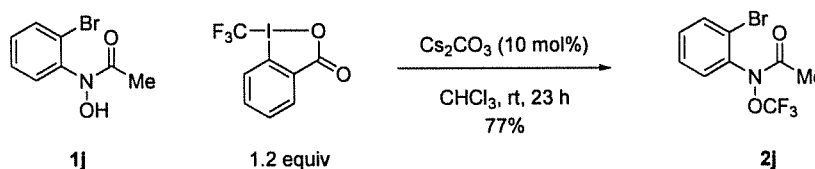
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Under N_2 atmosphere, to a mixture of *N*-(3-fluorophenyl)-*N*-hydroxyacetamide (**1i**) (243 mg, 1.44 mmol, 1.00 equiv) and Cs_2CO_3 (46.9 mg, 0.144 mmol, 10 mol%) in CHCl_3 (14.4 mL, 0.100 M) was added Togni reagent II (546 mg, 1.73 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 22 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on

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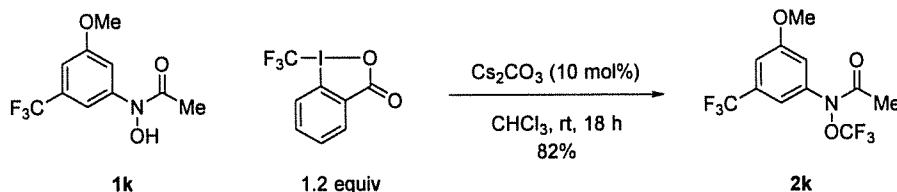
silica gel, eluting with hexanes:CH₂Cl₂ (1:1 to 1:3 (v/v)), to afford the title compound as a slightly yellow oil (260 mg, 1.09 mmol, 76% yield). $R_f = 0.55$ (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.41 (td, $J = 8.2, 6.0$ Hz, 1H), 7.19 (d, $J = 8.2$ Hz, 1H), 7.13 (dt, $J = 9.4, 2.2$ Hz, 1H), 7.08 (td, $J = 8.2, 1.7$ Hz, 1H), 2.28 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.5, 162.7 (d, $J = 246.8$ Hz), 141.6 (d, $J = 9.8$ Hz), 130.5 (d, $J = 8.8$ Hz), 122.8 (q, $J = 263.4$ Hz), 121.0, 115.9 (d, $J = 20.9$ Hz), 112.9 (d, $J = 24.0$ Hz), 21.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -65.0 (s), -111.2 (s). Mass Spectrometry: HRMS (EI-TOF) (m/z): calcd for C₉H₇NO₂F₄ ([M]⁺), 237.0413, found, 237.0417.

***N*-(2-Bromophenyl)-*N*-(trifluoromethoxy)acetamide (2j)**



Under N₂ atmosphere, to a mixture of *N*-(2-bromophenyl)-*N*-hydroxyacetamide (**1j**) (368 mg, 1.60 mmol, 1.00 equiv) and Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 23 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:1 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (367 mg, 1.23 mmol, 77% yield). $R_f = 0.55$ (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.70 (d, $J = 7.7$ Hz, 1H), 7.48 (d, $J = 7.7$ Hz, 1H), 7.42 (t, $J = 7.5$ Hz, 1H), 7.36–7.31 (m, 1H), 2.23 (br. s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.6, 139.6, 134.2, 132.0, 131.3, 128.7, 123.6, 123.0 (q, $J = 263.0$ Hz), 21.6. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₉NO₂F₃Br ([M + H]⁺), 297.9690, found, 297.9688.

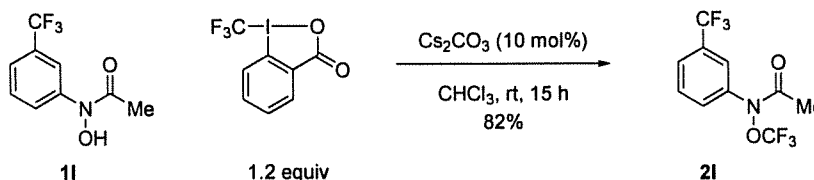
***N*-(3-Methoxy-5-(trifluoromethyl)phenyl)-*N*-(trifluoromethoxy)acetamide (2k)**



Under N_2 atmosphere, to a mixture of *N*-hydroxy-*N*-(3-methoxy-5-(trifluoromethyl)phenyl)acetamide (**1k**) (399 mg, 1.60 mmol, 1.00 equiv) and Cs_2CO_3 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl_3 (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 18 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (1:3 to 3:1 (v/v)), to afford the title compound as a slightly yellow oil (417 mg, 1.31 mmol, 82% yield). $R_f = 0.33$ (hexanes/ CH_2Cl_2 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 7.24 (br. s, 1H), 7.12 (br. s, 1H), 7.09 (br. s, 1H), 3.87 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 172.7, 160.4, 141.8, 132.7 (q, $J = 33.0$ Hz), 123.4 (q, $J = 271.1$ Hz), 122.8 (q, $J = 264.0$ Hz), 114.5, 113.9, 111.2, 56.0, 21.8. ^{19}F NMR (376 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): -63.4 (s), -65.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_3\text{F}_6$ ($[\text{M} + \text{H}]^+$), 318.0565, found, 318.0569.

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***N*-(Trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)acetamide (2l)**

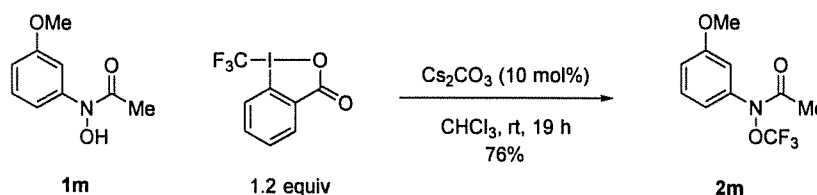


Under N_2 atmosphere, to a mixture of *N*-hydroxy-*N*-(3-(trifluoromethyl)phenyl)acetamide (**1l**) (351 mg, 1.60 mmol, 1.00 equiv) and Cs_2CO_3 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl_3 (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 15 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (1:1 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (378 mg, 1.32 mmol, 82% yield). $R_f = 0.50$

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(hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 7.66 (s, 1H), 7.64–7.60 (m, 1H), 7.60–7.56 (m, 2H), 2.33 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 172.8, 140.8, 132.0 (q, *J* = 33.0 Hz), 129.9, 128.3, 125.4 (q, *J* = 3.1 Hz), 123.5 (q, *J* = 271.1 Hz), 122.8 (q, *J* = 264.0 Hz), 121.7, 21.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -63.3 (s), -65.0 (s). Mass Spectrometry: HRMS (EI-TOF) (*m/z*): calcd for C₁₀H₇NO₂F₆ ([M]⁺), 287.0381, found, 287.0389.

***N*-(3-Methoxyphenyl)-*N*-(trifluoromethoxy)acetamide (2m)**



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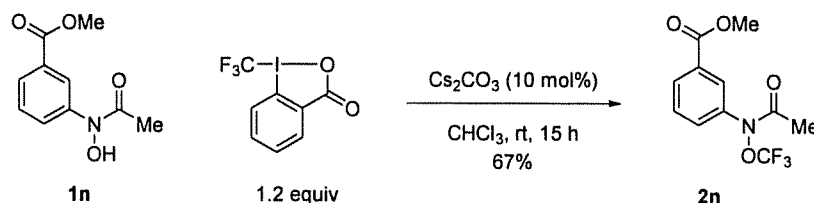
Under N₂ atmosphere, to a mixture of *N*-hydroxy-*N*-(3-methoxyphenyl)acetamide (**1m**) (290 mg, 1.60 mmol, 1.00 equiv) and Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 19 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:1 to 3:7 (v/v)), to afford the title compound as a yellow oil (303 mg, 1.21 mmol, 76% yield). *R_f* = 0.34 (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.35 (t, *J* = 8.2 Hz, 1H), 6.99–6.96 (m, 1H), 6.94 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.93–6.90 (m, 1H), 3.83 (s, 3H), 2.21 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 172.4, 160.4, 141.4, 130.2, 122.9 (q, *J* = 262.7 Hz), 118.5, 115.2, 112.0, 55.6, 22.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.8 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₀H₁₁NO₃F₃ ([M + H]⁺), 250.0691, found, 250.0687.

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Methyl 3-(*N*-(trifluoromethoxy)acetamido)benzoate (2n)

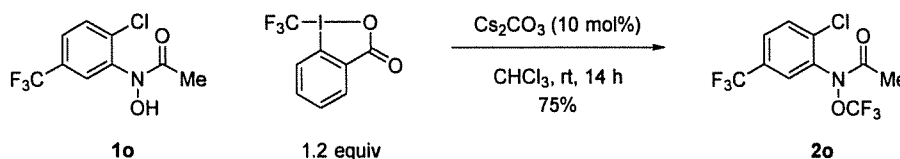


Under N₂ atmosphere, to a mixture of methyl 3-(*N*-hydroxyacetamido)benzoate (**1n**) (335 mg, 1.60 mmol, 1.00 equiv) and

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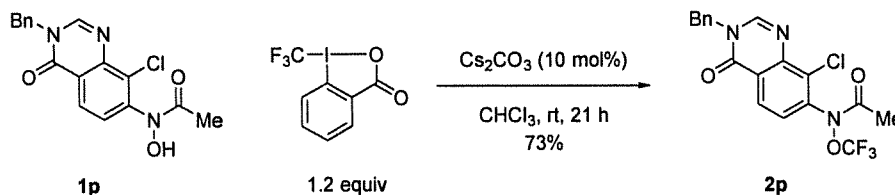
Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 15 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:3 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (298 mg, 1.08 mmol, 67% yield). *R_f* = 0.50 (CH₂Cl₂). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.07–8.04 (m, 2H), 7.59–7.56 (m, 1H), 7.55–7.50 (m, 1H), 3.94 (s, 3H), 2.29 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 172.7, 166.0, 140.6, 131.7, 130.0, 129.9, 129.5, 126.5, 122.8 (q, *J* = 263.7 Hz), 52.6, 21.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₁H₁₁NO₄F₃ ([M + H]⁺), 278.0640, found, 278.0640.

15 **Methyl 2-methyl-3-(*N*-(trifluoromethoxy)acetamido)benzoate (2o)**



Under N₂ atmosphere, to a mixture of *N*-(2-chloro-5-(trifluoromethyl)phenyl)-*N*-hydroxyacetamide (**1o**) (406 mg, 1.60 mmol, 1.00 equiv) and Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 14 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:1 to 1:3 (v/v)), to afford the title compound as a slightly yellow oil (388 mg, 1.21 mmol, 75% yield). *R_f* = 0.64 (hexanes/CH₂Cl₂ 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 7.73 (s, 1H), 7.69–7.64 (m, 2H), 2.35 (br. s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 173.3, 138.8, 137.5, 131.6, 130.7 (q, *J* = 33.7 Hz), 128.4 (d, *J* = 1.8 Hz), 127.9, 123.0 (q, *J* = 271.1 Hz), 123.0 (q, *J* = 263.8 Hz), 21.3. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -63.3 (s), -65.0 (s). Mass Spectrometry: HRMS (EI-TOF) (*m/z*): calcd for C₁₀H₆NO₂F₆Cl ([M]⁺), 320.9991, found, 320.9998.

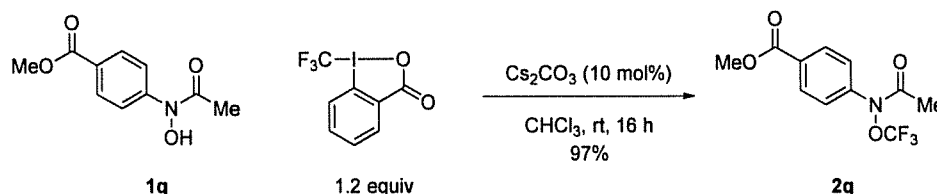
***N*-(3-Benzyl-8-chloro-4-oxo-3,4-dihydroquinazolin-7-yl)-*N*-(trifluoromethoxy)acetamide (2p)**



Under N₂ atmosphere, to a mixture of *N*-(3-benzyl-8-chloro-4-oxo-3,4-dihydroquinazolin-7-yl)-*N*-hydroxyacetamide (**1p**) (402 mg, 1.16 mmol, 1.00 equiv) and Cs₂CO₃ (37.8 mg, 0.116 mmol, 10 mol%) in CHCl₃ (11.6 mL, 0.100 M) was added Togni reagent II (439 g, 1.39 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 21 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (7:3 to 3:2 (v/v)), to afford the title compound as a white solid (351 mg, 0.852 mmol, 73% yield). R_f = 0.52 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.41 (s, 1H), 8.15 (s, 1H), 7.85 (s, 1H), 7.40–7.31 (m, 5H), 5.19 (s, 2H), 2.33 (br. s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 173.2, 159.8, 149.9, 148.9, 139.3, 136.9, 135.2, 129.8, 129.7, 129.3, 128.8, 128.2, 123.0 (q, *J* = 263.5 Hz), 121.6, 50.0, 21.3. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -64.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₈H₁₄N₃O₃ClF₃ ([*M* + *H*]⁺), 412.0676, found, 412.0673.

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Methyl 4-(*N*-(trifluoromethoxy)acetamido)benzoate (2q)

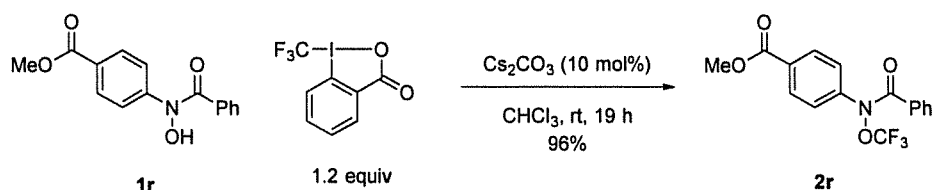


Under N₂ atmosphere, to a mixture of methyl 4-(*N*-hydroxyacetamido)benzoate (**1q**) (335 mg, 1.60 mmol, 1.00 equiv) and Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (7:3 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (428 mg, 1.54 mmol, 97% yield). R_f = 0.44 (CH₂Cl₂). NMR

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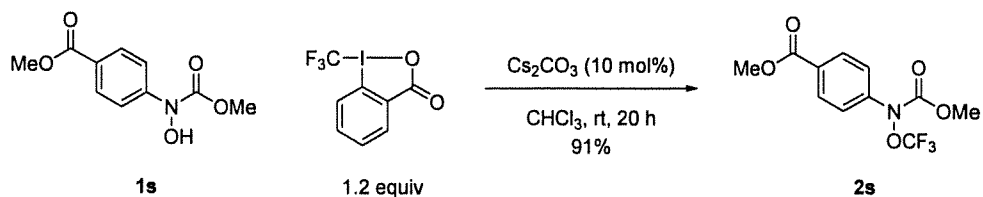
Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.13–8.09 (m, 2H), 7.49–7.45 (m, 2H), 3.93 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 172.3, 166.2, 143.9, 130.6, 129.9, 124.0, 122.8 (q, J = 264.1 Hz), 52.5, 21.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -65.00 (s).
 5 Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$), 278.0640, found, 278.0637.

Methyl 4-(*N*-(trifluoromethoxy)benzamido)benzoate (2r)



10 Under N_2 atmosphere, to a mixture of methyl 4-(*N*-hydroxybenzamido)benzoate (**1r**) (434 mg, 1.60 mmol, 1.00 equiv) and Cs_2CO_3 (52.1 mg, 0.160 mmol, 10 mol%) in CHCl_3 (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 19 h. The reaction mixture was
 15 filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes: CH_2Cl_2 (1:1 to 0:1 (v/v)), to afford the title compound as a slightly yellow oil (521 mg, 1.54 mmol, 96% yield). R_f = 0.67 (CH_2Cl_2). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.03 (d, J = 8.6 Hz, 2H), 7.65–7.61 (m, 2H), 7.47–7.41 (m, 3H), 7.32 (t, J = 7.7 Hz, 2H),
 20 3.90 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 170.7, 165.9, 145.2, 132.5, 132.1, 131.1, 131.0, 129.2, 128.6, 127.2, 122.8 (q, J = 265.8 Hz), 52.6. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -64.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$),
 25 340.0797, found, 340.0801.

Methyl 4-((methoxycarbonyl)(trifluoromethoxy)amino)benzoate (2s)

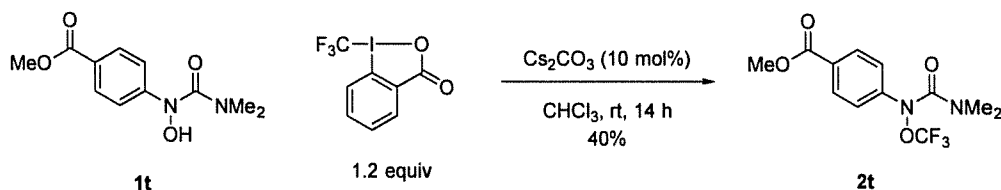


Under N_2 atmosphere, to a mixture of methyl 4-
 30 (hydroxy(methoxycarbonyl)amino)benzoate (**1s**) (360 mg, 1.60 mmol,

1.00 equiv) and Cs₂CO₃ (52.1 mg, 0.160 mmol, 10 mol%) in CHCl₃ (16.0 mL, 0.100 M) was added Togni reagent II (607 mg, 1.92 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 20 h. The reaction mixture was then washed with sat. aq. NaHCO₃ (30 mL) and the layers were separated. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:3 to 0:1 (v/v)), to afford the title compound as a colorless oil (427 mg, 1.45 mmol, 91% yield). R_f = 0.70 (CH₂Cl₂). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.09 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 3.93 (s, 3H), 3.89 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 166.2, 155.4, 144.7, 130.6, 129.6, 123.3, 122.8 (q, *J* = 263.1 Hz), 54.9, 52.5. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -66.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₁H₁₁NO₅F₃ ([M + H]⁺), 294.0589, found, 294.0589.

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Methyl 4-(3,3-dimethyl-1-(trifluoromethoxy)ureido)benzoate (2t)



Under N₂ atmosphere, to a mixture of methyl 4-(1-hydroxy-3,3-dimethylureido)benzoate (**1t**) (185 mg, 0.777 mmol, 1.00 equiv) and Cs₂CO₃ (25.3 mg, 0.0777 mmol, 10 mol%) in CHCl₃ (7.77 mL, 0.100 M) was added Togni reagent II (295 mg, 0.932 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 14 h. The reaction mixture was then washed with sat. aq. NaHCO₃ (30 mL) and the layers were separated. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with CH₂Cl₂, to afford the title compound as a colorless oil (94.8 mg, 0.310 mmol, 40% yield). R_f = 0.28 (CH₂Cl₂). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.08 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.60 Hz, 2H), 3.92 (s, 3H), 2.97 (s, 6H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 166.1, 158.0, 146.5, 131.4, 129.5, 122.9 (q, *J* = 259.8 Hz), 122.2, 52.5, 37.3. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -65.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₂H₁₄N₂O₄F₃ ([M + H]⁺), 307.0906, found, 307.0910.

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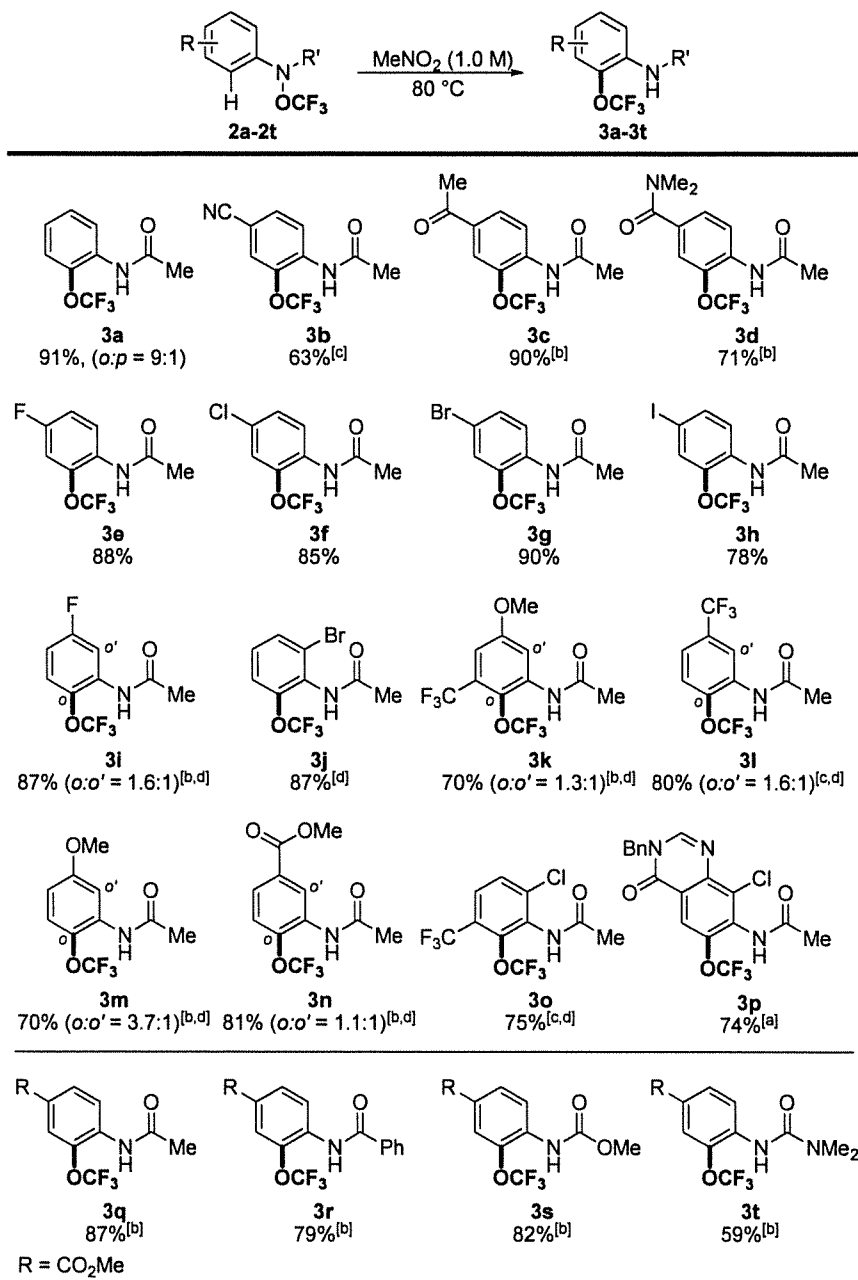
Example 3. OCF₃ Migration

With the protected *N*-aryl-*N*-(trifluoromethoxy)amines (**2a-2t**) in hand, attention was directed to examining the OCF₃-migration reaction. Systematic variation of different reaction parameters, including
5 solvent, concentration, and temperature, identified optimal reaction conditions. A significant degree of structural and electronic variation on the aryl ring was tolerated (Scheme 3). Products derived from electron-rich (**3m**) and electron-poor (**3b-3l**, **3n-3t**) aniline derivatives were formed in high yields, though electron-poor aniline
10 derivatives with exception of **3p** required higher reaction temperatures for full conversion. Notably, halogen functionalities, in particular Br and I, remained intact after reaction (**3e-3j**, **3o**, **3p**). These groups provide easy handles for further synthetic elaborations. Other functional groups including ester (**3n**, **3q-3t**),
15 nitrile (**3b**), ketone (**3c**), ether (**3k**, **3m**), heterocycle (**3p**) and multiple substitution on arene (**3k**, **3o**, **3p**) were well tolerated under the reaction conditions. In general, this reaction showed high levels of *ortho*-selectivity (**3a**, **3i-3o**); although, in the presence of two non-identical *ortho* positions, low levels of regiocontrol were
20 obtained (**3i**, **3k-3n**).

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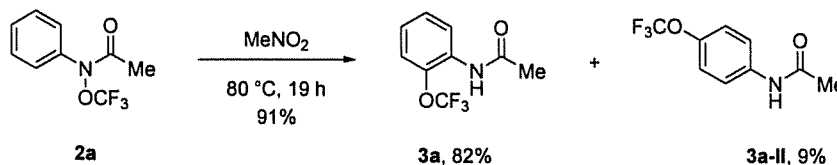
Scheme 3. Selected Examples of OCF₃-Migration Reaction^a

^aReaction time: 11-48 hours. Cited yields and isomeric ratios are for isolated material following chromatography. ^b120 °C. ^c140 °C. ^dLess

5 than 5% *para*-product was detected.

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***N*-(2-(Trifluoromethoxy)phenyl)acetamide (3a) and *N*-(4-(trifluoromethoxy)phenyl)acetamide (3a-II)**

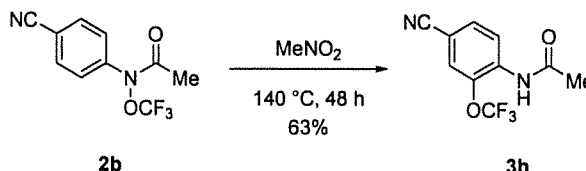


A solution of *N*-phenyl-*N*-(trifluoromethoxy)acetamide (**2a**) (128 mg, 100 μL , 0.584 mmol) in MeNO_2 (0.584 mL, 1.00 M) was heated at 80 $^\circ\text{C}$ under N_2 atmosphere for 19 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (9:1 to 1:1 (v/v)), to afford **3a** (105 mg, 0.479 mmol, 82% yield) and **3a-II** (11.2 mg, 0.0511 mmol, 9% yield).

Data for **3a**: white solid; $R_f = 0.36$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 8.39 (d, $J = 8.2$ Hz, 1H), 7.39 (br. s, 1H), 7.28 (t, $J = 7.7$ Hz, 1H), 7.25–7.24 (m, 1H), 7.12–7.08 (m, 1 H), 2.23 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 168.4, 138.1, 130.7, 127.7, 124.3, 122.1, 120.7 (q, $J = 257.7$ Hz), 120.4, 25.0. ^{19}F NMR (376 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): -58.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_9\text{NO}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 220.0585, found, 220.0583.

Data for **3a-II**: white solid; $R_f = 0.33$ (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 7.53 (d, $J = 8.9$ Hz, 2H), 7.18 (app d, $J = 8.9$ Hz, 3H), 2.19 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): 168.4, 145.4, 136.6, 121.9, 121.1, 120.6 (q, $J = 255.5$ Hz), 24.7. ^{19}F NMR (376 MHz, CDCl_3 , 25 $^\circ\text{C}$, δ): -58.8 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_9\text{NO}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 220.0585, found, 220.0583.

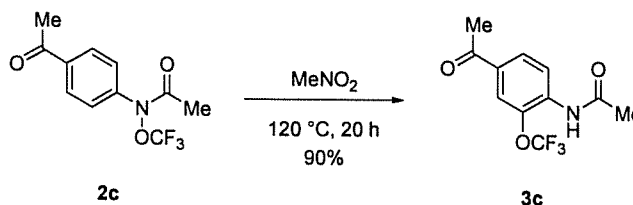
***N*-(4-Cyano-2-(trifluoromethoxy)phenyl)acetamide (3b)**



A solution of *N*-(4-cyanophenyl)-*N*-(trifluoromethoxy)acetamide (**2b**) (97.7 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 120 $^\circ\text{C}$ under N_2 atmosphere for 48 h. The reaction mixture was purified by

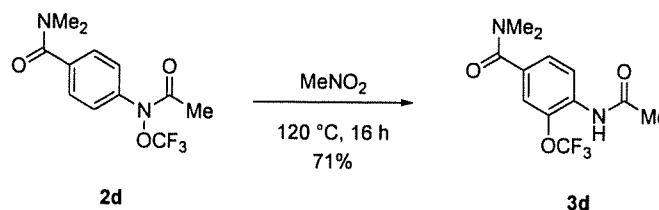
preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development. The purification afforded the title compound as a white crystalline solid (61.4 mg, 0.251 mmol, 63% yield). 20.0 mg (20%) of the starting material was recovered. Data for **3b**: R_f = 0.64 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.66 (d, J = 8.6 Hz, 1H), 7.61 (br. s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.54 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.6, 137.1, 135.0, 132.0, 123.7, 121.8, 120.5 (q, J = 260.2 Hz), 117.6, 107.2, 25.2. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 245.0538, found, 245.0539.

***N*-(4-Acetyl-2-(trifluoromethoxy)phenyl)acetamide (3c)**



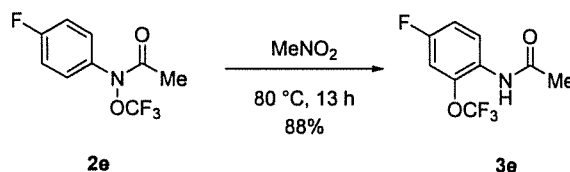
A solution of *N*-(4-acetylphenyl)-*N*-(trifluoromethoxy)acetamide (**2c**) (104 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 120 °C under N_2 atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (9:1 to 3:2 (v/v)), to afford the title compound as a white solid (93.6 mg, 0.358 mmol, 90% yield). R_f = 0.46 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.59 (d, J = 8.6 Hz, 1H), 7.89–7.86 (m, 2H), 7.58 (br. s, 1H), 2.59 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 195.7, 168.6, 137.6, 134.8, 132.9, 128.4, 120.8, 120.6 (q, J = 259.1 Hz), 119.8, 26.5, 25.1. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_3\text{F}_3$ ($[\text{M} + \text{H}]^+$), 262.0691, found, 262.0692.

4-Acetamido-*N,N*-dimethyl-3-(trifluoromethoxy)benzamide (3d)



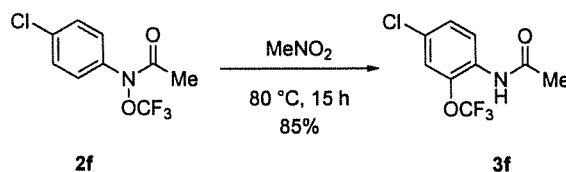
A solution of *N,N*-dimethyl-4-(*N*-(trifluoromethoxy)acetamido)benzamide (**2d**) (42.1 mg, 0.145 mmol) in MeNO₂ (0.145 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 16 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (3:7 (v/v)) for development (prep TLC was developed three times). The purification afforded the title compound as a white solid (30.0 mg, 0.103 mmol, 71% yield). *R_f* = 0.36 (hexanes/EtOAc 3:7 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.38 (d, *J* = 8.2 Hz, 1H), 7.72 (br. s, 1H), 7.35–7.30 (m, 2H), 3.08 (br. s, 3H), 2.99 (br. s, 3H), 2.23 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 169.7, 168.7, 137.8, 132.0, 131.8, 126.5, 121.8, 120.6 (q, *J* = 258.5 Hz), 119.9, 39.7, 35.7, 24.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₂H₁₄N₂O₃F₃ ([M + H]⁺), 291.0957, found, 291.0953.

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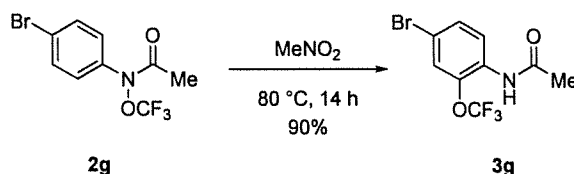
***N*-(4-Fluoro-2-(trifluoromethoxy)phenyl)acetamide (3e)**

A solution of *N*-(4-fluorophenyl)-*N*-(trifluoromethoxy)acetamide (**2e**) (94.9 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 80 °C under N₂ atmosphere for 13 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a beige solid (83.7 mg, 0.353 mmol, 88% yield). *R_f* = 0.33 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.38–8.30 (m, 1H), 7.30–7.26 (m, 1H), 7.08–6.98 (m, 2H), 2.22 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.3, 158.4 (d, *J* = 245.1 Hz), 138.4 (d, *J* = 10.0 Hz), 126.9 (d, *J* = 3.5 Hz), 123.4 (d, *J* = 8.5 Hz), 120.5 (q, *J* = 259.0 Hz), 114.3 (d, *J* = 21.5 Hz), 108.4 (d, *J* = 26.4 Hz), 24.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.4 (s), -115.8 (m). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₈NO₂F₄ ([M + H]⁺), 238.0491, found, 238.0488.

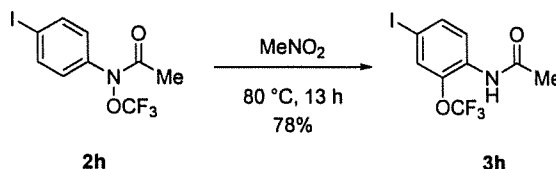
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***N*-(4-Chloro-2-(trifluoromethoxy)phenyl)acetamide (3f)**

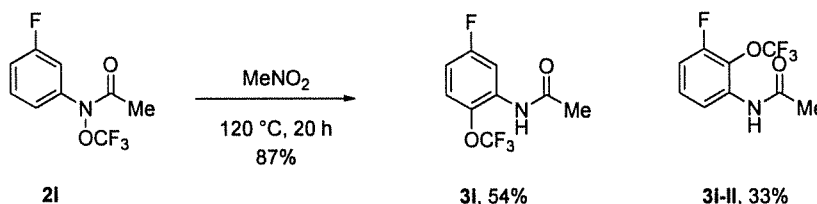
A solution of *N*-(4-chlorophenyl)-*N*-(trifluoromethoxy)acetamide (**2f**) (101 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 80 °C under N₂ atmosphere for 15 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a beige solid (86.2 mg, 0.340 mmol, 85% yield). *R_f* = 0.41 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.38 (d, *J* = 9.0 Hz, 1H), 7.34 (br. s, 1H), 7.28–7.27 (m, 1H), 7.27–7.26 (m, 1H), 2.23 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.3, 138.1, 129.4, 128.9, 127.8, 122.8, 120.8, 120.6 (q, *J* = 259.1 Hz), 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₈NO₂F₃Cl ([M + H]⁺), 254.0196, found, 254.0193.

***N*-(4-Bromo-2-(trifluoromethoxy)phenyl)acetamide (3g)**

A solution of *N*-(4-bromophenyl)-*N*-(trifluoromethoxy)acetamide (**2g**) (119 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 80 °C under N₂ atmosphere for 14 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (17:1 to 7:3 (v/v)), to afford the title compound as a beige solid (107 mg, 0.359 mmol, 90% yield). *R_f* = 0.42 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.32 (d, *J* = 9.2 Hz, 1H), 7.42–7.41 (m, 1H), 7.40 (s, 1H), 7.37 (br. s, 1H), 2.22 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 168.3, 138.2, 130.8, 129.9, 123.6, 123.1, 120.6 (q, *J* = 259.2 Hz), 115.9, 25.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₈NO₂F₃Br ([M + H]⁺), 297.9690, found, 297.9692.

***N*-(4-Iodo-2-(trifluoromethoxy)phenyl)acetamide (3h)**

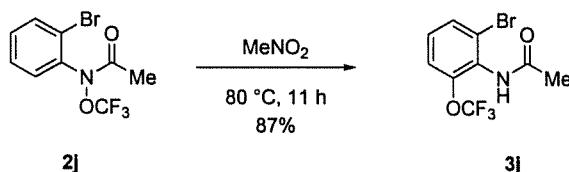
A solution of *N*-(4-iodophenyl)-*N*-(trifluoromethoxy)acetamide (**2h**) (138 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 80 °C under N₂ atmosphere for 13 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 2:3 (v/v)), to afford the title compound as a beige solid (108 mg, 0.313 mmol, 78% yield). *R_f* = 0.46 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.19 (d, *J* = 8.6 Hz, 1H), 7.59 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.56 (s, 1H), 7.36 (br. s, 1H), 2.22 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.3, 138.0, 136.8, 130.7, 129.2, 123.4, 120.6 (q, *J* = 259.1 Hz), 85.6, 25.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.3 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₉H₈NO₂F₃I ([M + H]⁺), 345.9552, found, 345.9548.

***N*-(5-Fluoro-2-(trifluoromethoxy)phenyl)acetamide (3i) and *N*-(3-fluoro-2-(trifluoromethoxy)phenyl)acetamide (3i-II)**

A solution of *N*-(3-fluorophenyl)-*N*-(trifluoromethoxy)acetamide (**2i**) (95.9 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development. The purification afforded **3i** (51.2 mg, 0.216 mmol, 54% yield) and **3i-II** (31.5 mg, 0.132 mmol, 33% yield). Data for **3i**: white solid; *R_f* = 0.67 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.25 (d, *J* = 9.0 Hz, 1H), 7.47 (br. s, 1H), 7.23–7.18 (m, 1H), 6.83–6.73 (m, 1H), 2.23 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.4, 161.0 (d, *J* = 243.9 Hz), 133.7, 132.2 (d, *J* = 12.1 Hz), 121.8 (d, *J* = 9.7 Hz), 120.7 (q, *J* = 258.0 Hz), 110.6 (d, *J* = 24.1

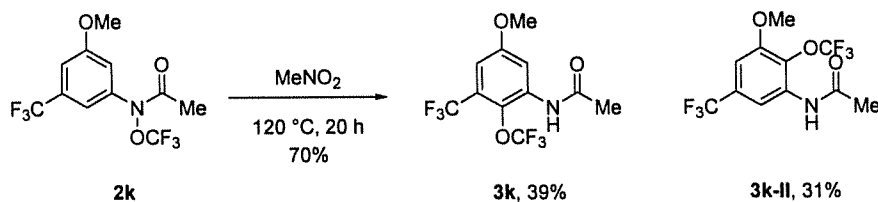
Hz), 109.1 (d, $J = 29.6$ Hz), 25.0. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.5 (s), -111.9 (q). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_4$ ($[\text{M} + \text{H}]^+$), 238.0491, found, 238.0492. Data for **3i-II**: white solid; $R_f = 0.56$ (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy:
 5 ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.15 (d, $J = 7.7$ Hz, 1H), 7.41 (br. s, 1 H), 7.29-7.23 (m, 1 H), 6.93 (t, $J = 9.0$ Hz, 1H), 2.23 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.4, 155.2 (d, $J = 250.3$ Hz), 133.5, 128.6 (d, $J = 8.5$ Hz), 126.3 (d, $J = 13.8$ Hz), 121.0 (q, $J = 259.9$ Hz), 117.3, 111.9 (d, $J = 18.3$ Hz), 24.9. ^{19}F NMR (376 MHz,
 10 CDCl_3 , 25 °C, δ): -58.9 (d), -127.3 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_4$ ($[\text{M} + \text{H}]^+$), 238.0491, found, 238.0490.

***N*-(2-Bromo-6-(trifluoromethoxy)phenyl)acetamide (3j)**



15 A solution of *N*-(2-bromophenyl)-*N*-(trifluoromethoxy)acetamide (**2j**) (119 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 80 °C under N_2 atmosphere for 11 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (3:2 (v/v)) for development. The purification afforded the title compound as a white crystalline solid
 20 (103 mg, 0.346 mmol, 87% yield). $R_f = 0.62$ (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 9.80 (br. s, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.46 (d, $J = 8.2$ Hz, 1H), 7.26 (t, $J = 8.2$ Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 168.2, 145.7, 131.6, 130.5, 129.4, 124.2, 120.8, 119.9 (q, $J = 256.5$
 25 Hz), 22.4. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): -58.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_8\text{NO}_2\text{F}_3\text{Br}$ ($[\text{M} + \text{H}]^+$), 297.9690, found, 297.9693.

***N*-(5-Methoxy-2-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)acetamide (3k) and *N*-(3-methoxy-2-(trifluoromethoxy)-5-(trifluoromethyl)phenyl)acetamide (3k-II)**



5 A solution of *N*-(3-methoxy-5-(trifluoromethyl)phenyl)-*N*-(trifluoromethoxy)acetamide (**2k**) (127 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development. The purification afforded **3k** (49.2 mg, 0.155 mmol, 39% yield) and **3k-II** (37.7 mg, 0.119 mmol, 31% yield). Data for **3k**: beige solid; R_f = 0.56 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.15 (br. s, 1H), 7.49 (br. s, 1H), 6.91 (d, *J* = 3.1 Hz, 1H), 3.84 (s, 3H), 2.22 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 168.5, 158.5, 134.0, 128.7, 125.6 (q, *J* = 32.4 Hz), 122.3 (q, *J* = 271.9 Hz), 120.9 (q, *J* = 260.0 Hz), 110.4, 108.8 (q, *J* = 4.3 Hz), 56.1, 24.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.2 (q), -61.3 (q). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₁H₁₀NO₃F₆ ([M + H]⁺), 318.0565, found, 318.0556.

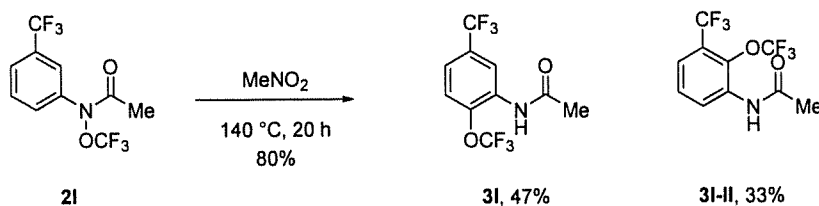
10 Data for **2k-II**: beige solid; R_f = 0.72 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.35 (br. s, 1H), 7.46 (br. s, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 3.93 (s, 3H), 2.23 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 168.5, 153.0, 133.5, 130.6 (q, *J* = 32.9 Hz), 129.3, 123.5 (q, *J* = 271.5 Hz), 121.0 (q, *J* = 260.1 Hz), 110.9, 104.7, 56.6, 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.7 (s), -63.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₁H₁₀NO₃F₆ ([M + H]⁺), 318.0565, found, 318.0555.

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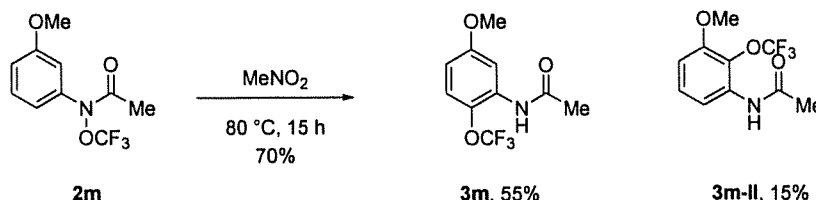
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***N*-(2-(Trifluoromethoxy)-5-(trifluoromethyl)phenyl)acetamide (3l) and *N*-(2-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)acetamide (3l-II)**



A solution of *N*-(trifluoromethoxy)-*N*-(3-(trifluoromethyl)phenyl)acetamide (**21**) (115 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 140 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (4:1 (v/v)) for development (prep TLC was developed twice). The purification afforded **31** (53.5 mg, 0.186 mmol, 47% yield) and **31-II** (37.4 mg, 0.129 mmol, 33% yield). Data for **31**: white solid; R_f = 0.66 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.79 (br. s, 1H), 7.55 (br. s, 1H), 7.32–7.39 (m, 2H), 2.26 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.6, 139.9, 131.1, 129.9 (q, *J* = 33.1 Hz), 123.5 (q, *J* = 270.8 Hz), 121.1, 120.5 (q, *J* = 259.6 Hz), 120.1, 119.2, 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.0 (s), -63.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₀H₈NO₂F₆ ([M + H]⁺), 288.0459, found, 288.0457. Data for **31-II**: white solid; R_f = 0.43 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.52 (br. s, 1H), 7.50 (br. s, 1H), 7.39–7.46 (m, 2H), 2.23 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.5, 135.7, 133.1, 128.3, 126.7, 125.2 (q, *J* = 32.0 Hz), 122.6 (d, *J* = 5.3 Hz), 122.5 (q, *J* = 271.6 Hz), 120.7 (q, *J* = 260.3 Hz), 24.7. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -55.7 (d), -61.1 (q). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₀H₈NO₂F₆ ([M + H]⁺), 288.0459, found, 288.0463.

***N*-(5-Methoxy-2-(trifluoromethoxy)phenyl)acetamide (3m) and *N*-(3-methoxy-2-(trifluoromethoxy)phenyl)acetamide (3m-II)**



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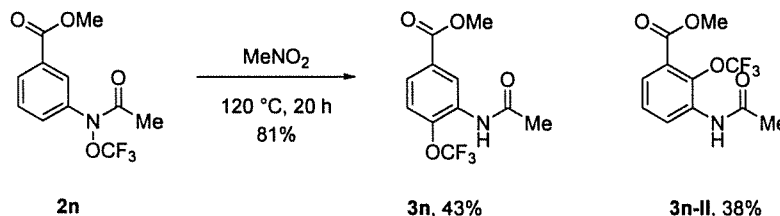
A solution of *N*-(3-methoxyphenyl)-*N*-(trifluoromethoxy)acetamide (**2m**) (99.7 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 80 °C under N₂ atmosphere for 15 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (4:1 (v/v)) for development (prep TLC was developed four times). The purification afforded **3m** (55.3 mg, 0.222 mmol, 55% yield) and **3m-II** (14.9 mg, 0.0600 mmol, 15% yield). Data for **3m**: white solid; R_f = 0.77 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.02 (d, *J* = 2.0 Hz,

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1H), 7.48 (br. s, 1H), 7.12 (dd, $J = 9.2, 1.1$ Hz, 1H), 6.59 (dd, $J = 9.0, 3.0$ Hz, 1H), 3.79 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.5, 158.5, 131.8, 131.6, 121.7, 120.8 (q, $J = 256.8$ Hz), 109.9, 106.8, 55.8, 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_3\text{F}_3$ ($[\text{M} + \text{H}]^+$), 250.0691, found, 250.0690. Data for **3m-II**: white solid; $R_f = 0.70$ (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 7.93 (d, $J = 8.2$ Hz, 1H), 7.40 (br. s, 1H), 7.23 (t, $J = 8.4$ Hz, 1H), 6.73 (d, $J = 8.2$ Hz, 1H), 3.87 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.4, 152.7, 132.9, 128.2, 127.6, 121.1 (q, $J = 258.7$ Hz), 113.8, 108.0, 56.3, 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -57.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_3\text{F}_3$ ($[\text{M} + \text{H}]^+$), 250.0691, found, 250.0692.

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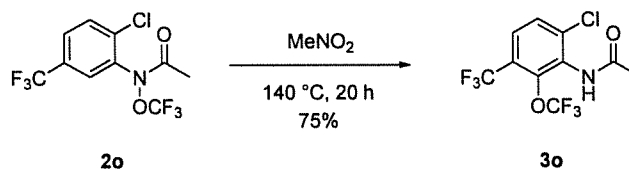
Methyl 3-acetamido-4-(trifluoromethoxy)benzoate (3n) and methyl 3-acetamido-2-(trifluoromethoxy)benzoate (3n-II)



A solution of methyl 3-(*N*-(trifluoromethoxy)acetamido)benzoate (**2n**) (111 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 120 °C under N_2 atmosphere for 20 h. The reaction mixture was purified by preparative TLC using Et_2O for development. The purification afforded 90.4 mg of a 1.14:1 mixture of **3n** and **3n-II** (81% overall yield). Compounds **3n** and **3n-II** were further separated for characterization by preparative TLC (eluting twenty times with hexanes: Et_2O (7:3 (v/v))). Data for **3n**: white solid; $R_f = 0.59$ (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 25 °C, δ): 9.02 (br. s, 1H), 7.82 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.41 (br. s, 1H), 7.31 (dd, $J = 8.7, 1.6$ Hz, 1H), 3.92 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.4, 166.0, 141.2, 130.3, 129.4, 125.9, 123.4, 120.5 (q, $J = 259.1$ Hz), 119.5, 52.6, 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -57.8 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$), 278.0640, found, 278.0640.

Data for **3n-II**: white solid; $R_f = 0.56$ (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.56 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 7.7$ Hz, 1H), 7.51 (br. s, 1H), 7.39 (t, $J = 8.0$ Hz, 1H), 3.93 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.5, 165.0, 136.5, 132.8, 128.1, 126.6, 126.2, 126.1, 120.8 (q, $J = 258.6$ Hz), 52.7, 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -57.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$), 278.0640, found, 278.0639.

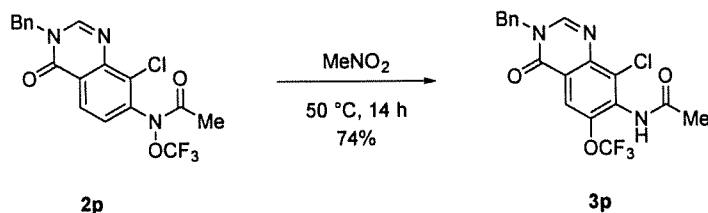
10 ***N*-(6-Chloro-2-(trifluoromethoxy)-3-(trifluoromethyl)phenyl)acetamide (3o)**



A solution of *N*-(2-chloro-5-(trifluoromethyl)phenyl)-*N*-(trifluoromethoxy)acetamide (**2o**) (129 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 140 °C under N_2 atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (1:19 (v/v)) for development (prep TLC was developed five times). The purification afforded the title compounds as a white solid (96.0 mg, 0.299 mmol, 75% yield). The product was obtained as a 5:3 mixture of atropisomers. The spectral data corresponds to the major atropisomer. $R_f = 0.41$ (hexanes/EtOAc 19:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 25 °C, δ): 7.70 (d, $J = 8.9$ Hz, 1H), 7.36 (d, $J = 8.9$ Hz, 1H), 6.89 (br. s, 1H), 2.25 (br. s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 168.4, 148.4, 132.3, 129.5, 127.9 (q, $J = 32.2$ Hz), 126.8, 122.3 (q, $J = 271.9$ Hz), 120.4 (q, $J = 259.5$ Hz), 118.7, 23.1. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -57.9 (s), -63.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_7\text{NO}_2\text{F}_6\text{Cl}$ ($[\text{M} + \text{H}]^+$), 322.0070, found, 322.0068.

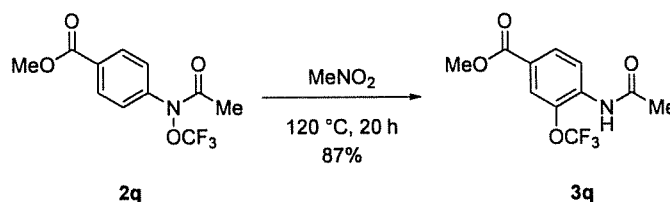
110

***N*-(3-Benzyl-8-chloro-4-oxo-6-(trifluoromethoxy)-3,4-dihydroquinazolin-7-yl)acetamide (3p)**



A solution of *N*-(3-benzyl-8-chloro-4-oxo-3,4-dihydroquinazolin-7-yl)-*N*-(trifluoromethoxy)acetamide (**2p**) (120 mg, 0.291 mmol) in MeNO₂ (0.582 mL, 0.500 M) was heated at 50 °C under N₂ atmosphere for 14 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:3 (v/v)), to afford the title compound as a white solid (89.0 mg, 0.216 mmol, 74% yield). *R*_f = 0.73 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.07 (s, 1H), 7.81 (s, 1H), 7.39–7.30 (m, 5H), 7.03 (br. s, 1H), 5.17 (s, 2H), 2.26 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.6, 157.3, 148.7, 148.4, 143.9, 139.7, 135.2, 129.3, 128.7, 128.6, 128.3, 128.2, 120.6 (q, *J* = 258.8 Hz), 116.3, 49.7, 23.2. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₈H₁₄N₃O₃ClF₃ ([*M* + *H*]⁺), 412.0676, found, 412.0673.

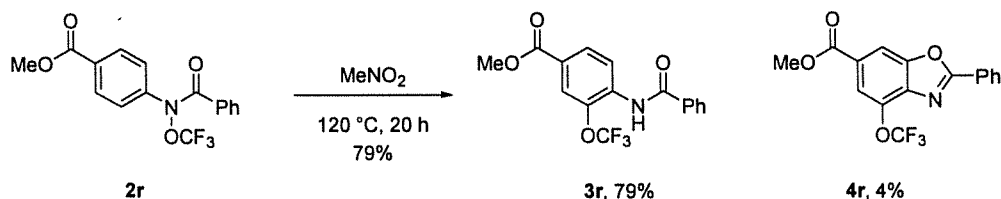
Methyl 4-(*N*-(trifluoromethoxy)acetamido)benzoate (3q)



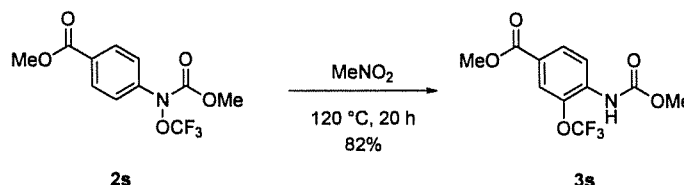
A solution of methyl 4-(*N*-(trifluoromethoxy)acetamido)benzoate (**2q**) (111 mg, 0.400 mmol) in MeNO₂ (0.400 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (9:1 to 7:3 (v/v)), to afford the title compound as a white solid (97.1 mg, 0.350 mmol, 87% yield). *R*_f = 0.51 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.56 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.6 Hz, 1H), 7.93 (s, 1H), 7.56 (br. s, 1H), 3.92 (s, 3H), 2.27 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.5, 165.6, 137.2, 134.7, 129.3, 125.8,

121.5, 120.8, 120.6 (q, $J = 258.9$ Hz), 52.5, 25.2. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{11}\text{H}_{11}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$), 278.0640, found, 278.0643.

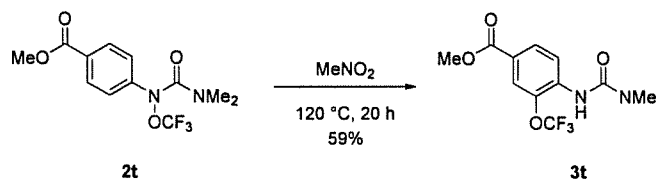
5 Methyl 4-benzamido-3-(trifluoromethoxy)benzoate (**3r**)



A solution of methyl 4-(*N*-(trifluoromethoxy)benzamido)benzoate (**2r**) (136 mg, 0.400 mmol) in MeNO_2 (0.400 mL, 1.00 M) was heated at 120 °C under N_2 atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (9:1 to 7:3 (v/v)), to afford the title compound as a white solid (107 mg, 0.315 mmol, 79% yield). The reaction also afforded methyl 2-phenyl-4-(trifluoromethoxy)benzo[d]oxazole-6-carboxylate (**4r**) as a white solid (5.4 mg, 0.016 mmol, 4% yield). Data for **3r**: $R_f = 0.72$ (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.74 (d, $J = 8.6$ Hz, 1H), 8.37 (br. s, 1H), 8.04 (dd, $J = 8.6, 1.7$ Hz, 1H), 7.98 (s, 1H), 7.90–7.84 (m, 2H), 7.63–7.58 (m, 1H), 7.56–7.51 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 165.6, 165.5, 137.7, 135.0, 134.2, 132.8, 129.5, 129.3, 127.2, 126.0, 121.7, 120.8, 120.7 (q, $J = 259.1$ Hz), 52.5. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{16}\text{H}_{13}\text{NO}_4\text{F}_3$ ($[\text{M} + \text{H}]^+$), 340.0797, found, 340.0793. Data for **4r**: $R_f = 0.73$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.36–8.25 (m, 3H), 8.10 (d, $J = 8.2$ Hz, 1H), 7.79 (d, $J = 8.2$ Hz, 1H), 7.65–7.49 (m, 3H), 3.97 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 166.8, 165.7, 150.6, 146.2, 132.4, 129.2, 128.1, 127.3, 126.8, 126.6, 119.7, 112.4, 52.5.

Methyl 4-((methoxycarbonyl)amino)-3-(trifluoromethoxy)benzoate (3s)

A solution of methyl 4-((methoxycarbonyl)(trifluoromethoxy)amino)benzoate (**2s**) (130 mg, 0.443 mmol) in MeNO₂ (0.443 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (19:1 (v/v)) for development (prep TLC was developed three times). The purification afforded the title compound as a white crystalline solid (106 mg, 0.362 mmol, 82% yield). R_f = 0.63 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.33 (d, *J* = 8.60 Hz, 1H), 7.97 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.92 (s, 1H), 7.13 (br. s, 1H), 3.91 (s, 3H), 3.83 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 165.7, 153.3, 136.9, 135.0, 129.4, 125.0, 121.7, 120.6 (q, *J* = 258.9 Hz), 119.1, 53.0, 52.5. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₁H₁₁NO₅F₃ ([M + H]⁺), 294.0589, found, 294.0587.

Methyl 4-(3,3-dimethylureido)-3-(trifluoromethoxy)benzoate (3t)

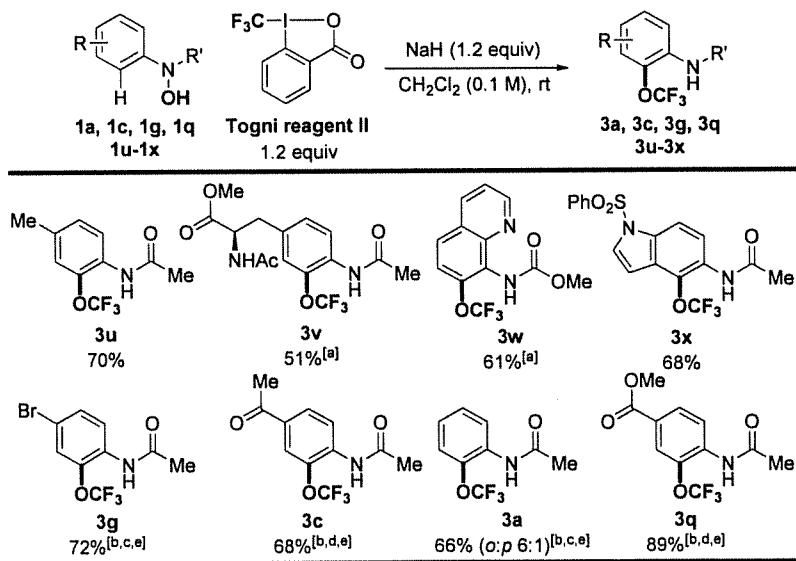
A solution of methyl 4-(3,3-dimethyl-1-(trifluoromethoxy)ureido)benzoate (**2t**) (43.6 mg, 0.142 mmol) in MeNO₂ (0.142 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as a colorless oil (25.7 mg, 0.0839 mmol, 59% yield). R_f = 0.58 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.42 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.88 (s, 1H), 6.98 (br. s, 1H), 3.89 (s, 3H), 3.06 (s, 6H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 165.9, 154.3, 136.9, 136.6, 129.4, 124.0, 121.7, 120.7 (q, *J* = 258.4 Hz), 119.6, 52.3, 36.5. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.2 (s). Mass Spectrometry: HRMS

(ESI-TOF) (m/z): calcd for $C_{12}H_{14}N_2O_4F_3$ ($[M + H]^+$), 307.0906, found, 307.0902.

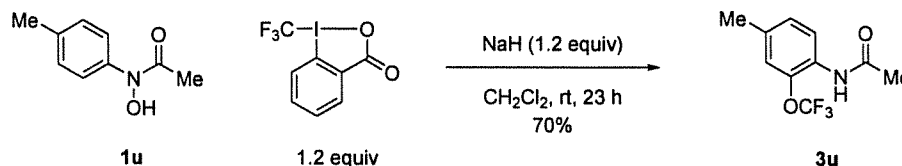
Example 4. One-Pot Method

5 Next, it was explored as to whether the two-step sequence could be converted into a one-pot transformation to further simplify the reaction protocol. Exposure of **1u** to Togni reagent II and NaH in CH_2Cl_2 at room temperature provided the desired product **3u** in 70% isolated yield (Scheme 4). These reaction conditions tolerate α -amino acid ester (**3v**), quinoline (**3w**), and indole (**3x**).
 10 Moreover, products from Scheme 3 such as **3a**, **3c**, **3g**, and **3q** can be directly obtained from the corresponding hydroxylamines via a one-pot reaction protocol without the isolation of intermediates **2**. However removal of CH_2Cl_2 at the end of the trifluoromethylation reaction followed by re-
 15 dissolving the resulting residue in $MeNO_2$ is needed, because the OCF_3 -migration for these substrates requires higher reaction temperature.

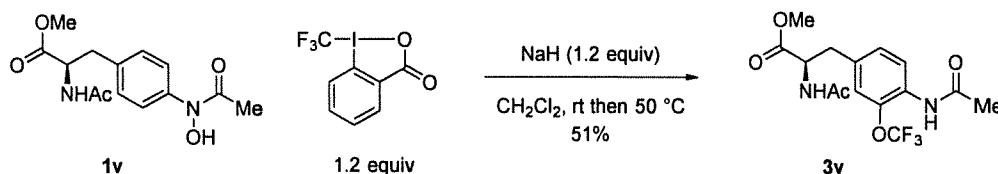
Scheme 4. Selected examples of one-pot synthesis of *ortho*-trifluoromethoxylated aniline derivatives. Cited yields are for
 20 isolated material following chromatography.



[a] Following the trifluoromethylation, the reaction mixture was heated to 50 °C. [b] Following the trifluoromethylation, the reaction
 25 mixture was concentrated, the residue was dissolved in $MeNO_2$, and the resulting mixture was heated. [c] 80 °C. [d] 120 °C. [e] NMR yield.

***N*-(4-Methyl-2-(trifluoromethoxy)phenyl)acetamide (3u)**

Under N_2 atmosphere, to a mixture of *N*-hydroxy-*N*-(*p*-tolyl)acetamide (1u) (78.2 mg, 0.473 mmol, 1.00 equiv) and NaH (13.6 mg, 0.568 mmol, 1.20 equiv) in CH_2Cl_2 (4.73 mL, 0.100 M) was added Togni reagent II (179 mg, 0.568 mmol, 1.2 equiv) and the reaction mixture was stirred at rt for 23 h. The reaction mixture diluted with CH_2Cl_2 (30 mL) and washed with water (30 mL). The layers were separated, the organic layer was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by preparative TLC using hexanes:EtOAc (4:1 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as a white solid (76.8 mg, 0.329 mmol, 70% yield). $R_f = 0.42$ (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.21 (d, $J = 8.2$ Hz, 1H), 7.31 (br. s, 1H), 7.08 (d, $J = 8.2$ Hz, 1H), 7.05 (br. s, 1H), 2.33 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 168.3, 138.2, 134.7, 128.2, 128.0, 122.2, 120.9, 120.7 (q, $J = 257.4$ Hz), 24.8, 21.0. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_{11}\text{NO}_2\text{F}_3$ ($[\text{M} + \text{H}]^+$), 234.0742, found, 234.0737.

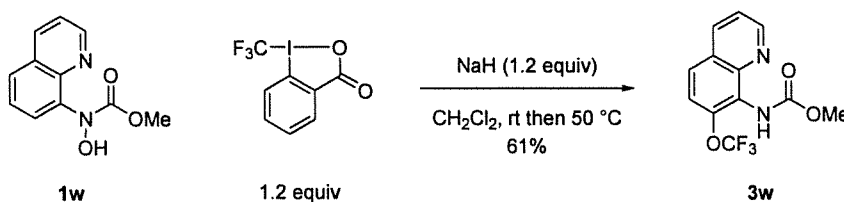
Methyl (R)-2-acetamido-3-(4-(*N*-hydroxyacetamido)phenyl)propanoate (3v)

Under N_2 atmosphere, to a mixture of methyl (*R*)-2-acetamido-3-(4-(*N*-hydroxyacetamido)phenyl)propanoate (1v) (100 mg, 0.340 mmol, 1.00 equiv) and NaH (9.80 mg, 0.410 mmol, 1.20 equiv) in CH_2Cl_2 (3.40 mL, 0.100 M) was added Togni reagent II (128.8 mg, 0.410 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 13 h. The reaction mixture was then heated to 50 °C for 24 h. The reaction was quenched with water, extracted with CH_2Cl_2 , dried (MgSO_4), filtered

and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 to 1:3 (v/v)), and then recrystallized from hexanes/CH₂Cl₂ to afford the title compound as a slightly yellow solid (63.0 mg, 0.174 mmol, 51% yield). *R_f* = 0.12 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.31 (d, *J* = 8.4 Hz, 1H), 7.37 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.98 (s, 1H), 5.96 (d, *J* = 7.0 Hz, 1H), 4.86 (dd, *J* = 5.6, 12.8 Hz, 1H), 3.73 (s, 3H), 3.15 (dd, *J* = 5.6, 14.0 Hz, 1H), 3.08 (dd, *J* = 5.6, 14.0 Hz, 1H), 2.22 (s, 3H), 2.00 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 171.8, 169.8, 168.4, 138.0, 132.5, 129.6, 128.6, 122.1, 121.2, 120.7 (q, *J* = 147.4 Hz), 53.2, 52.6 (d, *J* = 14.0 Hz), 37.3, 25.0, 23.3. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₅H₁₈N₂O₅F₃ ([M + H]⁺), 363.1168, found, 363.1164.

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Methyl hydroxy(7-(trifluoromethoxy)quinolin-8-yl)carbamate (3w)



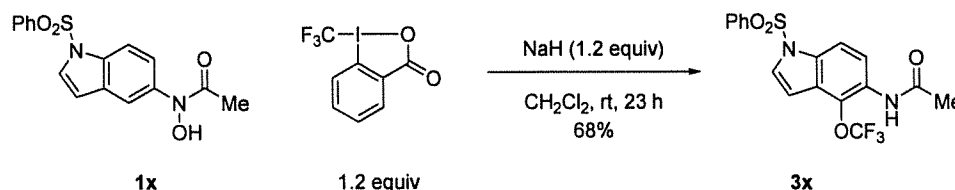
Under N₂ atmosphere, to a mixture of methyl hydroxy(quinolin-8-yl)carbamate (**1w**) (100 mg, 0.458 mmol, 1.00 equiv) and NaH (13.2 mg, 0.550 mmol, 1.20 equiv) in CH₂Cl₂ (4.58 mL, 0.100 M) was added Togni reagent II (173.6 mg, 0.550 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 13 h. The reaction was then heated to 50 °C for 24 h. The reaction was quenched with water, extracted with CH₂Cl₂, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 3:1 (v/v)), to afford the title compound as a brown solid (81.0 mg, 0.283 mmol, 61% yield). *R_f* = 0.21 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.92 (dd, *J* = 1.4, 4.1 Hz, 1H), 8.18 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.83 (s, 1H), 7.69 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 9.1 Hz, 1H), 7.48 (dd, *J* = 4.2, 8.3 Hz, 1H), 3.83 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, δ): 154.6, 150.6, 143.0, 142.1, 136.3, 126.9, 126.8, 125.4, 122.1, 121.4, 120.9 (q, *J* = 257.4 Hz), 53.2. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.8

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(s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}N_2O_3F_3$ ($[M + H]^+$), 287.0644, found, 287.0639.

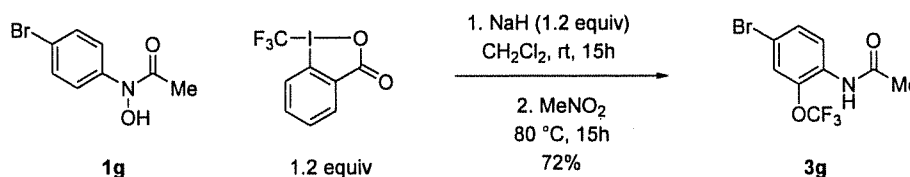
***N*-(1-(phenylsulfonyl)-4-(trifluoromethoxy)-1*H*-indol-5-yl)acetamide**

5 (3x)



Under N_2 atmosphere, to a mixture *N*-hydroxy-*N*-(1-(phenylsulfonyl)-1*H*-indol-5-yl)acetamide (**1x**) (132 mg, 0.400 mmol, 1.00 equiv) and NaH (11.5 mg, 0.480 mmol, 1.20 equiv) in CH_2Cl_2 (4.00 mL, 0.100 M) was
 10 added Togni reagent II (152 mg, 0.480 mmol, 1.2 equiv) and the reaction mixture was stirred at rt for 23 h. The reaction mixture diluted with CH_2Cl_2 (30 mL) and washed with water (30 mL). The layers were separated, the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by preparative TLC
 15 using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as an off-white solid (108 mg, 0.271 mmol, 68% yield). R_f = 0.24 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: 1H NMR (700 MHz, $CDCl_3$, 25 $^\circ C$, δ): 8.13 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.63–7.54 (m, 2H), 7.52–7.43 (m, 2H), 7.33 (br. s, 1H), 6.70 (br. s, 1H), 2.22 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 $^\circ C$, δ): 168.6, 138.0, 134.4, 132.8, 131.2, 129.7, 127.9, 127.1, 127.0, 125.2, 121.2 (q, J = 258.8 Hz), 120.4, 113.2, 105.7, 24.6. ^{19}F NMR (376 MHz, $CDCl_3$, 25 $^\circ C$, δ): -57.9 (s). Mass Spectrometry: HRMS (ESI-
 20 TOF) (m/z): calcd for $C_{17}H_{14}N_2O_4SF_3$ ($[M + H]^+$), 399.0626, found, 399.0625.

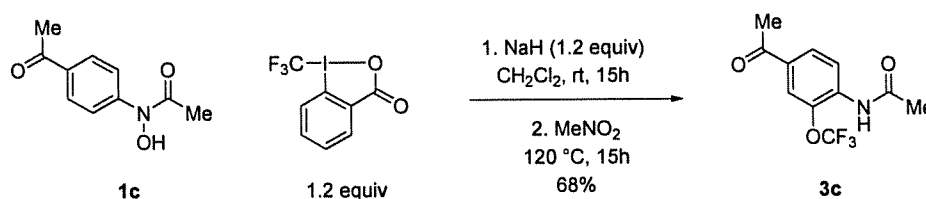
***N*-(4-bromo-2-(trifluoromethoxy)phenyl)acetamide (3g)**



30 Under N_2 atmosphere, to a mixture of *N*-(4-bromophenyl)-*N*-hydroxyacetamide (**1g**) (11.5 mg, 0.0502 mmol, 1.00 equiv) and NaH

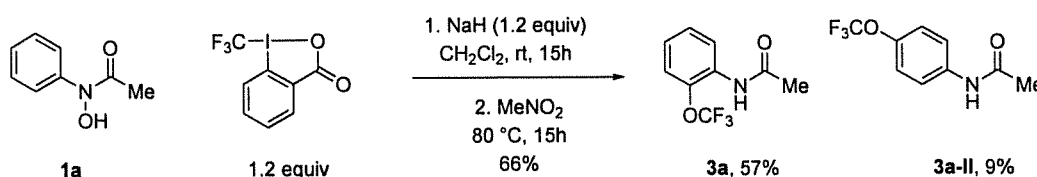
(1.4 mg, 0.060 mmol, 1.2 equiv) in CH₂Cl₂ (0.500 mL, 0.100 M) was added Togni reagent II (19.0 mg, 0.0600 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 15 h and was then concentrated *in vacuo*. MeNO₂ (0.500 mL) was added and the reaction mixture was stirred at 80 °C for 15h. Trifluorotoluene (6.14 μL, 0.050 mmol, 1.00 equiv) and CDCl₃ (0.250 mL) were added and the reaction mixture was analyzed by ¹⁹F NMR. The ¹⁹F NMR analysis indicated 72% yield of the desired product.

10 ***N*-(4-acetyl-2-(trifluoromethoxy)phenyl)acetamide (3c)**



Under N₂ atmosphere, to a mixture of *N*-(4-acetylphenyl)-*N*-hydroxyacetamide (**1c**) (9.7 mg, 0.050 mmol, 1.0 equiv) and NaH (1.4 mg, 0.060 mmol, 1.2 equiv) in CH₂Cl₂ (0.500 mL, 0.100 M) was added Togni reagent II (19.0 mg, 0.0600 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 15 h and was then concentrated *in vacuo*. MeNO₂ (0.500 mL) was added and the reaction mixture was stirred at 120 °C for 15h. Trifluorotoluene (6.14 μL, 0.050 mmol, 1.00 equiv) and CDCl₃ (0.250 mL) were added and the reaction mixture was analyzed by ¹⁹F NMR. The ¹⁹F NMR analysis indicated 68% yield of the desired product.

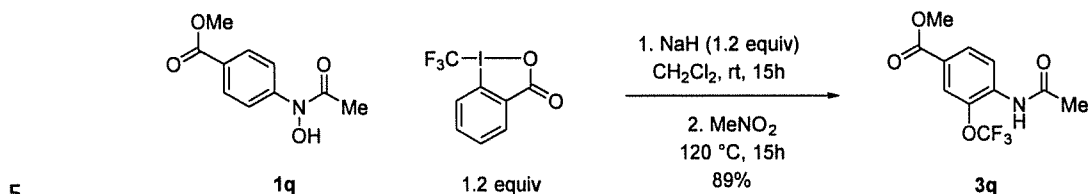
***N*-(2-(Trifluoromethoxy)phenyl)acetamide (3a) and *N*-(4-(trifluoromethoxy)phenyl)acetamide (3a-II)**



Under N₂ atmosphere, to a mixture of *N*-hydroxy-*N*-phenylacetamide (**1a**) (7.6 mg, 0.050 mmol, 1.0 equiv) and NaH (1.4 mg, 0.060 mmol, 1.2 equiv) in CH₂Cl₂ (0.500 mL, 0.100 M) was added Togni reagent II (19.0 mg, 0.0600 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 15 h and was then concentrated *in vacuo*. MeNO₂ (0.500 mL) was added and the reaction mixture was stirred at 80 °C for 15h. Trifluorotoluene (6.14 μL, 0.050 mmol, 1.00 equiv) and CDCl₃ (0.250

mL) were added and the reaction mixture was analyzed by ^{19}F NMR. The ^{19}F NMR analysis indicated 66% yield of the desired product.

Methyl 4-acetamido-3-(trifluoromethoxy)benzoate (3q)



Under N_2 atmosphere, to a mixture of methyl 4-(*N*-hydroxyacetamido)benzoate (**1q**) (10.5 mg, 0.0500 mmol, 1.00 equiv) and NaH (1.4 mg, 0.060 mmol, 1.2 equiv) in CH_2Cl_2 (0.500 mL, 0.100 M) was added Togni reagent II (19.0 mg, 0.0600 mmol, 1.2 equiv). The resulting mixture was stirred at rt for 15h and was then concentrated *in vacuo*. MeNO_2 (0.500 mL) was added and the reaction mixture was stirred at 120 °C for 15h. Trifluorotoluene (6.14 μL , 0.050 mmol, 1.00 equiv) and CDCl_3 (0.250 mL) were added and the reaction mixture was analyzed by ^{19}F NMR. The ^{19}F NMR analysis indicated 89% yield of the desired product.

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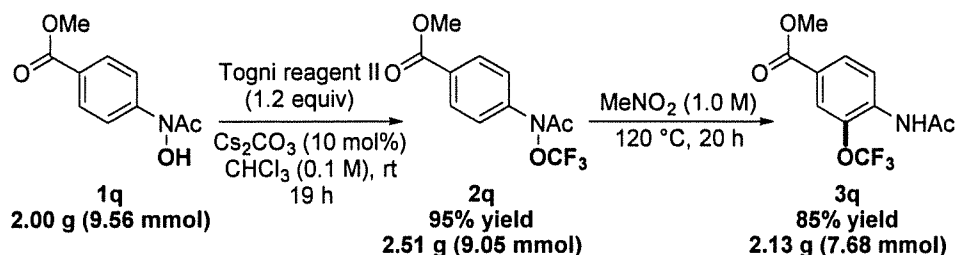
Example 5. Gram Scale Synthesis

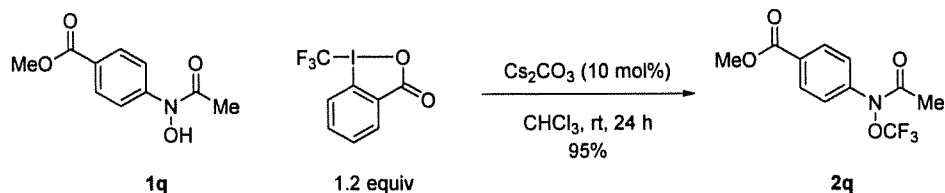
To demonstrate the practicality and effectiveness of the approach for the synthesis of *o*- OCF_3 aniline derivatives, the trifluoromethoxylation reaction of **1q** and OCF_3 -migration of **2q** on a gram scale was performed (Scheme 5). Reaction of 2.00 g (9.56 mmol) of **1q** with 1.2 equiv Togni reagent II in the presence of 10 mol % Cs_2CO_3 in degassed chloroform gave **2q** (2.51 g) in 95% isolated yield. Heating 2.51 g (9.49 mmol) of **2q** in MeNO_2 at 120 °C afforded **3q** (2.13 g) in 85% isolated yield.

20

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Scheme 5. Gram scale synthesis.



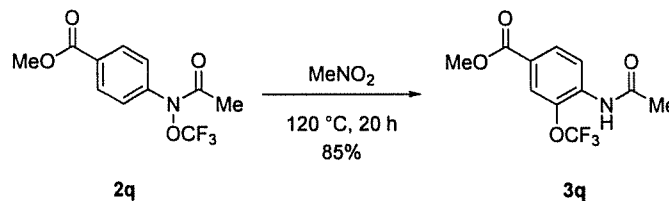
Methyl 4-(*N*-(trifluoromethoxy)acetamido)benzoate (2q)

Under N₂ atmosphere, to a mixture of methyl 4-(*N*-hydroxyacetamido)benzoate (**1q**) (2.00 g, 9.56 mmol, 1.00 equiv) and

5 Cs₂CO₃ (311 mg, 0.956 mmol, 10 mol%) in CHCl₃ (95.6 mL, 0.100 M) was added Togni reagent II (3.63 g, 11.5 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 24 h. The reaction mixture was then washed with sat. aq. NaHCO₃ (100 mL) and the layers were separated. The organic layer was dried (MgSO₄), filtered, and

10 concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (7:3 to 0:1 (v/v)). The purification afforded the title compound (2.51 g, 9.05 mmol, 95% yield), which was spectroscopically identical to the compound prepared according to the standard procedure (*vide supra*).

15

Methyl 4-acetamido-3-(trifluoromethoxy)benzoate (3q)

A solution of methyl 4-(*N*-(trifluoromethoxy)acetamido)benzoate (**2q**) (2.51 g, 9.05 mmol) in MeNO₂ (9.05 mL, 1.00 M) was heated at 120 °C

20 under N₂ atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (9:1 to 7:3 (v/v)), to afford the title compound (2.13 g, 7.68 mmol, 85% yield), which was spectroscopically identical to the compound prepared according to the standard procedure

25 (*vide supra*).

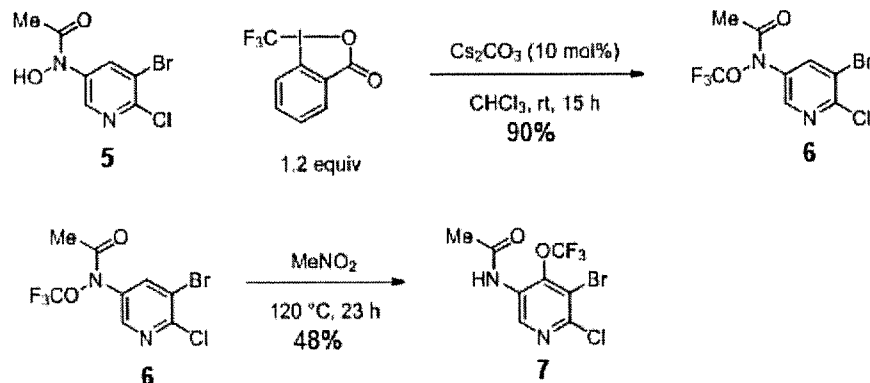
Example 6. Trifluoromethoxylation of Heteroaryl Substrates

The effectiveness of this approach was also explored using heteroaryl substrates. For the synthesis of *o*-OCF₃ pyridino derivatives, the

30 trifluoromethoxylation reaction of **5** and OCF₃-migration of **6** on a gram was performed (Scheme 6). Reaction of **5** with 1.2 equiv Togni

reagent II in the presence of 10 mol % Cs₂CO₃ in degassed chloroform gave **6** in 90% isolated yield. Heating of **6** in MeNO₂ at 120 °C for 23 hours afforded **7** (2.13 g) in 85% isolated yield.

5 **Scheme 6.** Synthesis of trifluoromethoxy pyridine derivative.



N-(5-Bromo-6-chloropyridin-3-yl)-N-(trifluoromethoxy)acetamide (6):

Under N₂ atmosphere, to a mixture of *N*-(5-bromo-6-chloropyridin-3-yl)-*N*-hydroxyacetamide (**5**) (221 mg, 0.832 mmol, 1.00 equiv) and Cs₂CO₃ (27.1 mg, 0.0832 mmol, 10 mol%) in CHCl₃ (8.32 mL, 0.100 M) was added Togni reagent II (316 mg, 0.998 mmol, 1.20 equiv) and the reaction mixture was stirred at rt for 15 h. The reaction mixture was diluted with CH₂Cl₂, washed with sat. aq. NaHCO₃ (30 mL) and the layers were separated. The organic layer was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:CH₂Cl₂ (1:3 to 1:4 (v/v)), to afford 250 mg of the title compound as a slightly yellow oil (90% yield). *R*_f = 0.55 (CH₂Cl₂:hexanes 1:1). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.41 (d, *J* = 0.85 Hz, 1H), 7.99 (d, *J* = 0.85 Hz, 1H), 2.38 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 172.8, 149.9, 143.0, 137.2, 136.1, 122.7 (q, *J* = 265.2 Hz), 120.1, 21.5. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -65.1 (s).

N-(5-bromo-6-chloro-2-(trifluoromethoxy)pyridin-3-yl)acetamide (7):

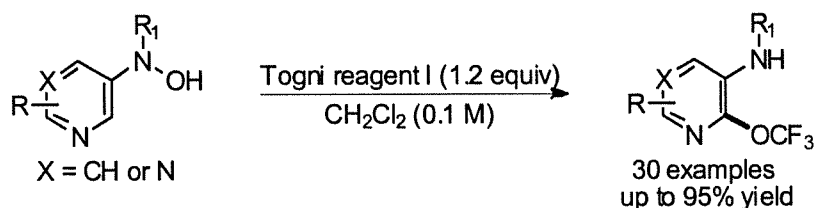
A solution of *N*-(5-bromo-6-chloro-2-(trifluoromethoxy)pyridin-3-yl)acetamide (**6**) (102 mg, 0.306 mmol) in MeNO₂ (0.306 mL, 1.00 M) was heated at 120 °C under N₂ atmosphere for 23 h. The reaction mixture was purified by preparative TLC using hexanes:EtOAc (93:7 (v/v)) for development. The purification afforded 49 mg of the title compound

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as a white solid (48% yield). $R_f = 0.49$ (hexanes/EtOAc 4:1 (v/v)).
 NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.12 (s, 1H),
 7.30 (br. s, 1H), 2.27 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ):
 168.7, 142.4, 140.4, 134.8, 123.7, 119.9 (q, $J = 263.4$ Hz), 117.4,
 5 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.7 (s).

Example 7. Trifluoromethoxylation of Pyridine Substrates

Herein is disclosed the first efficient and scalable one-pot protocol
 for regioselective synthesis of a broad spectrum of
 10 trifluoromethoxylated pyridines and pyrimidines using commercially
 available, bench-stable Togni reagent I.



Methyl (5-bromo-6-methoxypyridin-3-yl)(hydroxyl)carbamate (**8a**) as
 used as the model substrate. This compound could be readily prepared
 15 from the corresponding nitropyridine through a one-pot
 reduction/protection procedure. Exposure of **8a** to Togni reagent II
 in the presence of cesium carbonate (0.1 equiv) in chloroform at room
 temperature for 15 hours afforded the desired product **9a** in only 29%
 yield.²⁸ Examination of different trifluoromethylation reagents such
 20 as Togni reagent I, Umemoto reagent, and Shibata-Johnson reagent²³
 revealed that Togni reagent I was superior to other reagents and
 delivered the desired product **9a** in 42% yield. Higher yield was
 obtained in the absence of Cs_2CO_3 . Screening of solvents showed that
 CH_2Cl_2 gave the best result, providing the desired product **9a** in 87%
 25 NMR yield.

With the optimized reaction conditions in hand, the scope and
 generality of the trifluoromethoxylation reaction was explored. A
 wide range of functional groups and substitution patterns were
 30 tolerated (Scheme 7). Halogen functionalities, in particular Br and
 I, remain intact after the reaction, providing useful synthetic
 handles for further elaborations (**9a-h**, **9k**, **9r**, **9s**, **9u**, **9v**). Other
 functional groups such as alkyl- and aryl-ethers (**9i**, **9k-m**, **9v-x**),

aldehydes (**9m**), ketone (**9x**), alkene (**9v**), alkyne (**9w**), amide (**9y**), esters (**9v-w**), and benzo[1,3]dioxole (**9y**) proved compatible under the reaction conditions. In addition, this methodology was successfully applied to pyridines bearing a wide array of heteroaryl substituents
5 such as furan (**9m**), pyrazole (**9n**), 1,2,4-triazole (**9o**), benzimidazole (**9p**), benzotriazole (**9q**, **9t**), indole (**9r**, **9y**), 7-azaindole (**9s**), thiazole (**9t**), and 2,6-dichloropurine (**9u**). More excitingly, our mild reaction conditions allow late-stage trifluoromethoxylation of complex organic molecules. For examples, estrone and Tadalafil
10 conjugated pyridines (**8x**, **8y**) were trifluoromethoxylated to afford the desired product **9x** and **9y** in 71% and 66% yield, respectively. Remarkably, no epimerization was observed under these mild reaction conditions. These results further demonstrated the synthetic utility of our strategy.

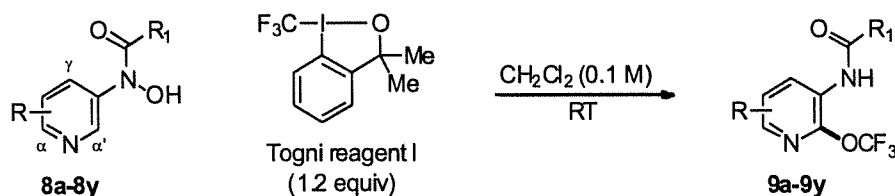
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Several features of the reaction are noteworthy. First of all, the reaction is sensitive to the electronic properties of substituents on pyridine. Substrates with an electron donating substituent *para* to the protected *N*-hydroxylamine readily undergo rearrangement to
20 yield the desired trifluoromethoxylated products at or below room temperature (**9a-b**, **9i**, **9k-n**, **9p**, **9r-s**, **9v-y**). In the absence of such substituents, higher reaction temperatures are required for the OCF₃-migration step (**9c-h**, **9o**, **9q**, **9t-u**). These observations are consistent with the formation of nitrenium ion through heterolytic cleavage of
25 N-O bond (*vide infra*).²⁴ Secondly, for the reactions that take place at or below room temperature, the OCF₃ group is introduced exclusively to the α' -position.²⁵ Since α - and α' -carbon of pyridines are metabolically labile sites, incorporation of an electron withdrawing OCF₃ group to the α' -position could improve the metabolic stability of
30 the molecule.²⁶ If the α' -position is blocked, product of γ -OCF₃ pyridine is formed instead (**9g** and **9h**). Interestingly, atropisomers are obtained in these cases. This is because the plane containing the OCF₃ group is orthogonal to the pyridine plane, which prevents the free rotation of amide group (see Supporting Information).^{1b, 3a-3d}
35 Thirdly, the regioselectivity erodes as the reaction temperature increases (**9d-f**, **9o**, **9u**). Finally, substrates with the protected *N*-hydroxylamino-group at α -, γ -, or α' -position do not give the product

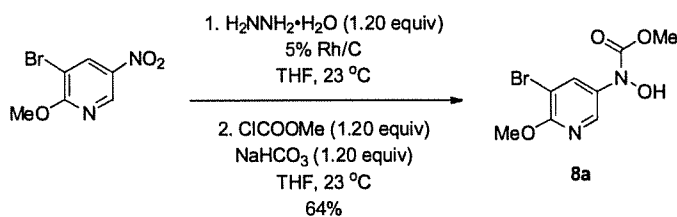
of trifluoromethoxylation. Presumably, the formation of nitrenium ion is energetically disfavored in these cases, because it involves placing the positive charge on the endocyclic nitrogen atom.²⁷ Products **9a-9y** are shown in Figure 2.

5

Scheme 7.



Methyl (5-bromo-6-methoxypyridin-3-yl) (hydroxy) carbamate (8a)

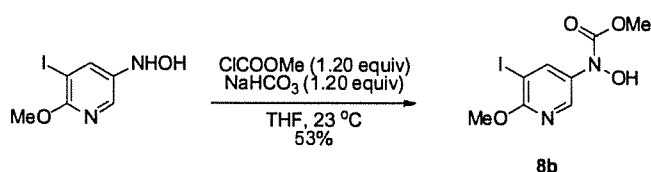


- 10 Under N₂ atmosphere, to a suspension of 3-bromo-2-methoxy-5-nitropyridine (5.00 g, 21.5 mmol, 1.00 equiv) and 5% Rh/C (0.123 g, 0.30 mol% Rh) in THF (107 mL, 0.200 M) hydrazine monohydrate (1.56 g, 25.8 mmol, 1.20 equiv) was added dropwise. The reaction mixture was monitored *via* TLC using EtOAc:hexanes 1:1 (v/v) as an eluent
- 15 until the disappearance of the starting 3-bromo-2-methoxy-5-nitropyridine ($R_f = 0.90$ (EtOAc:hexanes 1:1 (v/v))) and the appearance of the hydroxylamine intermediate ($R_f = 0.61$ (EtOAc:hexanes 1:1 (v/v))). Subsequently, sodium bicarbonate (2.14 g, 25.8 mmol, 1.20 equiv) was added to the reaction mixture followed by a solution of
- 20 methyl chloroformate (2.42 g, 25.75 mmol, 1.20 equiv) in THF (6.58 mL, 0.200 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated in vacuo. The residue was
- 25 purified by chromatography on silica gel, eluting with EtOAc:hexanes (3:7 to 1:1 (v/v)), to afford the title compound as a slightly light yellow solid (3.82 g, 13.8 mmol, 64% yield).

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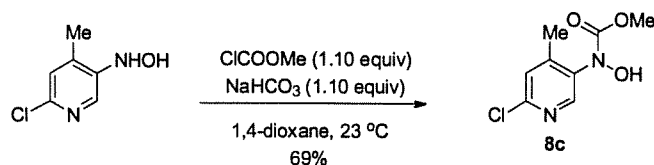
$R_f = 0.54$ (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.60 (s, 1H) 8.29 (d, $J = 2.44$ Hz, 1H) 8.13 (d, $J = 2.44$ Hz, 1H) 3.93 (s, 3H) 3.74 (s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 156.97, 155.40, 138.89, 135.74, 134.47, 105.44, 55.01, 53.67. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_{10}\text{BrN}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 276.9818, found, 276.9821.

Methyl hydroxy(5-iodo-6-methoxypyridin-3-yl)carbamate (8b)

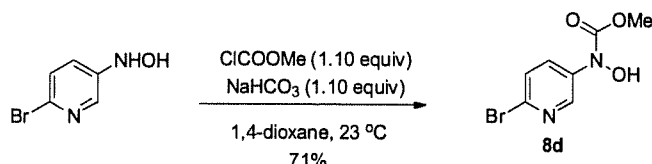


Under N_2 atmosphere, to a suspension of 3-iodo-2-methoxy-5-nitropyridine (0.500 g, 1.79 mmol, 1.00 equiv) and 5% Rh/C (10.3 mg, 0.30 mol% Rh) in THF (8.93 mL, 0.200 M) hydrazine monohydrate (0.130 g, 2.14 mmol, 1.20 equiv) was added dropwise. After the reaction mixture was stirred at 23 °C for 1 h, it was filtered through a short pad of celite and concentrated *in vacuo* to afford the title compound as a slightly brown solid (0.467 g, 1.76 mmol, 98% yield). The product was used directly without further purification. Under N_2 atmosphere, to a stirred suspension of *N*-(5-iodo-6-methoxypyridin-3-yl)hydroxylamine (0.350 g, 1.32 mmol, 1.00 equiv) and NaHCO_3 (0.131 g, 1.58 mmol, 1.20 equiv) in THF (6.58 mL, 0.200 M) at 23 °C was slowly added a solution of methyl chloroformate (0.148 g, 1.58 mmol, 1.20 equiv) in THF (6.58 mL, 0.200 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (1:1 to 1:0 (v/v)), to afford the title compound as a slightly light brown solid (0.229 g, 0.710 mmol, 54% yield). $R_f = 0.63$ (EtOAc:hexanes 1:0 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.54 (br. s, 1H) 8.26 (br. s, 2H) 3.89 (br. s, 3H) 3.73 (br. s, 3H). ^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 158.8, 154.9, 141.5, 139.4, 134.0, 79.1, 54.8, 53.1. HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_{10}\text{IN}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 324.9680, found, 324.9682.

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Methyl (6-chloro-4-methylpyridin-3-yl) (hydroxy) carbamate (8c)

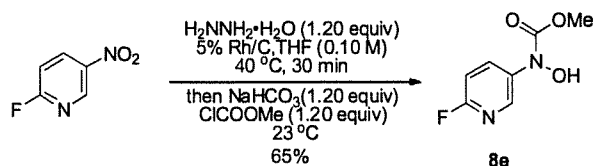
Under N₂ atmosphere, hydrazine monohydrate (1.04 g, 20.9 mmol, 1.20 equiv) was added dropwise to a suspension of 2-chloro-4-methyl-5-nitropyridine (3.00 g, 17.4 mmol, 1.00 equiv) and 5% Rh/C (0.300 g, 0.838 mol% Rh) in THF (85.0 mL, 0.204 M) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h and filtered through a short pad of celite. The celite was washed with EtOAc. The organic solutions were combined and concentrated *in vacuo* to afford the title compound as a white solid (2.70 g, 17.1 mmol, 98% yield). The product was used directly without further purification. Under N₂ atmosphere, a solution of methyl chloroformate (0.623 g, 6.59 mmol, 1.10 equiv) in 1,4-dioxane (10.0 mL, 0.660 M) was slowly added to a stirred suspension of *N*-(6-chloro-4-methylpyridin-3-yl)hydroxylamine (0.950 g, 5.99 mmol, 1.00 equiv) and NaHCO₃ (0.554 g, 6.59 mmol, 1.10 equiv) in 1,4-dioxane (40.0 mL, 0.150 M) at 23 °C. After the reaction was complete (4 h), the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a red solid (0.890 g, 4.11 mmol, 69% yield). *R_f* = 0.27 (hexanes/EtOAc 3:2 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.53 (s, 1H), 8.29 (s, 1H), 7.52 (s, 1H), 3.68 (s, 3H), 2.23 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 155.6, 148.8, 148.4, 147.9, 137.7, 125.6, 53.2, 16.8. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₈H₁₀ClN₂O₃ ([M + H]⁺), 217.0374, found, 217.0373.

Methyl (6-bromopyridin-3-yl) (hydroxy) carbamate (8d)

Under N₂ atmosphere, hydrazine monohydrate (0.888 g, 17.7 mmol, 1.20 equiv) was added dropwise to a suspension of 2-bromo-5-nitropyridine (3.00 g, 14.8 mmol, 1.00 equiv) and 5% Rh/C (0.290 g, 0.952 mol% Rh)

in THF (75.0 mL, 0.197 M) at 23 °C. After the reaction was complete (2.5 h), the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic solutions were combined and concentrated *in vacuo* to afford the title compound as a yellow solid (2.70 g, 14.3 mmol, 97% yield). The product was used directly without further purification. Under N₂ atmosphere, a solution of methyl chloroformate (0.520 g, 5.50 mmol, 1.10 equiv) in 1,4-dioxane (10.0 mL, 0.550 M) was added dropwise to a stirred suspension of *N*-(6-bromopyridin-3-yl)hydroxylamine (0.940 g, 5.00 mmol, 1.00 equiv) and NaHCO₃ (0.462 g, 5.50 mmol, 1.10 equiv) in 1,4-dioxane (40.0 mL, 0.125 M) at 23 °C. After the reaction was complete (3 h), the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The combined organic layers were concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a yellow solid (0.870 g, 3.52 mmol, 71% yield). *R*_f = 0.27 (hexanes/EtOAc 3:2 (v/v)). ¹H NMR (500 MHz, (CD₃)₂SO, 25 °C, δ): 10.74 (s, 1H), 8.58 (d, *J* = 2.7 Hz, 1H), 7.89 (dd, *J* = 2.7, 3.8 Hz, 1H), 7.64 (d, *J* = 3.8 Hz, 1H), 3.78 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, 25 °C, δ): 154.4, 140.9, 138.8, 134.9, 129.6, 127.5, 53.4. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₇H₈BrN₂O₃ ([M + H]⁺), 246.9713, found, 246.9712.

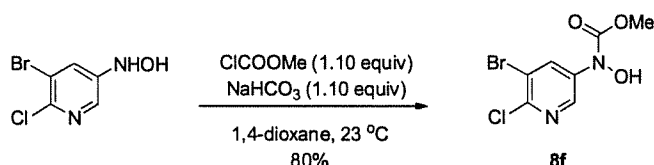
Methyl (6-fluoropyridin-3-yl) (hydroxy) carbamate (8e)



Under N₂ atmosphere, a suspension of 2-fluoro-5-nitropyridine (1.00 g, 7.04 mmol, 1.00 equiv) and 5% Rh/C (80.8 mg, 0.60 mol% Rh) in THF (35.2 mL, 0.200 M) was heated to 40 °C. Hydrazine monohydrate (0.422 g, 8.44 mmol, 1.20 equiv) was added all at once. The reaction mixture was stirred at 40 °C for 30 min and then cooled down to 23 °C. NaHCO₃ (0.708 g, 8.44 mmol, 1.2 equiv) was added, followed by dropwise addition of methyl chloroformate (0.800 g, 8.44 mmol, 1.20 equiv) in THF (35.2 mL, 0.240 M) at 23 °C. After the reaction was complete (1 h), the reaction mixture was filtered through a short pad of celite,

washed with EtOAc, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 2:1 (v/v)), to afford the title compound as a red solid (0.850 g, 4.57 mmol, 65% yield). $R_f = 0.22$ (hexanes:EtOAc 2:1 (v/v)). $^1\text{H NMR}$ (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.67 (s, 1H) 8.36 (d, $J = 1.29$ Hz, 1H) 8.09–8.06 (m, 1H) 7.21 (dd, $J = 8.82, 3.23$ Hz, 1H) 3.76 (s, 3H). $^{13}\text{C NMR}$ (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 159.3 (d, $J = 232.8$ Hz), 154.8, 138.8 (d, $J = 15.8$ Hz), 137.3 (d, $J = 5.25$ Hz), 133.8 (d, $J = 8.75$ Hz), 109.2 (d, $J = 40.3$ Hz), 53.3. $^{19}\text{F NMR}$ (376 MHz, CDCl_3 , 25 °C, δ): -74.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_7\text{H}_8\text{FN}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 187.0513, found, 187.0513.

Methyl (5-bromo-6-chloropyridin-3-yl) (hydroxy) carbamate (8f)

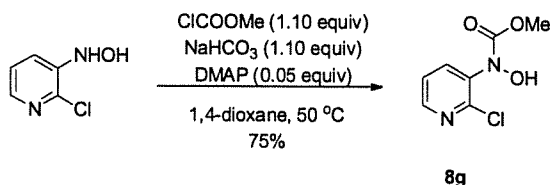


Under N_2 atmosphere, hydrazine monohydrate (0.506 g, 10.1 mmol, 1.20 equiv) was added dropwise to a suspension of 3-bromo-2-chloro-5-nitropyridine (2.00 g, 8.42 mmol, 1.00 equiv) and Pt/C (0.200 g, 0.609 mol% Pt) in THF (75.0 mL, 0.112 M) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h, filtered through a short pad of celite, washed with EtOAc, and concentrated *in vacuo*. The residue was dissolved in ether and filtered off. The filtrate was kept at -20 °C overnight and filtered again to remove the solid. The filtrate was concentrated *in vacuo* to afford the title compound as a yellow solid (1.22 g, 5.46 mmol, 65% yield). The product was used directly without further purification. Under N_2 atmosphere, a solution of methyl chloroformate (0.256 g, 2.71 mmol, 1.10 equiv) in 1,4-dioxane (10.0 mL, 0.271 M) was added dropwise to a stirred suspension of *N*-(5-bromo-6-chloropyridin-3-yl)hydroxylamine (0.550 g, 2.46 mmol, 1.00 equiv) and NaHCO_3 (0.227 g, 2.71 mmol, 1.10 equiv) in 1,4-dioxane (15.0 mL, 0.164 M) at 23 °C. The reaction mixture was stirred for 6 h and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 3:2 (v/v)), to afford the title compound as a yellow solid (0.55 g, 1.95 mmol, 80% yield). $R_f = 0.42$ (hexanes/EtOAc 3:2 (v/v)). $^1\text{H NMR}$ (500

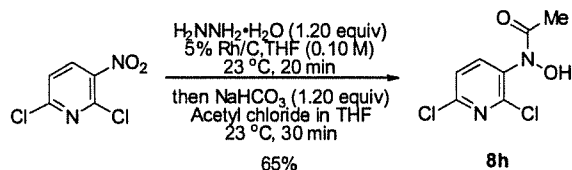
128

MHz, (CD₃)₂SO, 25 °C, δ): 10.89 (s, 1H), 8.63 (d, *J* = 2.3 Hz, 1H), 8.33 (d, *J* = 2.3 Hz, 1H), 3.80 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, 25 °C, δ): 154.3, 143.0, 138.9, 138.4, 131.7, 118.5, 53.6. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₇H₇BrClN₂O₃ ([M + H]⁺), 282.9301, found, 282.9302.

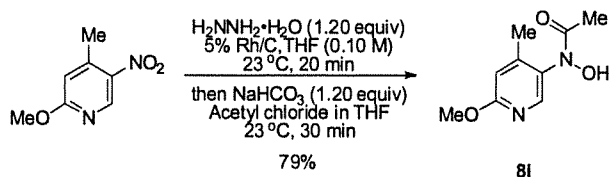
Methyl (2-chloropyridin-3-yl) (hydroxy) carbamate (8g)



Under N₂ atmosphere, hydrazine monohydrate (1.89 g, 37.8 mmol, 1.20 equiv) was added dropwise to a suspension of 2-chloro-3-nitropyridine (5.00 g, 31.5 mmol, 1.00 equiv) and Rh/C (0.500 g, 0.771 mol% Rh) in THF (150 mL, 0.210 M) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h, filtered through a short pad of celite, washed with EtOAc, and concentrated *in vacuo* to afford of the title compound as a red solid (4.50 g, 31.1 mmol, 98% yield). The product was used directly without further purification. Under N₂ atmosphere, a solution of methyl chloroformate (0.140 g, 1.53 mmol, 1.10 equiv) in dioxane (7.00 mL, 0.220 M) was slowly added via a syringe pump (at a rate of 10.0 mL/h) to a stirred suspension of *N*-(2-chloropyridin-3-yl)hydroxylamine (0.200 g, 1.39 mmol, 1.00 equiv), NaHCO₃ (0.130 g, 1.53 mmol, 1.10 equiv) and DMAP (8.50 mg, 0.0700 mmol, 0.0500 equiv) in dioxane (7.00 mL, 0.200 M) at 50 °C. After the addition was complete, the reaction mixture was stirred at 50 °C for another 12 h and then filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 1:1 (v/v)), to afford the title compound as a yellow gum (0.210 g, 1.04 mmol, 75% yield). *R_f* = 0.19 (hexanes/EtOAc 5:1 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.63 (s, 1H), 8.39 (dd, *J* = 4.73, 1.72 Hz, 1H), 7.96 (dd, *J* = 7.74, 1.72 Hz, 1H), 7.52 (dd, *J* = 7.74, 4.73 Hz, 1H), 3.69 (s, 3 H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 155.3, 148.9, 148.1, 137.9, 136.6, 124.0, 53.2. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₇H₈ClN₂O₃ ([M + H]⁺), 203.0218, found, 203.0231.

***N*-(2,6-Dichloropyridin-3-yl)-*N*-hydroxyacetamide (8h)**

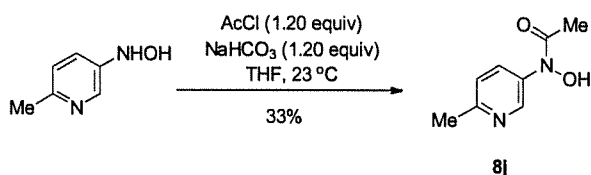
Under N₂ atmosphere, a suspension of 2-fluoro-5-nitropyridine (1.00 g, 7.04 mmol, 1.00 equiv) and 5% Rh/C (80.8 mg, 0.60 mol% Rh) in THF (35.2 mL, 0.200 M) was heated to 40 °C. Hydrazine monohydrate (0.422 g, 8.44 mmol, 1.20 equiv) was added all at once. The reaction mixture was stirred at 40 °C for 30 min and then cooled down to 23 °C. NaHCO₃ (0.708 g, 8.44 mmol, 1.2 equiv) was added, followed by dropwise addition of methyl chloroformate (0.800 g, 8.44 mmol, 1.20 equiv) in THF (35.2 mL, 0.240 M) at 23 °C. The reaction mixture was stirred at 23 °C for 1 h and then filtered through a short pad of celite, washed with EtOAc, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 2:1 (v/v)), to afford the title compound as a red solid (0.850 g, 4.57 mmol, 65% yield). R_f = 0.22 (hexanes:EtOAc 2:1 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.95 (br. s., 1H), 8.01 (d, *J* = 7.74 Hz, 1H), 7.67 (d, *J* = 8.17 Hz, 1H), 2.19 (br. s., 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 171.0, 147.5, 146.9, 140.9, 135.9, 124.6, 20.8. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₇H₇Cl₂N₂O₂ ([M + H]⁺), 220.9879, found, 220.9878.

***N*-Hydroxy-*N*-(6-methoxy-4-methylpyridin-3-yl)acetamide (8i)**

Under N₂ atmosphere, a suspension of 2-methoxy-4-methyl-5-nitropyridine (491 mg, 2.92 mmol, 1.00 equiv) and 5% Rh/C (33.6 mg, 0.60 mol% Rh) in dioxane (14.6 mL, 0.200 M) was stirred at 40 °C. Hydrazine monohydrate (146 mg, 3.50 mmol, 1.20 equiv) in dioxane (14.6 mL, 0.240 M) was added via a syringe pump (at a rate of 15.0 mL/h). The reaction mixture was stirred at 40 °C for 1 h and then cooled down to 23 °C. NaHCO₃ (290 mg, 3.50 mmol, 1.2 equiv) was added,

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followed by dropwise addition of acetyl chloride (270 mg, 3.50 mmol, 1.20 equiv) in THF (29.2 mL, 0.120 M) at 23 °C. The reaction mixture was stirred at 23 °C for 1 h and then filtered through a short pad of celite, washed with EtOAc, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (4:1 to 1:1 (v/v)), to afford the title compound as a brown solid (450 mg, 2.29 mmol, 79% yield). $R_f = 0.08$ (hexanes:EtOAc 4:1 (v/v)). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 90 °C, δ): 10.21 (br. s., 1H), 8.01 (s, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 2.18 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 170.9, 162.9, 148.1, 145.7, 132.4, 110.9, 53.4, 20.8, 17.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_{13}\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 197.0921, found, 197.0936.

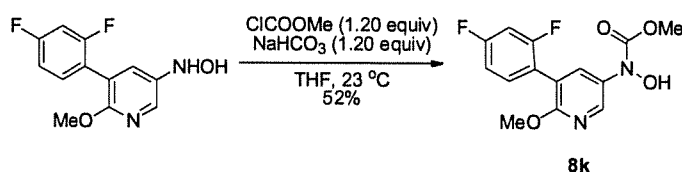
***N*-Hydroxy-*N*-(6-methylpyridin-3-yl)acetamide (8j)**

Under N_2 atmosphere, hydrazine monohydrate (0.870 g, 17.4 mmol, 1.20 equiv) was added dropwise to a suspension of 2-methyl-5-nitropyridine (2.00 g, 14.5 mmol, 1.00 equiv) and Rh/C (0.120 g, 0.402 mol% Rh) in THF (75.0 mL, 0.193 M) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h, filtered through a short pad of celite, washed with EtOAc, and concentrated *in vacuo* to afford the title compound as a yellow solid (1.63 g, 13.1 mmol, 91% yield). The product was used directly without further purification. Under N_2 atmosphere, a solution of acetyl chloride (0.300 g, 3.87 mmol, 1.20 equiv) in THF (16.00 mL, 0.240 M) was added dropwise to a stirred suspension of *N*-(6-methylpyridin-3-yl)hydroxylamine (**S6**) (0.400 g, 3.22 mmol, 1.00 equiv) and NaHCO_3 (0.330 g, 3.87 mmol, 1.20 equiv) in THF (16.00 mL, 0.200 M) at 23 °C. The reaction mixture was stirred at 23 °C for another 30 min and then filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with EtOAc to afford the title compound as a light yellow solid (0.176 g, 1.06 mmol, 33% yield). $R_f = 0.17$ (EtOAc). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.77 (br. s, 1H), 8.72 (br. s,

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1H), 7.87 (dd, $J = 8.17, 2.15$ Hz, 1H), 7.25 (d, $J = 8.60$ Hz, 1H), 2.43 (s, 3H), 2.21 (br. s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 170.4, 153.6, 140.5, 136.0, 127.4, 122.6, 23.4, 22.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}_2$ ($[\text{M} + \text{H}]^+$), 167.0815, found, 167.0816.

Methyl (5-(2,4-difluorophenyl)-6-methoxypyridin-3-yl) (hydroxy) carbamate (8k)



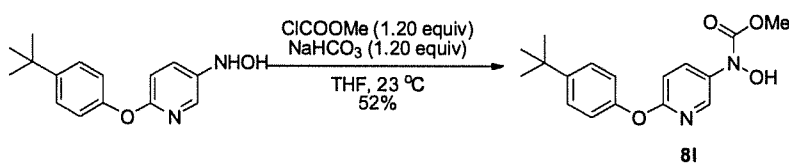
Under N_2 atmosphere, to a suspension of 3-(2,4-difluorophenyl)-2-methoxy-5-nitropyridine (0.300 g, 1.13 mmol, 1.00 equiv) and 5% Rh/C (6.5 mg, 0.30 mol% Rh) in THF (11.3 mL, 0.100 M) hydrazine monohydrate (0.083 g, 1.35 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 1 h and filtered through a short pad of celite. The pad of celite was washed with EtOAc. The combined organic solution was concentrated *in vacuo* to afford the title compound as a slightly light yellow solid (0.245 g, 0.973 mmol, 86% yield). The product was used directly without further purification.

Under N_2 atmosphere, to a stirred suspension of *N*-(5-(2,4-difluorophenyl)-6-methoxypyridin-3-yl)hydroxylamine (0.250 g, 0.99 mmol, 1.00 equiv) and NaHCO_3 (0.099 g, 6.46 mmol, 1.20 equiv) in THF (4.96 mL, 0.200 M) at 23 °C was slowly added a solution of methyl chloroformate (0.112 g, 1.19 mmol, 1.20 equiv) in THF (4.96 mL, 0.200 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (1:2 to 1:1 (v/v)), to afford the title compound as a slightly yellow solid (0.163 g, 0.52 mmol, 52% yield). $R_f = 0.31$ (EtOAc:hexanes 1:1 (v/v)). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.54 (s, 1H), 8.32 (s, 1H), 7.77 (s, 1H), 7.49 (q, $J = 8.03$ Hz, 1H), 7.35 (t, $J = 9.68$ Hz, 1H), 7.18 (t, $J = 8.17$ Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 162.2 (d, $J = 246.9$ Hz), 159.5 (d, $J = 247.5$ Hz),

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157.7, 155.1, 139.9, 133.7, 133.4, 132.9 (m), 119.9 (d, $J = 15.2$ Hz), 116.9, 111.7 (dd, $J = 22.8$ Hz, $J = 5.3$ Hz), 104.2 (t, $J = 26.3$ Hz), 53.81, 53.1. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): -111.2 (m), -112.1 (m). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{14}\text{H}_{13}\text{F}_2\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 311.0838, found, 311.0841.

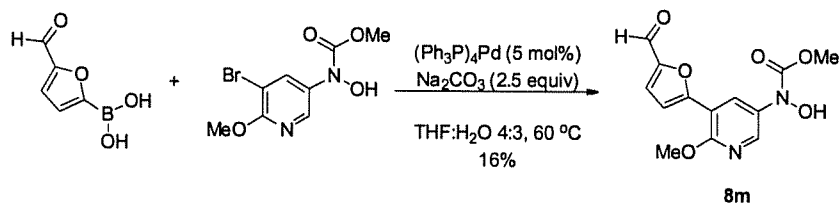
Methyl (6-(4-(*tert*-butyl)phenoxy)pyridin-3-yl) (hydroxy) carbamate (81)



Under N_2 atmosphere, to a suspension of 2-(4-(*tert*-butyl)phenoxy)-5-nitropyridine (0.600 g, 2.20 mmol, 1.00 equiv) and 5% Rh/C (12.7 mg, 0.30 mol% Rh) in THF (11.0 mL, 0.200 M) hydrazine monohydrate (0.160 g, 2.64 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 1 h and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated *in vacuo* to afford the title compound as an off-white solid (0.495 g, 1.92 mmol, 86% yield). The product was used directly without further purification. Under N_2 atmosphere, to a stirred suspension of *N*-(6-(4-(*tert*-butyl)phenoxy)pyridin-3-yl)hydroxylamine (0.491 g, 0.990 mmol, 1.00 equiv) and NaHCO_3 (0.099 g, 1.19 mmol, 1.20 equiv) in THF (4.96 mL, 0.100 M) at 23 °C was slowly added a solution of methyl chloroformate (0.112 g, 1.19 mmol, 1.20 equiv) in THF (4.96 mL, 0.100 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, the reaction mixture was filtered through a short pad of celite and the celite was washed with EtOAc. The organic layers were combined and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (1:2 to 1:1 (v/v)), to afford the title compound as a off-white solid (0.163 g, 0.52 mmol, 52% yield). $R_f = 0.48$ (EtOAc:hexanes 1:1 (v/v)). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.53 (s, 1H), 8.23 (d, $J = 2.58$ Hz, 1H), 7.91 (dd, $J = 9.03$, 2.58 Hz, 1H), 7.42 (d, $J = 8.60$ Hz, 2H), 7.08–6.97 (m, 3H), 3.72 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 160.0, 155.0, 151.7, 146.8, 140.2, 134.8, 133.4, 126.4, 120.5, 111.0, 53.1, 34.2,

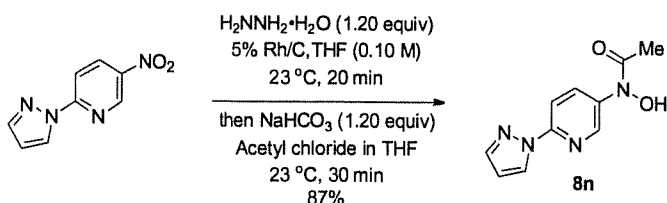
31.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₇H₂₁N₂O₄ ([M + H]⁺), 317.1496, found, 317.1497.

Methyl (5-(5-formylfuran-2-yl)-6-methoxypyridin-3-yl)(hydroxy) carbamate (8m)



Methyl (5-bromo-6-methoxypyridin-3-yl)(hydroxy)carbamate (0.400 g, 1.44 mmol, 1.00 equiv), (5-formylfuran-2-yl)boronic acid (0.283 g, 2.02 mmol, 1.40 equiv), Na₂CO₃ (0.383 g, 3.61 mmol, 2.5 equiv), THF:H₂O 4:3 (8.42 mL, 0.200 M), and palladium-tetrakis(triphenylphosphine) 10 (0.0830 g, 0.0700 mmol, 0.05 equiv) were degassed via three freeze-pump-thaw cycles. The resulting mixture was heated at 60 °C overnight and then allowed to cool to room temperature after which water was added. The mixture was then extracted with dichloromethane and the organic extracts was dried with MgSO₄, filtered and concentrated in 15 vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (3:8 to 1:1 (v/v)), to afford the pure cross-coupled product as a slightly light orange solid (0.070 g, 0.24 mmol, 16% yield). R_f = 0.21 (EtOAc:hexanes 4:6 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.65 (s, 1H), 9.65 (s, 1H), 8.38 (d, J = 2.58 Hz, 1H), 8.32 (d, J = 2.58 Hz, 1H), 7.68 (d, J = 3.44 Hz, 1H), 7.28 (d, J = 3.87 Hz, 1H), 4.05 (s, 3H), 3.76 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 178.2, 156.4, 155.0, 152.4, 151.6, 139.9, 133.8, 127.7, 125.2, 113.6, 111.4, 54.2, 53.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₃H₁₃N₂O₆ ([M + H]⁺), 294.0799, found, 25 294.0801.

N-(6-(1H-Pyrazol-1-yl)pyridin-3-yl)-N-hydroxyacetamide (8n)



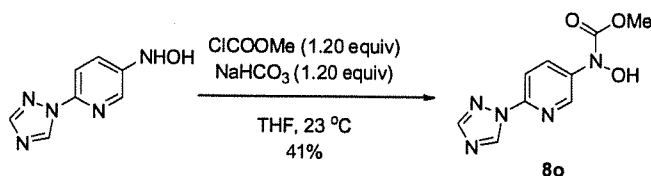
Under N₂ atmosphere, a solution of 2-fluoro-5-nitropyridine (0.71 g, 5.00 mmol, 1.00 equiv) was added to a mixture of 1H-pyrazole (0.51 g, 7.50 mmol, 1.50 equiv) and Cs₂CO₃ (2.44 g, 7.50 mmol, 1.50 equiv) in DMF (25.0 mL, 0.300 M) and the reaction mixture was stirred at 23 °C for 20 h. The reaction mixture was poured to LiCl solution (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (0.910 g, 4.78 mmol, 96% yield). R_f = 0.77 (hexanes:EtOAc 5:1 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 9.29 (br. s., 1H), 8.75 (d, *J* = 8.17 Hz, 1H), 8.73–8.71 (m, 1H), 8.12 (d, *J* = 9.04 Hz, 1H), 7.99–7.98 (m, 1H), 6.72–6.70 (m, 1H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 153.7, 145.0, 144.4, 142.3, 135.3, 128.5, 112.2, 110.0.

Under N₂ atmosphere, a suspension of 5-nitro-2-(1H-pyrazol-1-yl)pyridine 200 mg, 1.05 mmol, 1.00 equiv) and 5% Rh/C (12.6 mg, 0.60 mol% Rh) in THF (10.5 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (63.1 mg, 1.26 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (106 mg, 1.26 mmol, 1.20 equiv) was added, followed by dropwise addition of acetyl chloride (98.9 mg, 1.26 mmol, 1.20 equiv) in THF (10.5 mL, 0.120 M) at 23 °C. The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (200 mg, 0.917 mmol, 87% yield). R_f = 0.26 (hexanes:EtOAc 1:1(v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.95 (br. s., 1H), 8.77 (br. s., 1H), 8.59 (d, *J* = 2.15 Hz, 1H), 8.22 (dd, *J* = 9.03, 2.58 Hz, 1H), 7.95 (d, *J* = 9.03 Hz, 1H), 7.82 (s, 1H), 6.60–6.56 (m, 1H), 2.27 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 170.6, 146.9, 142.1, 139.1, 136.7, 130.1, 126.9, 111.7, 108.2, 22.2.

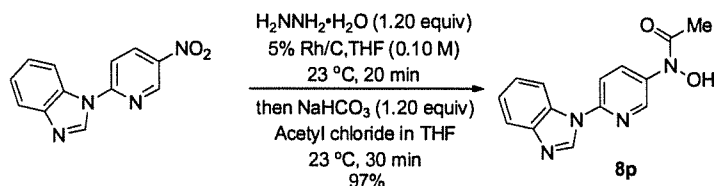
Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₀H₁₁N₄O₂ ([M + H]⁺), 219.0877, found, 219.0877.

Methyl (6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl) (hydroxy) carbamate (8o)

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Under N₂ atmosphere, to a suspension of 5-nitro-2-(1H-1,2,4-triazol-1-yl)pyridine (0.500 g, 2.26 mmol, 1.00 equiv) and 5% Rh/C (15.0 mg, 0.30 mol% Rh) in THF (13.0 mL, 0.200 M) hydrazine monohydrate (0.190 g, 3.14 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 1 h. The reaction mixture was filtered through a short pad of celite, washed with EtOAc, and concentrated in vacuo to afford the title compound as a slightly light yellow (0.691 g, 2.38 mmol, 91% yield). The product was used directly without further purification. R_f = 0.36 (EtOAc:hexanes 1:0 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 9.20 (s, 1H), 8.80 (s, 1H), 8.73 (d, J = 2.15 Hz, 1H), 8.22 (s, 1H), 8.05 (d, J = 2.58 Hz, 1H), 7.71 (d, J = 9.03 Hz, 1H), 7.45 (dd, J = 8.82, 2.80 Hz, 1H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 152.3, 147.9, 141.7, 141.0, 132.8, 123.0, 113.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₇H₈N₅O ([M + H]⁺), 178.0723, found, 178.0723. Under N₂ atmosphere, to a stirred suspension of N-(6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)hydroxylamine (0.150 g, 0.85 mmol, 1.00 equiv) and NaHCO₃ (0.084 g, 1.02 mmol, 1.20 equiv) in THF (4.23 mL, 0.100 M) at 23 °C was slowly added a solution of methyl chloroformate (0.095 g, 1.02 mmol, 1.20 equiv) in THF (4.23 mL, 0.100 M) via a syringe pump (at a rate of 10.0 mL/h). After the addition was complete, a white solid precipitated from the reaction mixture. The reaction mixture was then filtered through and the solid was washed with water to afford the title compound as a white solid (0.081 g, 0.34 mmol, 41% yield). R_f = 0.08 (MeOH:EtOAc 1:9 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.80 (s, 1H), 9.33 (s, 1H), 8.72 (d, J = 2.58 Hz, 1H), 8.29 (s, 1H), 8.19–8.17 (m, 1H), 7.89 (d, J = 9.03 Hz, 1H), 3.80 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 154.6, 152.9, 144.6, 141.8, 139.2, 138.5, 130.2, 112.9, 53.4. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₉N₅O₃Na ([M + Na]⁺), 258.0598, found, 258.0598.

***N*-(6-(1*H*-Benzo[*d*]imidazol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8p)**

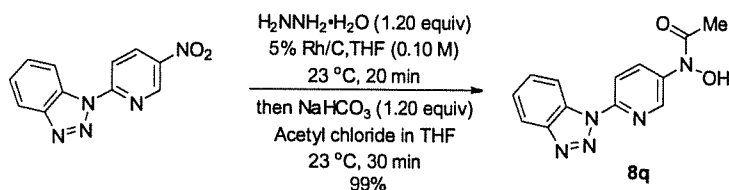
Under N_2 atmosphere, a solution of 2-fluoro-5-nitropyridine (1.32 g, 9.31 mmol, 1.10 equiv) in DMF (20.0 mL, 0.466 M) was added to a mixture of 1*H*-benzo[*d*]imidazole (1.00 g, 8.46 mmol, 1.00 equiv) and Cs_2CO_3 (2.76 g, 8.46 mmol, 1.50 equiv) in DMF (22.3 mL, 0.379 M) at 23 °C. The resulting mixture was stirred at 23 °C for 7 h. The reaction mixture was poured to LiCl solution (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (1.38 g, 5.75 mmol, 68% yield). $R_f = 0.29$ (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.46 (d, $J = 2.58$ Hz, 1H), 8.75–8.72 (m, 1H), 8.72–8.68 (m, 1H), 8.22 (d, $J = 8.17$ Hz, 1H), 7.90 (d, $J = 7.74$ Hz, 1H), 7.79 (dd, $J = 8.82, 1.94$ Hz, 1H), 7.49–7.46 (m, 1H), 7.45–7.42 (m, 1H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 153.6, 145.9, 144.9, 141.9, 141.1, 134.7, 131.8, 125.5, 124.7, 121.3, 113.7, 112.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{12}\text{H}_9\text{N}_4\text{O}_2$ ($[\text{M} + \text{H}]^+$), 241.0720, found, 241.0724.

Under N_2 atmosphere, a suspension of 1-(5-nitropyridin-2-yl)-1*H*-benzo[*d*]imidazole (600 mg, 2.50 mmol, 1.00 equiv) and 5% Rh/C (28.7 mg, 0.60 mol% Rh) in THF (25.0 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (150 mg, 3.00 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO_3 (252 mg, 3.00 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (236 mg, 3.00 mmol, 1.20 equiv) in THF (25.0 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (650 mg, 2.42 mmol, 97% yield). $R_f = 0.15$ (EtOAc). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 11.01 (br. s., 1H), 8.92 (s, 2H),

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8.28 (dd, $J = 9.03$, 2.58 Hz, 1H), 8.25 (d, $J = 7.74$ Hz, 1 H), 7.97 (d, $J = 9.03$ Hz, 1H), 7.77 (d, $J = 7.74$ Hz, 1H), 7.40–7.36 (m, 1H), 7.35–7.32 (m, 1H), 2.29 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 170.8, 145.5, 144.1, 142.2, 139.7, 136.6, 131.9, 130.0, 123.9, 123.0, 119.9, 114.4, 113.7, 22.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{14}\text{H}_{13}\text{N}_4\text{O}_2$ ($[\text{M} + \text{H}]^+$), 269.1033, found, 269.1037.

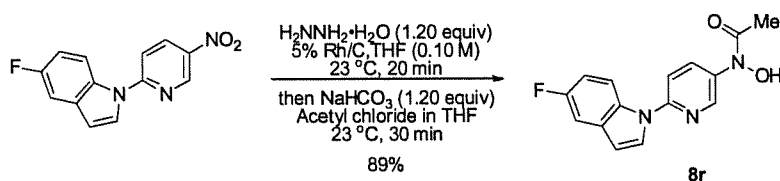
***N*-(6-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8q)**



10 Under N_2 atmosphere, to a mixture of 1*H*-benzo[*d*][1,2,3]triazole (0.890 g, 7.50 mmol, 1.50 equiv) and Cs_2CO_3 (2.44 g, 7.50 mmol, 1.50 equiv) in DMF (25.0 mL, 0.300 M) was added 2-fluoro-5-nitropyridine (0.71 g, 5.00 mmol, 1.00 equiv) and the reaction mixture was stirred at 23 °C for 20 h. The reaction mixture was poured to LiCl solution (100 mL),
 15 extracted with EtOAc. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (0.870 g, 3.61 mmol, 72% yield). $R_f = 0.54$ (hexanes:EtOAc 5:1 (v/v)).
 ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 9.52 (br. s., 1H), 8.90 (d, $J = 9.03$ Hz, 1H), 8.65 (d, $J = 8.17$ Hz, 1H), 8.51 (d, $J = 9.04$ Hz, 1H), 8.28 (d, $J = 8.17$ Hz, 1H), 7.82 (t, $J = 7.53$ Hz, 1H), 7.63 (t, $J = 7.53$ Hz, 1H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 153.8, 146.3, 145.1, 142.7, 135.4, 130.9, 130.2, 126.1, 120.1, 114.7, 114.3. Under
 N_2 atmosphere, a suspension of 1-(5-nitropyridin-2-yl)-1*H*-
 25 benzo[*d*][1,2,3]triazole (**S15**) (253 mg, 1.05 mmol, 1.00 equiv) and 5% Rh/C (12.6 mg, 0.60 mol% Rh) in THF (21.0 mL, 0.0500 M) was stirred at 23 °C. Hydrazine monohydrate (63.1 mg, 1.26 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO_3 (106 mg, 1.26 mmol, 1.20 equiv) was added, followed by dropwise
 30 addition of a solution of acetyl chloride (98.9 mg, 1.26 mmol, 1.20 equiv) in THF (10.5 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was

concentrated in vacuo. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (281 mg, 1.04 mmol, 99% yield). $R_f = 0.34$ (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 11.07 (s, 1H), 9.02 (d, $J = 2.58$ Hz, 1H), 8.56 (d, $J = 8.17$ Hz, 1H), 8.39 (dd, $J = 9.03, 2.58$ Hz, 1H), 8.28 (d, $J = 9.03$ Hz, 1H), 8.22–8.19 (m, 1H), 7.72 (td, $J = 7.64, 1.08$ Hz, 1H), 7.55 (ddd, $J = 8.07, 6.99, 0.86$ Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 171.2, 146.4, 146.0, 139.0, 137.5, 130.8, 130.0, 129.2, 125.3, 119.6, 114.3, 114.2, 22.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{13}\text{H}_{12}\text{N}_5\text{O}_2$ ($[\text{M} + \text{H}]^+$), 270.0986, found, 270.0986.

***N*-(6-(5-Fluoro-1*H*-indol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8r)**

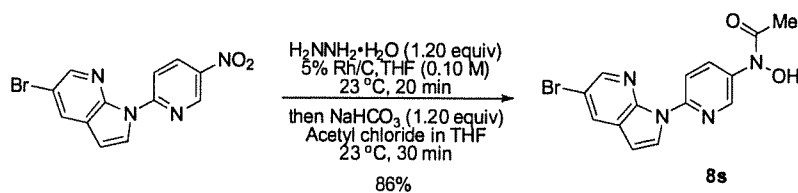


Under N_2 atmosphere, 5-fluoro-1*H*-indole (1.14 g, 8.45 mmol, 1.20 equiv) was dissolved in DMF (35.2 mL, 0.240 M) and stirred at 0 °C. NaH (0.338g, 8.45 mmol, 1.20 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, 2-fluoro-5-nitropyridine (1.00 g, 7.04 mmol, 1.00 equiv) was added and then the reaction mixture was slowly warmed up to 60 °C and stirred at 60 °C for 16 h. The reaction mixture was poured to a solution of LiCl (100 mL), extracted with EtOAc, and washed with brine. The combined organic layers was dried (MgSO_4), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (10:1 to 5:1 (v/v)), to afford the title compound as a yellow solid (1.63 g, 6.34 mmol, 90% yield). $R_f = 0.20$ (hexanes:EtOAc 5:1 (v/v)). ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.39 (d, $J = 2.15$ Hz, 1H), 8.58 (dd, $J = 9.03, 2.58$ Hz, 1H), 8.51 (dd, $J = 9.25, 4.52$ Hz, 1H), 7.76 (d, $J = 3.87$ Hz, 1H), 7.54 (d, $J = 9.04$ Hz, 1H), 7.30 (dd, $J = 9.03, 2.58$ Hz, 1H), 7.11 (td, $J = 9.03, 2.58$ Hz, 1H), 6.78 (d, $J = 3.01$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 159.5 (d, $J = 238.8$ Hz), 155.8, 145.6 (d, $J = 3.50$ Hz), 140.4, 134.0, 132.1 ($J = 9.94$ Hz), 126.5, 116.4 (d, $J = 9.00$ Hz), 112.5 (d, $J = 24.7$ Hz), 112.0, 108.9 (d, $J = 3.76$ Hz), 106.8 (d, $J = 23.6$ Hz). ^{19}F NMR (376 MHz, CDCl_3 , 25

$^{\circ}\text{C}$, δ): -121.5.0 (m). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{13}\text{H}_9\text{FN}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$), 258.0673, found, 258.0675.

Under N_2 atmosphere, a suspension of 5-fluoro-1-(5-nitropyridin-2-yl)-1*H*-indole (0.500 g, 1.94 mmol, 1.00 equiv) and 5% Rh/C (21.8 mg, 0.60 mol% Rh) in THF (20.0 mL, 0.100 M) was stirred at 23 $^{\circ}\text{C}$. Hydrazine monohydrate (117 mg, 2.33 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 $^{\circ}\text{C}$ for 20 min. NaHCO_3 (196 mg, 2.33 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (183 mg, 2.33 mmol, 1.20 equiv) in THF (20 mL, 0.120 M). The reaction mixture was stirred at 23 $^{\circ}\text{C}$ for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (0.490 g, 1.72 mmol, 89% yield). R_f = 0.14 (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 $^{\circ}\text{C}$, δ): 10.95 (br. s., 1H), 8.84 (br. s., 1H), 8.39 (dd, J = 8.82, 4.52 Hz, 1H), 8.23-8.17 (m, 1H), 8.09 (d, J = 3.44 Hz, 1H), 7.79 (d, J = 8.60 Hz, 1H), 7.43 (dd, J = 9.25, 2.37 Hz, 1H), 7.10 (td, J = 9.14, 2.37 Hz, 1H), 6.75 (d, J = 3.01 Hz, 1H), 2.27 (br. s., 3H), ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 $^{\circ}\text{C}$, δ): 170.6, 157.8 (d, J = 233.2 Hz), 148.0, 139.4, 135.4, 131.3, 130.6 (d, J = 10.1 Hz), 130.2, 128.2, 115.2 (d, J = 9.14 Hz), 113.6, 110.8 (d, J = 25.2 Hz), 105.6 (d, J = 23.3 Hz), 105.2 (d, J = 3.38 Hz), 22.1. ^{19}F NMR (376 MHz, CDCl_3 , 25 $^{\circ}\text{C}$, δ): -123.6 (m). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{15}\text{H}_{13}\text{FN}_3\text{O}_2$ ($[\text{M} + \text{H}]^+$), 286.0986, found, 286.0989.

***N*-(6-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8s)**



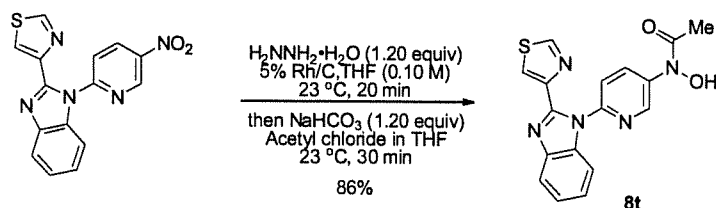
30

Under N_2 atmosphere, 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (1.66 g, 8.45 mmol, 1.20 equiv) was dissolved in DMF (35.2 mL, 0.240 M) and

stirred at 0 °C. NaH (0.338g, 8.45 mmol, 1.20 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, 2-fluoro-5-nitropyridine (1.00 g, 7.04 mmol, 1.00 equiv) was added and then the reaction mixture was slowly warmed up to 60 °C and stirred at 60 °C for 16 h. The reaction mixture was poured to a solution of LiCl (100 mL), extracted with EtOAc. The combined organic layers washed with brine, dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (20:1 to 10:1 (v/v)), to afford the title compound as a yellow solid (1.26 g, 3.94 mmol, 56% yield). *R_f* = 0.69 (hexanes:EtOAc 5:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 9.31 (d, *J* = 2.58 Hz, 1H), 9.30 (d, *J* = 9.04 Hz, 1H), 8.64 (d, *J* = 2.58 Hz, 1H), 8.62 (d, *J* = 2.58 Hz, 1H), 8.49 (d, *J* = 4.30 Hz, 1H), 8.46 (d, *J* = 2.15 Hz, 1H), 8.10 (d, *J* = 2.15 Hz, 1H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.8, 146.4, 144.9, 144.3, 141.1, 134.0, 131.9, 127.8, 125.8, 114.6, 114.4, 104.5. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₂H₈BrN₄O₂ ([M + H]⁺), 318.9825, found, 318.9826. Under N₂ atmosphere, a suspension of 5-bromo-1-(5-nitropyridin-2-yl)-1*H*-pyrrolo[2,3-*b*]pyridine (350 mg, 1.10 mmol, 1.00 equiv) and 5% Rh/C (12.6 mg, 0.60 mol% Rh) in THF (11.0 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (65.9 mg, 1.32 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (111 mg, 1.32 mmol, 1.2 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (104 mg, 1.32 mmol, 1.20 equiv) in THF (11.0 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (330 mg, 0.950 mmol, 86% yield). *R_f* = 0.17 (hexanes:EtOAc 1:1 (v/v)). ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.94 (br. s., 1H), 8.83 (br. s., 1H), 8.71 (d, *J* = 8.60 Hz, 1H), 8.46 (br. s., 1H), 8.39 (d, *J* = 3.44 Hz, 1H), 8.36 (br. s., 1H), 8.24 (d, *J* = 9.03 Hz, 1H), 6.74 (d, *J* = 3.44 Hz, 1H), 2.27 (br. s., 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 170.6, 145.5, 145.0, 143.3, 139.6, 136.0, 131.6, 129.6, 128.1, 124.4,

114.7, 112.7, 102.4, 22.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{12}BrN_4O_2$ ($[M + H]^+$), 347.0138, found, 347.0142.

5 N-Hydroxy-N-(6-(2-(thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyridin-3-yl)acetamide (8t)



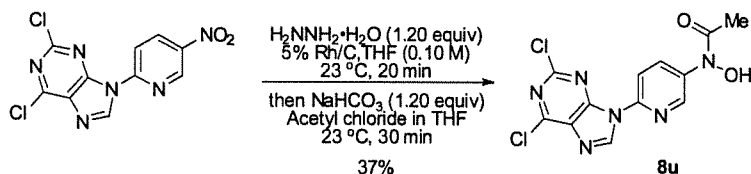
Under N_2 atmosphere, a solution of 2-fluoro-5-nitropyridine (0.710 g, 5.00 mmol, 1.00 equiv) in DMF (5 mL, 1.00 M) was added to a mixture of 4-(1H-benzo[d]imidazol-2-yl)thiazole (1.51 g, 7.50 mmol, 1.50 equiv) and CS_2CO_3 (2.44 g, 7.50 mmol, 1.50 equiv) in DMF (20.0 mL, 0.372 M) at 23 °C. The resulting mixture was stirred at 23 °C for 12 h. The reaction mixture was poured to LiCl solution (100 mL), extracted with EtOAc. The combined organic layers was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (2.30 g, 7.11 mmol, 95% yield). R_f = 0.34 (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: 1H NMR (700 MHz, $CDCl_3$, 25 °C, δ): 9.41 (d, J = 2.15 Hz, 1 H), 8.63 (d, J = 2.15 Hz, 1H), 8.60–8.56 (m, 1H), 8.28 (d, J = 2.15 Hz, 1H), 7.87 (d, J = 7.74 Hz, 1H), 7.55 (d, J = 7.74 Hz, 1H), 7.44–7.38 (m, 2H), 7.38–7.34 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$, 25 °C, δ): 154.8, 153.1, 146.6, 146.4, 145.2, 143.1, 143.0, 135.3, 133.4, 125.0, 124.4, 121.9, 121.5, 120.4, 111.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{10}N_5O_2S$ ($[M + H]^+$), 324.0550, found, 324.0555.

Under N_2 atmosphere, a suspension of 4-(1-(5-nitropyridin-2-yl)-1H-benzo[d]imidazol-2-yl)thiazole (323 mg, 1.00 mmol, 1.00 equiv) and 5% Rh/C (11.5 mg, 0.60 mol% Rh) in THF (10.0 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (60.1 mg, 1.20 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. $NaHCO_3$ (101 mg, 1.20 mmol, 1.20 equiv) was added, followed by dropwise addition of acetyl chloride (94.2 mg, 1.20 mmol, 1.20 equiv) in THF (10 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in

vacuo. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (303 mg, 0.862 mmol, 86% yield). $R_f = 0.14$ (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 11.04 (s, 1H), 9.01 (d, $J = 1.72$ Hz, 1H), 8.91 (br. s., 1H), 8.44 (d, $J = 1.72$ Hz, 1H), 8.26 (dd, $J = 8.60$, 2.58 Hz, 1H), 7.80 (d, $J = 8.17$ Hz, 1H), 7.51 (d, $J = 8.60$ Hz, 1H), 7.38–7.33 (m, 2H), 7.32–7.29 (m, 1H), 2.31 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 171.0, 154.7, 146.6, 146.1, 145.1, 142.3, 139.4, 138.0, 135.8, 128.6, 123.8, 123.2, 122.6, 121.5, 119.4, 111.1, 22.4.

10 Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{17}\text{H}_{14}\text{N}_5\text{O}_2\text{S}$ ($[\text{M} + \text{H}]^+$), 352.0863, found, 352.0869.

***N*-(6-(2,6-Dichloro-9*H*-purin-9-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8u)**



15 Under N_2 atmosphere, a solution of 2-fluoro-5-nitropyridine (0.78 g, 5.50 mmol, 1.10 equiv) in DMF (5 mL, 1.1 M) was added to a mixture of 2,6-dichloro-9*H*-purine (0.950 g, 5.00 mmol, 1.00 equiv) and Cs_2CO_3 (1.63 g, 5.00 mmol, 1.00 equiv) in DMF (20 mL, 0.25 M) at 23 °C. The reaction mixture was stirred at 23 °C for 12 h, poured to LiCl solution

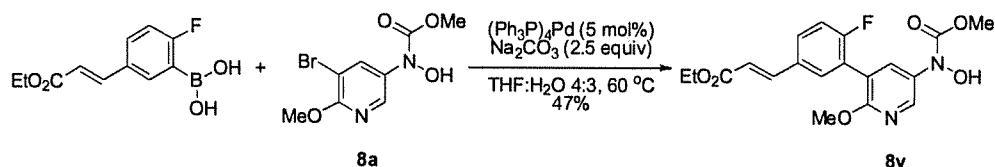
20 (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (10:1 to 4:1 (v/v)), to afford the title compound as a yellow solid (0.500g, 1.61 mmol, 32% yield). $R_f = 0.50$ (hexanes:EtOAc 4:1 (v/v)). NMR

25 Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 25 °C, δ): 9.40 (d, $J = 2.44$ Hz, 1H), 9.30 (s, 1H), 8.95 (d, $J = 8.85$ Hz, 1H), 8.81 (dd, $J = 9.00$, 2.59 Hz, 1H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 154.4, 153.3, 152.0, 150.7, 145.2, 143.8, 143.3, 135.4, 132.8, 115.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{10}\text{H}_5\text{Cl}_2\text{N}_6\text{O}_2$ ($[\text{M} + \text{H}]^+$), 310.9846,

30 found, 310.9848. Under N_2 atmosphere, a suspension of 2,6-dichloro-9-(5-nitropyridin-2-yl)-9*H*-purine (270 mg, 0.870 mmol, 1.00 equiv) and 5% Rh/C (10.0 mg, 0.60 mol% Rh) in THF (8.7 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (52.0 mg, 1.04 mmol, 1.20

equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (87.4 g, 1.04 mmol, 1.2 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (81.6 mg, 1.04 mmol, 1.20 equiv) in THF (8.7 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 to EtOAc (v/v)), to afford the title compound as a yellow solid (110 mg, 0.324 mmol, 37% yield). *R_f* = 0.13 (EtOAc). NMR Spectroscopy: ¹H NMR (500 MHz, (CD₃)₂SO, 25 °C, δ): 11.07 (br. s., 1H), 9.34 (s, 1H), 8.95 (d, *J* = 2.44 Hz, 1H), 8.39 (dd, *J* = 9.00, 2.59 Hz, 1H), 8.28 (d, *J* = 8.85 Hz, 1H), 2.29 (s, 3H). ¹³C NMR (125 MHz, (CD₃)₂SO, 25 °C, δ): 171.0, 152.1, 151.7, 150.3, 145.7, 142.2, 139.5, 138.1, 131.8, 129.7, 115.7, 22.3. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₂H₈C₁₃N₆O₂ ([M + H]⁺), 339.0159, found, 339.0172.

Ethyl (E)-3-(4-fluoro-3-(5-(hydroxy(methoxycarbonyl)amino)-2-methoxy-pyridin-3-yl)phenyl)acrylate (8v)

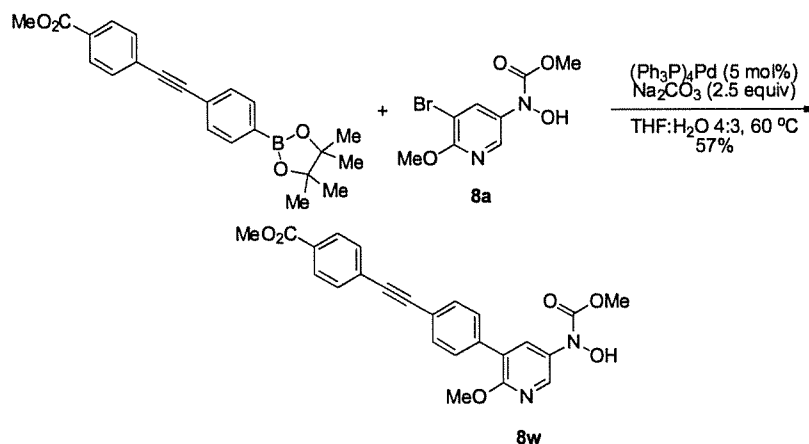


Methyl (5-bromo-6-methoxypyridin-3-yl)(hydroxy)carbamate (**1a**) (0.300 g, 1.08 mmol, 1.00 equiv), (*E*)-(5-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-fluorophenyl)boronic acid (0.361 g, 1.52 mmol, 1.40 equiv), Na₂CO₃ (0.287 g, 2.71 mmol, 2.5 equiv), and palladium-tetrakis(triphenylphosphine) (0.062 g, 0.05 mmol, 0.05 equiv) in THF:H₂O 4:3 (6.32 mL, 0.200 M), were degassed via three freeze-pump-thaw cycles. The resulting mixture was heated at 60 °C overnight and then allowed to cool to room temperature after which water was added (twice the volume of THF:H₂O 4:3 used). The mixture was then extracted with dichloromethane (twice the volume of THF:H₂O 4:3 used) and the organic extracts was dried with MgSO₄, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (3:8 to 1:1 (v/v)), to afford the pure cross-coupled product as a yellow solid (0.198 g, 0.51 mmol, 47%

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yield). $R_f = 0.36$ (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.55 (s, 1H), 8.33 (d, $J = 2.58$ Hz, 1H), 7.90–7.79 (m, 3H), 7.68 (d, $J = 15.92$ Hz, 1H), 7.35 (t, $J = 9.03$ Hz, 1H), 6.67 (d, $J = 16.35$ Hz, 1H), 4.18 (q, $J = 7.17$ Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 1.25 (t, $J = 7.10$ Hz, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 166.2, 160.4 (d, $J = 250.2$ Hz), 157.7, 155.2, 143.0, 140.1, 133.9, 133.4, 131.9 (d, $J = 3.5$ Hz), 130.8 (d, $J = 3.5$ Hz), 130.3 (d, $J = 8.6$ Hz), 124.1 (d, $J = 16.2$ Hz), 118.6, 117.3, 116.3 (d, $J = 22.7$ Hz), 60.1, 53.8, 53.1, 14.2. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -111.3 (m).

Methyl 4-((4-(5-(hydroxy(methoxycarbonyl)amino)-2-methoxypyridin-3-yl)phenyl)ethynyl)benzoate (8w)

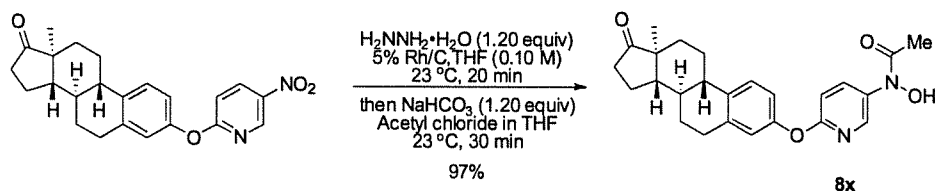


Methyl (5-bromo-6-methoxypyridin-3-yl)(hydroxy)carbamate (**1a**) (0.300 g, 1.08 mmol, 1.00 equiv), methyl 4-((4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethynyl)benzoate (0.152 g, 1.52 mmol, 1.40 equiv), Na_2CO_3 (0.287 g, 2.71 mmol, 2.5 equiv), THF:H₂O 4:3 (6.32 mL, 0.200 M), and palladium-tetrakis(triphenylphosphine) (0.062 g, 0.05 mmol, 0.05 equiv) were degassed via three freeze-pump-thaw cycles. The resulting mixture was heated at 60 °C overnight and then allowed to cool to room temperature after which water was added (twice the volume of THF:H₂O 4:3 used). The mixture was then extracted with dichloromethane (twice the volume of THF:H₂O 4:3 used) and the organic extracts was dried with MgSO_4 , filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with EtOAc:hexanes (3:8 to 1:1 (v/v)), to afford the pure cross-coupled product as a white solid (0.199 g, 0.63 mmol, 57% yield).

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$R_f = 0.38$ (EtOAc:hexanes 1:1 (v/v)). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.40 (s, 1H), 8.29 (d, $J = 2.58$ Hz, 1H), 8.03–7.99 (m, 2H), 7.89 (d, $J = 3.01$ Hz, 1H), 7.73–7.70 (m, 2H), 7.68–7.63 (m, 4H), 3.93 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 165.6, 157.3, 155.2, 139.3, 136.4, 133.9, 132.5, 131.7, 131.6, 129.5, 129.4, 127.0, 122.2, 121.1, 92.1, 89.2, 53.8, 53.1, 52.4.

***N*-Hydroxy-*N*-(6-(((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)pyridin-3-yl)acetamide (8x)**

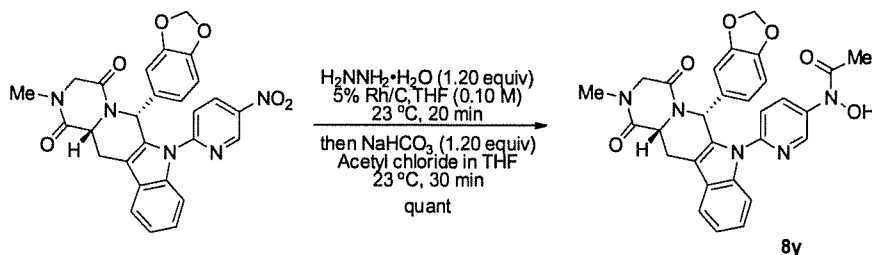


Under N_2 atmosphere, a solution of 2-fluoro-5-nitropyridine (0.320 g, 2.22 mmol, 1.20 equiv) in DMF (8.50 mL, 0.261 M) was added to a mixture of estrone (0.500 g, 1.85 mmol, 1.00 equiv) and Cs_2CO_3 (0.720 g, 2.22 mmol, 1.20 equiv) in DMF (10.0 mL, 0.185 M) at 23 °C. The resulting mixture was stirred at 23 °C for 12 h. The reaction mixture was poured to LiCl solution (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a light yellow solid (0.650g, 1.66 mmol, 89% yield). $R_f = 0.52$ (hexanes:EtOAc 2:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.06 (d, $J = 2.58$ Hz, 1H), 8.46 (dd, $J = 9.03, 2.58$ Hz, 1H), 7.36 (d, $J = 8.60$ Hz, 1H), 7.03 (d, $J = 9.03$ Hz, 1H), 6.93 (dd, $J = 8.60, 2.58$ Hz, 1H), 6.89 (d, $J = 2.58$ Hz, 1H), 2.97–2.92 (m, 2H), 2.52 (dd, $J = 19.36, 8.60$ Hz, 1H), 2.46–2.40 (m, 1H), 2.33 (td, $J = 11.19, 4.30$ Hz, 1H), 2.20–2.12 (m, 1H), 2.11–2.02 (m, 2H), 1.99 (dt, $J = 12.91, 3.01$ Hz, 1H), 1.68–1.45 (m, 6H), 0.93 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 220.9, 167.2, 150.7, 145.3, 140.3, 138.8, 137.7, 135.0, 127.0, 121.5, 118.8, 111.5, 50.6, 48.1, 44.3, 38.1, 36.0, 31.7, 29.6, 26.5, 25.9, 21.7, 14.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 393.1809, found, 393.1812.

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Under N₂ atmosphere, a suspension of (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-((5-nitropyridin-2-yl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (300 mg, 0.760 mmol, 1.00 equiv) and 5% Rh/C (8.70 mg, 0.60 mol% Rh) in THF (7.60 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (45.9 mg, 0.910 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (76.4 mg, 0.91 mmol, 1.20 equiv) was added, followed by dropwise addition of acetyl chloride (71.4 mg, 0.91 mmol, 1.20 equiv) in THF (7.6 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in vacuo. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a yellow solid (310 mg, 0.737 mmol, 97% yield). R_f = 0.13 (hexanes:EtOAc 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.76 (s, 1H), 8.34 (d, *J* = 1.83 Hz, 1H), 8.00 (dd, *J* = 8.85, 2.44 Hz, 1H), 7.31 (d, *J* = 8.54 Hz, 1H), 7.01 (d, *J* = 8.85 Hz, 1H), 6.86 (dd, *J* = 8.24, 2.44 Hz, 1H), 6.81 (d, *J* = 2.44 Hz, 1H), 2.87–2.80 (m, 2H), 2.50 (dt, *J* = 3.66, 1.83 Hz, 3H), 2.36–2.48 (m, 2H), 2.26 (br. s., 1H), 2.20 (br. s., 3H), 2.07 (dd, *J* = 18.92, 8.85 Hz, 1H), 2.01–1.91 (m, 2H), 1.82–1.75 (m, 1H), 1.63–1.32 (m, 6H), 0.85 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 219.7, 170.5, 160.0, 151.9, 139.7, 138.0, 135.9, 134.2, 133.0, 126.6, 120.8, 118.3, 110.9, 49.6, 47.3, 43.6, 37.6, 35.4, 31.4, 29.0, 25.9, 25.4, 21.9, 21.2, 13.5. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₂₅H₂₉N₂O₄ ([M + H]⁺), 421.2122, found, 421.2125.

***N*-(6-((6*R*,12*aR*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1,4-dioxo-1,3,4,6,12,12*a*-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indol-7(2*H*)-yl)pyridin-3-yl)-*N*-hydroxyacetamide (8y)**



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Under N₂ atmosphere, to a mixture of (6*R*,12*aR*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-2,3,6,7,12,12*a*-hexahydro-pyrazino[1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione (1.00 g, 2.60 mmol, 1.00 equiv) and K₂CO₃ (0.36 g, 2.60 mmol, 1.00 equiv) in DMF (26.0 mL, 0.100 M) was added 2-fluoro-5-nitropyridine (0.550 g, 3.90 mmol, 1.50 equiv) and the reaction mixture was stirred at 23 °C for 40 h. The reaction mixture was poured to water (100 mL), extracted with EtOAc, washed with brine. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 to 1:3 (v/v)), to afford the title compound as a yellow solid (0.810 g, 1.58 mmol, 61% yield) R_f = 0.51 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, DMSO, 25 °C, δ): 9.44 (d, *J* = 2.58 Hz, 1H), 8.53 (dd, *J* = 8.82, 2.80 Hz, 1H), 7.73-7.69 (m, 1H), 7.55-7.50 (m, 1H), 7.41 (d, *J* = 9.03 Hz, 1H), 7.35-7.28 (m, 2H), 7.00 (s, 1H), 6.52-6.44 (m, 3H), 5.80 (dd, *J* = 6.45, 1.29 Hz, 2H), 4.38 (dd, *J* = 11.62, 4.30 Hz, 1H), 4.16-4.10 (m, 1H), 3.93 (d, *J* = 17.21 Hz, 1H), 3.84 (dd, *J* = 16.13, 4.52 Hz, 1H), 3.27 (ddd, *J* = 16.35, 11.62, 1.29 Hz, 1H), 3.06-3.01 (m, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 166.5, 166.4, 154.6, 147.6, 147.0, 145.6, 141.6, 136.6, 134.6, 134.0, 133.9, 127.6, 124.6, 122.8, 121.9, 119.6, 118.0, 113.3, 110.9, 108.2, 107.8, 101.2, 55.6, 55.4, 52.4, 33.8, 23.9. Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₂₇H₂₂N₅O₆ ([M + H]⁺), 512.1565, found, 512.1567. Under N₂ atmosphere, a suspension of (6*R*,12*aR*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-7-(5-nitropyridin-2-yl)-2,3,6,7,12,12*a*-hexahydropyrazino [1',2':1,6]pyrido[3,4-*b*]indole-1,4-dione (300 mg, 0.590 mmol, 1.00 equiv) and 5% Rh/C (6.80 mg, 0.60 mol% Rh) in THF (5.90 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (35.4 mg, 0.710 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (59.6 mg, 0.710 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (55.7 mg, 0.710 mmol, 1.20 equiv) in THF (5.90 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a white solid (320 mg, 0.59 mmol, quant yield). R_f = 0.17 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 11.03 (br. s.,

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1H), 8.96 (br. s., 1H), 8.22 (d, $J = 8.60$ Hz, 1 H), 7.78–7.70 (m, 1H), 7.43–7.34 (m, 2H), 7.23–7.16 (m, 2H), 6.68 (br. s., 1H), 6.54–6.47 (m, 1H), 6.28 (d, $J = 1.72$ Hz, 1H), 6.19 (dd, $J = 8.17, 1.72$ Hz, 1H), 5.84 (dd, $J = 12.91, 2.58$ Hz, 2H), 4.53 (d, $J = 11.62$ Hz, 1H), 4.19 (d, $J = 16.78$ Hz, 1H), 3.92 (d, $J = 17.21$ Hz, 1H), 3.66 (d, $J = 15.92$ Hz, 1H), 2.97–2.87 (m, 3H), 2.44–2.43 (m, 1 H), 2.31 (br. s., 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 166.9, 166.4, 146.8, 146.0, 137.0, 136.4, 135.4, 134.6, 126.0, 123.1, 120.9, 120.3, 119.5, 119.0, 110.3, 109.3, 107.5, 107.1, 100.9, 54.9, 54.2, 51.5, 32.8, 23.3, 22.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{29}\text{H}_{26}\text{N}_5\text{O}_6$ ($[\text{M} + \text{H}]^+$), 540.1878, found, 540.1881.

Methyl (5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl) carbamate (9a): A solution of methyl (5-bromo-6-methoxypyridin-3-yl)(hydroxy)carbamate (8a) (50.0 mg, 0.180 mmol) and Togni reagent I (71.5 mg, 0.217 mmol, 1.20 equiv) in CH_2Cl_2 (1.80 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 16 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (19:1 (v/v)) for development (prep TLC was developed three times). The purification afforded the title compound as a white solid (47.3 mg, 0.137 mmol, 76% yield). $R_f = 0.69$ (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 25 °C, δ): 8.65 (br. s, 1H), 6.62 (br. s, 1H), 3.93 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 153.8, 153.6, 141.9, 135.6, 120.1 (q, $J = 261.6$ Hz), 117.3, 102.6, 55.1, 53.0. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_9\text{H}_9\text{BrF}_3\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 344.9692, found, 344.9705.

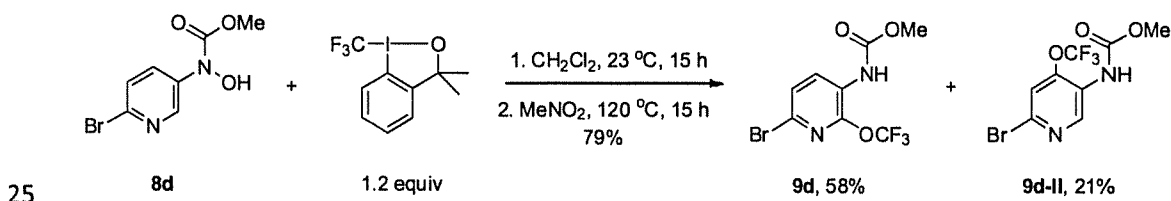
Methyl (5-iodo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl) carbamate (9b): A solution of methyl hydroxy(5-iodo-6-methoxypyridin-3-yl)carbamate (9b) (50.0 mg, 0.154 mmol) and Togni reagent I (61.1 mg, 0.185 mmol, 1.20 equiv) in CH_2Cl_2 (1.54 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 18 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (97:3 (v/v)) for development (prep TLC was developed six times). The purification afforded the title compound as a white solid (44.2 mg, 0.113 mmol, 73% yield). $R_f = 0.53$ (EtOAc:hexanes 1:9 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, CDCl_3 , 25 °C, δ): 8.81 (br. s, 1H), 6.58 (br. s.,

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1H), 3.91 (s, 3H), 3.80 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 155.8, 153.8, 143.4, 141.6, 120.1 (q, *J* = 261.8 Hz), 117.4, 73.9, 55.4, 52.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₉F₃IN₂O₄ ([M + H]⁺),
 5 392.9554, found, 392.9556.

Methyl (6-chloro-4-methyl-2-(trifluoromethoxy)pyridin-3-yl) carbamate (9c): A solution of methyl (6-chloro-4-methylpyridin-3-yl)(hydroxy)carbamate (**8c**) (108 mg, 0.500 mmol) and Togni reagent I (198 mg, 0.600 mmol, 1.20 equiv) in CH₂Cl₂ (5.00 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 15 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (5.00 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 15 h. The reaction mixture was concentrated *in vacuo* and purified by chromatography on silica gel, eluting with hexanes:EtOAc (8:1 to 4:1
 10 (v/v)), to afford **2c** (99.0 mg, 0.348 mmol, 70% yield). Data for **9c**: white solid; R_f = 0.45 (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.44 (d, *J* = 8.53 Hz, 1H), 7.38 (d, *J* = 8.53 Hz, 1H), 6.85 (br. s, 1H), 3.83 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 154.4, 151.6, 150.6, 145.5, 124.1, 120.0 (q, *J* =
 20 261.9 Hz), 119.9, 53.4 (d, *J* = 7.51 Hz), 18.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₉ClF₃N₂O₃ ([M + H]⁺), 285.0248, found, 285.0249.

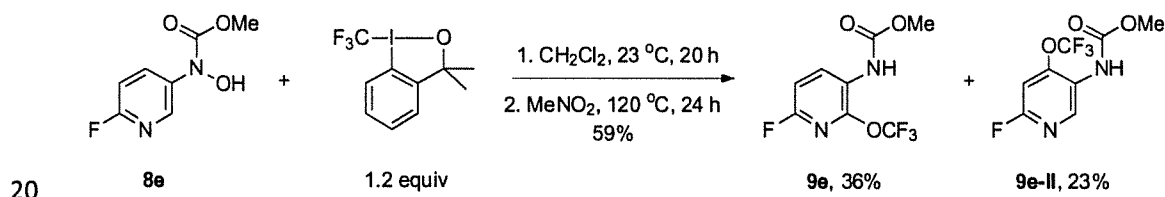
Methyl (6-bromo-2-(trifluoromethoxy)pyridin-3-yl) carbamate (9d) and methyl (6-bromo-4-(trifluoromethoxy)pyridin-3-yl) carbamate (9d-II)



A solution of methyl (6-bromopyridin-3-yl)(hydroxy)carbamate (**8d**) (124 mg, 0.226 mmol) and Togni reagent I (198 mg, 0.600 mmol, 1.20 equiv) in CH₂Cl₂ (5.00 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 15 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (5.00 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 15 h. The reaction mixture
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was concentrated *in vacuo* and purified by chromatography on silica gel, eluting with hexanes:EtOAc (19:1 to 9:1 (v/v)), to afford **9d** (91 mg, 0.289 mmol, 58% yield) and **9d-II** (33 mg, 0.105 mmol, 21% yield). Data for **9d**: white solid; *R_f* = 0.57 (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.44 (d, *J* = 8.53 Hz, 1H), 7.38 (d, *J* = 8.53 Hz, 1H), 6.85 (br. s, 1H), 3.83 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.4, 143.8, 130.3, 129.6, 126.6, 123.5, 120.0 (q, *J* = 265.2 Hz), 53.2. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₈H₇BrF₃N₂O₃ ([M + H]⁺), 314.9587, found, 314.9585. Data for **9d-II**: white solid; *R_f* = 0.45 (EtOAc:hexanes 1:4 (v/v)) NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 9.23 (br. s, 1H), 7.35 (q, *J* = 2.01 Hz, 1H), 6.77 (br. s, 1H), 3.84 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.1, 144.8, 142.7, 134.8, 126.5, 120.2 (q, *J* = 265.2 Hz), 116.9, 53.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₈H₇BrF₃N₂O₃ ([M + H]⁺), 314.9587, found, 314.9586.

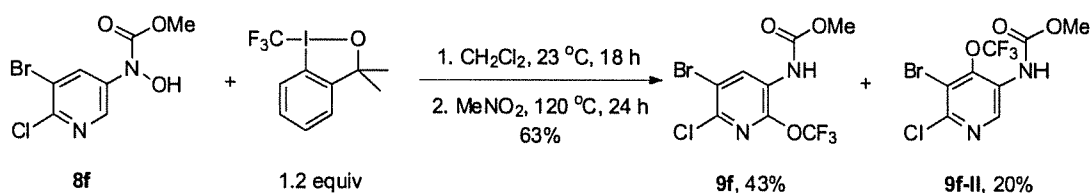
Methyl (6-fluoro-2-(trifluoromethoxy)pyridin-3-yl)carbamate (9e) and methyl (6-fluoro-4-(trifluoromethoxy)pyridin-3-yl)carbamate (9e-II)



A solution of methyl (6-fluoropyridin-3-yl)(hydroxy)carbamate (**8e**) (93.1 mg, 0.500 mmol) and Togni reagent I (198 mg, 0.600 mmol, 1.20 equiv) in CH₂Cl₂ (5.00 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (5.00 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 24 h. The crude residue was purified by flash chromatography eluting hexanes and then EtOAc:hexanes (1:4 (v/v)). The purification afforded a 1.6:1 mixture of **9e** and **9e-II**, which was further purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (19:1 (v/v)) for development (prep TLC was developed five times). The purification afforded **9e** (45.8 mg, 0.180 mmol, 36% yield) and **9e-II** (28.7 mg, 0.113 mmol, 23%

yield). Data for **9e**: white solid; $R_f = 0.48$ (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 25 °C, δ): 8.64 (br. s, 1H), 6.87 (dd, $J = 8.66, 3.14$ Hz, 1H), 6.79 (br. s, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 155.6 (d, $J = 242.1$ Hz), 153.7, 142.2, 133.5, 121.4, 120.0 (q, $J = 262.7$ Hz), 107.1 (d, $J = 35.6$ Hz), 53.1. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.8 (s), -75.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_7\text{F}_4\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 255.0387, found, 255.0387. Data for **9e-II**: off-white solid; $R_f = 0.44$ (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ^1H NMR (400 MHz, CDCl_3 , 25 °C, δ): 8.98 (br. s, 1H), 6.83 (quin, $J = 2.13$ Hz, 1H), 6.69 (br. s, 1H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 159.2 (d, $J = 234.5$ Hz), 153.5, 147.5, 140.3, 124.6, 120.2 (q, $J = 262.2$ Hz), 99.2 (d, $J = 45.2$ Hz), 53.3. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -58.2 (s), -69.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_8\text{H}_7\text{F}_4\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 255.0387, found, 255.0390.

Methyl (5-bromo-6-chloro-2-(trifluoromethoxy)pyridin-3-yl) carbamate (9f) and methyl (5-Bromo-6-chloro-4-(trifluoromethoxy)pyridin-3-yl) carbamate (9f-II)



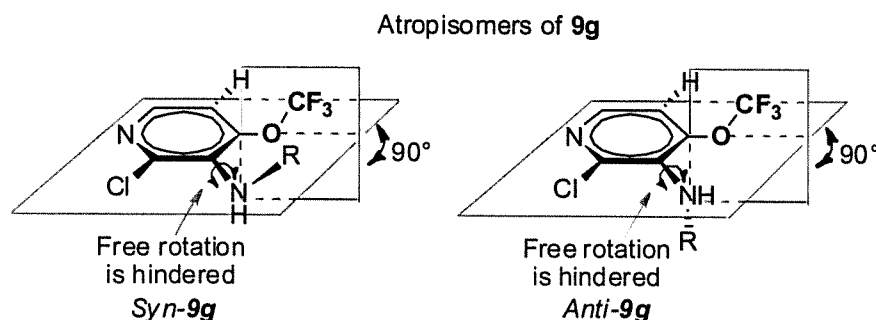
A solution of methyl (5-bromo-6-chloropyridin-3-yl)(hydroxy)carbamate (**8f**) (141 mg, 0.500 mmol) and Togni reagent I (198 mg, 0.600 mmol, 1.20 equiv) in CH_2Cl_2 (5.00 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO_2 (5.00 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 24 h. The crude residue was purified by flash chromatography eluting with EtOAc:hexanes (1:19 to 1:4 (v/v)), to afford **9f** (75.6 mg, 0.216 mmol, 43% yield) and **9f-II** (34.6 mg, 0.0990 mmol, 20% yield). Data for **9f**: white solid; $R_f = 0.52$ (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.86 (s, 1H), 6.85 (br. s, 1H), 3.84 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 153.2, 142.3, 139.7, 133.3, 123.7, 119.9 (q, $J = 263.4$ Hz), 117.6, 53.4. ^{19}F

NMR (376 MHz, CDCl₃, 25 °C, δ): -56.8 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₆BrClF₃N₂O₃ ([M + H]⁺), 348.9197, found, 348.9196. Data for **9f-II**: slightly yellow solid; R_f = 0.43 (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 9.19 (br. s, 1H), 6.78 (br. s, 1H), 3.84 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 153.1, 146.4, 143.8, 140.9, 129.5, 120.5 (q, J = 263.7 Hz), 116.4, 53.6. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -55.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₆BrClF₃N₂O₃ ([M + H]⁺), 348.9197, found, 348.9198.

10 **Methyl (2-chloro-4-(trifluoromethoxy)pyridin-3-yl)carbamate (9g)**

A solution of methyl (2-chloropyridin-3-yl)(hydroxy)carbamate (**8g**) (101 mg, 0.500 mmol) and Togni reagent I (198 mg, 0.600 mmol, 1.20 equiv) in CH₂Cl₂ (5.00 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 15 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (5.00 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 15 h. The reaction mixture was concentrated *in vacuo* and purified by chromatography on silica gel, eluting with hexanes:EtOAc (10:1 to 5:1 (v/v)), to afford 9g (73.0 mg, 0.270 mmol, 53% yield) and 9g' (45.0 mg, 0.166 mmol, 33% yield). Data for 9g: white solid; R_f = 0.72 (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.10 (d, J = 5.59 Hz, 1H) 7.31 (d, J = 5.16 Hz, 1H) 6.25 (br. s, 1H) 3.80 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.9, 153.1, 145.0, 143.8, 123.3, 120.8, 120.1 (q, J = 261.6 Hz), 53.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.3 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₇ClF₃N₂O₃ ([M + H]⁺), 271.0092, found, 271.0093. Data for 9g': white solid; R_f = 0.48 (EtOAc:hexanes 1:4 (v/v)) NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.32 (d, J = 5.59 Hz, 1H) 7.23-7.20 (m, 1H) 6.28 (br. s, 1H) 3.80 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.9, 152.8, 150.6, 148.2, 123.3, 120.2 (q, J = 261.5 Hz), 113.3, 53.5. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -58.4 (s). Mass Spectrometry:

HRMS (ESI-TOF) (m/z): calcd for $C_8H_7ClF_3N_2O_3$ ($[M + H]^+$), 271.0092, found, 271.0095.



R = CO₂Me

***N*-(2,6-Dichloro-4-(trifluoromethoxy)pyridin-3-yl)acetamide (9h)**

5 A solution of *N*-(2,6-dichloropyridin-3-yl)-*N*-hydroxyacetamide (**8h**) (50.0 mg, 0.226 mmol) and Togni reagent I (89.5 mg, 0.271 mmol, 1.20 equiv) in CH₂Cl₂ (2.26 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (2.26 mL, 0.100 M) and the

10 reaction mixture was stirred at 120 °C for 22 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (17:3 (v/v)) for development (prep TLC was developed five times) followed by recrystallization from Et₂O:hexanes. The purification afforded the title compound as a 1.4:1 mixture of atropisomers (45.8

15 mg, 0.158 mmol, 70% yield). The products could not readily be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Data for the mixture of **9h**: white solid; R_f = 0.48 and 0.59 (EtOAc:hexanes 2:3 (v/v)). ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 7.36 (s, 1H), 7.24 (q, *J* = 1.8 Hz, 1H), 6.91 (br. s, 1H), 6.89 (br. s, 1H), 2.23 (s, 3H), 2.22 (s, 3H). ¹³C NMR (125

20 MHz, CDCl₃, 25 °C, δ): 168.3, 153.9, 151.8, 149.4, 149.1, 146.8, 145.9, 123.1, 122.4, 120.0 (q, *J* = 262.1 Hz), 119.9 (q, *J* = 263.1 Hz), 119.5, 113.7, 23.1. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.8 (s), -57.9 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for

25 C₈H₆Cl₂F₃N₂O₂ ($[M + H]^+$), 288.9753, found, 288.9756.

***N*-(6-Methoxy-4-methyl-2-(trifluoromethoxy)pyridin-3-yl)acetamide**

(**9i**): A solution of *N*-hydroxy-*N*-(6-methoxy-4-methylpyridin-3-yl)acetamide (**8i**) (50.0 mg, 0.255 mmol) and Togni reagent I (101 mg, 0.306 mmol, 1.20 equiv) in CH₂Cl₂ (2.55 mL, 0.100 M) was stirred at

30

23 °C under N₂ atmosphere for 18 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed five times). The purification afforded the title compound as a white solid (54.5 mg, 0.206 mmol, 81% yield). R_f = 0.63 (EtOAc:hexanes 3:2 (v/v)). NMR Spectroscopy (at rt, a mixture of rotamers was observed: ¹H NMR (400 MHz, CDCl₃, 60 °C, δ): 6.89 (br. s, 1H), 6.49 (br. s, 1H), 3.86 (s, 3H), 2.20 (br. s, 3H), 2.14 (br. s, 3H). ¹³C NMR (100 MHz, CDCl₃, 60 °C, δ): 169.3, 161.0, 152.1, 150.1, 120.4 (q, *J* = 260.2 Hz), 113.9, 109.2, 54.0, 23.0, 18.3. ¹⁹F NMR (376 MHz, CDCl₃, 60 °C, δ): -56.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₁₂F₃N₂O₃ ([M + H]⁺), 265.0795, found, 265.0801.

***N*-(6-Methyl-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9j)**

A solution of *N*-hydroxy-*N*-(6-methylpyridin-3-yl)acetamide (**8j**) (50.0 mg, 0.301 mmol) and Togni reagent I (119.2 mg, 0.361 mmol, 1.20 equiv) in CH₂Cl₂ (3.01 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 21 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (3.01 mL, 0.100 M) and the reaction mixture was stirred at 120 °C for 15 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (4:1 (v/v)) for development (prep TLC was developed four times). The purification afforded the title compound as a white solid (35.8 mg, 0.153 mmol, 51% yield). R_f = 0.24 (EtOAc:hexanes 4:1 (v/v)). ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.57 (d, *J* = 8.28 Hz, 1H), 7.39 (br. s, 1H), 7.02 (d, *J* = 8.28 Hz, 1H), 2.44 (s, 3H), 2.22 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 60 °C, δ): 168.8, 151.1, 144.7, 130.5, 121.6, 121.1, 120.2 (q, *J* = 261.0 Hz), 24.8, 23.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.1 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₉H₁₀F₃N₂O₂ ([M + H]⁺), 235.0689, found, 235.0690.

Methyl (5-(2,4-difluorophenyl)-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)carbamate (9k):

A solution of methyl (5-(2,4-difluorophenyl)-6-methoxypyridin-3-yl)(hydroxy)carbamate (**8k**) (50.0 mg, 0.161 mmol) and Togni reagent I (63.8 mg, 0.193 mmol, 1.20 equiv) in CH₂Cl₂ (1.58 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 15 h. The reaction mixture was purified

by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (19:1 (v/v)) for development (prep TLC was developed 3x). The purification afforded the title compound as a white solid (46.6 mg, 0.123 mmol, 77% yield). $R_f = 0.60$ (EtOAc:hexanes 1:4 (v/v)).

5 ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.38 (br. s., 1H), 7.35 (td, $J = 8.41, 6.53$ Hz, 1H), 6.97–6.85 (m, 2H), 6.65 (br. s, 1H), 3.88 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 163.0 (dd, $J = 248.1$ Hz, $J = 11.6$ Hz), 160.2 (dd, $J = 249.4$ Hz, $J = 11.5$ Hz), 154.7, 154.0, 142.8, 134.3, 132.6 (m), 120.3 (q, $J = 261.0$ Hz), 119.4 (dd, $J = 15.3$ Hz, $J = 3.8$ Hz), 116.2, 115.6, 111.4 (dd, $J = 21.2$ Hz, $J = 3.1$ Hz), 104.3 (t, $J = 25.5$ Hz), 54.5, 52.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s), -110.3 (s), -110.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{15}\text{H}_{12}\text{F}_5\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 379.0712, found, 379.0719.

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Methyl (6-(4-(tert-butyl)phenoxy)-2-(trifluoromethoxy)pyridin-3-yl)carbamate (91): A solution of methyl (6-(4-(tert-butyl)phenoxy)pyridin-3-yl)(hydroxy)carbamate (81) (50.0 mg, 0.158 mmol) and Togni reagent I (62.9 mg, 0.190 mmol, 1.20 equiv) in

20 CH_2Cl_2 (1.58 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 16 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (19:1 (v/v)) for development (prep TLC was developed four times). The purification afforded the title compound as a colorless oil (38.1 mg, 0.0991 mmol, 63% yield). $R_f = 0.57$

25 (EtOAc:hexanes 1:4 (v/v)). ^1H NMR (400 MHz, CDCl_3 , 25 °C, δ): 8.43 (br. s, 1H), 7.45–7.33 (m, 2H), 7.12–7.00 (m, 2H), 6.71 (app. d, $J = 8.8$ Hz, 2H), 3.80 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 156.7, 153.9, 151.6, 147.9, 143.1, 132.9, 126.6, 120.2, 120.1 (q, $J = 261.6$ Hz), 118.4, 108.3, 52.9, 34.6, 31.6. ^{19}F NMR (376 MHz,

30 CDCl_3 , 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{18}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 385.1370, found, 385.1375.

Methyl (5-(5-formylfuran-2-yl)-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)carbamate (9m): A solution of methyl (5-(5-formylfuran-

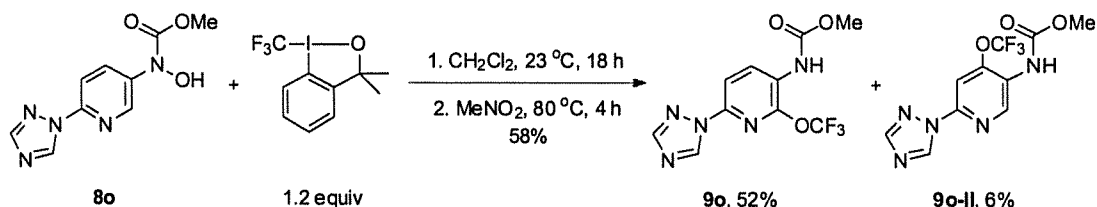
35 2-yl)-6-methoxypyridin-3-yl)(hydroxy)carbamate (8m) (31.6 mg, 0.108 mmol) and Togni reagent I (42.9 mg, 0.130 mmol, 1.20 equiv) in

CH₂Cl₂ (1.08 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 16 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as an off-white solid (24.8 mg, 0.0688 mmol, 64% yield). *R_f* = 0.50 (EtOAc:hexanes 3:7 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.70 (s, 1H), 8.94 (br. s, 1H), 7.32 (d, *J* = 3.44 Hz, 1H), 7.13 (d, *J* = 3.44 Hz, 1H), 6.68 (br. s, 1H), 4.03 (s, 3H), 3.83 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 177.9, 154.0, 153.9, 153.2, 152.0, 143.2, 130.2, 122.4, 120.1 (q, *J* = 261.8 Hz), 116.7, 113.1, 110.6, 54.7, 53.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₄H₁₂F₃N₂O₆ ([M + H]⁺), 361.0642, found, 361.0643.

15 N-(6-(1H-Pyrazol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9n): A solution of *N*-(6-(1H-pyrazol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8n**) (50.0 mg, 0.229 mmol) and Togni reagent I (90.8 mg, 0.275 mmol, 1.20 equiv) in CH₂Cl₂ (2.29 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 18 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (9:1 (v/v)) for development (prep TLC was developed three times). The purification afforded the title compound as a white solid (58.0 mg, 0.203 mmol, 89% yield). *R_f* = 0.30 (EtOAc:hexanes 3:7 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.85 (d, *J* = 8.60 Hz, 1H), 8.34 (d, *J* = 2.58 Hz, 1H), 7.83 (d, *J* = 9.03 Hz, 1H), 7.70 (s, 1H), 7.43 (br. s, 1H), 6.43 (m, 1H), 2.25 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.6, 143.9, 143.5, 142.5, 133.2, 127.2, 120.9, 120.2 (q, *J* = 262.1 Hz), 109.8, 108.2, 24.8. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₁H₁₀F₃N₄O₂ ([M + H]⁺), 287.0750, found, 275.0754.

Methyl (6-(1H-1,2,4-triazol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)carbamate (9o) and methyl (6-(1H-1,2,4-triazol-1-yl)-4-(trifluoromethoxy)pyridin-3-yl)carbamate (9o-II)

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A solution of methyl (6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl)(hydroxy)carbamate (**8o**) (100 mg, 0.425 mmol) and Togni reagent I (168 mg, 0.510 mmol, 1.20 equiv) in CH₂Cl₂ (4.25 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (4.25 mL, 0.100 M) and the reaction mixture was stirred at 80 °C for 4 h. The reaction mixture was placed in the freezer. The solid was filtered and washed with hexanes. Filtration afforded **2o** (61.7 mg, 0.203 mmol, 48% yield) as a slightly brown solid. The filtrate was concentrated *in vacuo* and purified by preparative TLC (thickness: 1 mm) using hexanes:Et₂O (7:3 (v/v)) for development (prep TLC was developed six times). The purification afforded **9o** (3.7 mg, 0.0122 mmol, 3%) and 9.3 mg (0.0307 mmol, 7% yield) of a 1:4.6 mixture of **9o** and **9o-II**. The combined reaction yield was 58%. The characterization data for **9o-II** was obtained by further purification of the mixture by preparative TLC using hexanes:EtOAc (7:3 (v/v)) for development (prep TLC was developed six times). Data for **9o**: white solid; $R_f = 0.41$ (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.95 (s, 1H), 8.75 (d, $J = 7.93$ Hz, 1H), 8.08 (s, 1H), 7.80 (d, $J = 8.54$ Hz, 1H), 7.00 (br. s, 1H), 3.85 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 153.5, 153.2, 143.2, 141.4, 140.6, 131.4, 123.0, 120.1 (q, $J = 262.8$ Hz), 110.9, 53.2. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₉F₃N₅O₃ ([M + H]⁺), 304.0652, found, 304.0658. Data for **9o-II**: white solid; $R_f = 0.27$ (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.30 (br. s, 1H), 9.14 (s, 1H), 8.08 (s, 1H), 7.81 (s, 1H), 6.88 (br. s, 1H), 3.83 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 153.3, 153.0, 145.9, 145.3, 141.8, 141.2, 126.1, 120.3 (q, $J = 262.0$ Hz), 102.7, 53.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.3 (d). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₀H₉F₃N₅O₃ ([M + H]⁺), 304.0652, found, 304.0657.

***N*-(6-(1*H*-Benzo[*d*]imidazol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9p):** A solution of *N*-(6-(1*H*-benzo[*d*]imidazol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8p**) (100 mg, 0.373 mmol) and Togni reagent I (148 mg, 0.448 mmol, 1.20 equiv) in CH₂Cl₂ (3.73 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 19 h. The reaction mixture was concentrated *in vacuo* (to about 10% initial volume) and the residue was triturated with hexanes. The purification afforded the title compound as a beige solid (117 mg, 0.348 mmol, 93% yield). *R_f* = 0.21 (EtOAc:hexanes 4:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.00 (d, *J* = 8.60 Hz, 1H), 8.52 (s, 1H), 8.04 (d, *J* = 8.17 Hz, 1H), 7.86 (d, *J* = 7.74 Hz, 1H), 7.60 (br. s, 1H), 7.49 (d, *J* = 8.60 Hz, 1H), 7.43-7.35 (m, 2H), 2.31 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.9, 144.3, 144.2, 141.8, 140.9, 133.1, 131.9, 124.8, 123.9, 121.5, 120.7, 120.2 (q, *J* = 262.4 Hz), 112.8, 111.6, 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₅H₁₂F₃N₄O₂ ([*M* + *H*]⁺), 337.0907, found, 337.0910.

***N*-(6-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9q):** A solution of *N*-(6-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8q**) (100 mg, 0.371 mmol) and Togni reagent I (147 mg, 0.445 mmol, 1.20 equiv) in CH₂Cl₂ (3.71 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 18 h. The reaction mixture was then stirred at 50 °C for 4h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with hexanes. The purification afforded the title compound as a slightly yellow solid (108 mg, 0.319 mmol, 86% yield). *R_f* = 0.37 (EtOAc:hexanes 2:3 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, (CD₃)₂SO, 25 °C, δ): 10.04 (s, 1H), 8.73 (d, *J* = 8.53 Hz, 1H), 8.42-8.32 (m, 1H), 8.30-8.18 (m, 2H), 7.77 (t, *J* = 7.65 Hz, 1H), 7.63-7.51 (m, 1H), 2.18 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 169.4, 146.0, 144.9, 142.7, 136.8, 130.5, 129.6, 125.5, 122.5, 119.9, 119.8 (q, *J* = 260.0 Hz), 113.0, 112.6, 23.6. ¹⁹F NMR (376 MHz, (CD₃)₂SO, 25 °C, δ): -57.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₄H₁₁F₃N₅O₂ ([*M* + *H*]⁺), 338.0859, found, 338.0860.

***N*-(6-(5-Fluoro-1*H*-indol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9r):** A solution of *N*-(6-(5-fluoro-1*H*-indol-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8r**) (50.0 mg, 0.175 mmol) and Togni reagent I (69.3 mg, 0.210 mmol, 1.20 equiv) in CH₂Cl₂ (1.75 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 15 h. The reaction mixture was concentrated *in vacuo*. The crude residue was triturated with hexanes. The crude residue was purified by flash chromatography eluting with EtOAc:hexanes (3:17 to 1:1(v/v)). The purification afforded the title compound as a yellow solid (45.0 mg, 0.127 mmol, 73% yield). *R*_f = 0.36 (EtOAc:hexanes 2:3 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 8.89 (d, *J* = 8.78 Hz, 1H), 8.20 (dd, *J* = 9.03, 4.52 Hz, 1H), 7.64 (d, *J* = 3.51 Hz, 1H), 7.35 (br. s, 1H), 7.32 (d, *J* = 8.78 Hz, 2H), 7.28 (dd, *J* = 9.29, 2.51 Hz, 1H), 7.04 (td, *J* = 9.10, 2.64 Hz, 1H), 6.67 (d, *J* = 3.51 Hz, 1H), 2.29 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.7, 158.8 (d, *J* = 236.1 Hz), 144.8, 143.9, 133.0, 131.6, 131.1 (d, *J* = 10.0 Hz), 126.9, 120.2 (q, *J* = 262.1 Hz), 119.6, 114.4 (d, *J* = 9.1 Hz), 111.7 (d, *J* = 25.2 Hz), 111.0, 106.3 (m), 106.2, 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.4 (s), -122.9 (m). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₆H₁₂F₄N₃O₂ ([*M* + *H*]⁺), 354.0860, found, 354.0865.

***N*-(6-(5-Bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9s):** A solution of *N*-(6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8s**) (50.0 mg, 0.144 mmol) and Togni reagent I (57.1 mg, 0.172 mmol, 1.20 equiv) in CH₂Cl₂ (1.44 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 20 h. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by flash chromatography eluting with EtOAc:hexanes (1:19 to 2:3(v/v)). The crude product was triturated with hexanes. The purification afforded the title compound as a white solid (38.2 mg, 0.0920 mmol, 64% yield). *R*_f = 0.39 (EtOAc:hexanes 3:7 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.89 (d, *J* = 9.03 Hz, 1H), 8.81 (d, *J* = 8.60 Hz, 1H), 8.41 (d, *J* = 2.15 Hz, 1H), 8.19 (d, *J* = 3.87 Hz, 1H), 8.05 (d, *J* = 2.15 Hz, 1H), 7.34 (br. s, 1H), 6.57 (d, *J* = 3.87 Hz, 1H), 2.28 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.5, 145.8, 144.0, 143.5, 142.6, 133.0, 131.4, 127.5, 125.0, 120.2 (q, *J* = 261.8 Hz), 120.0, 113.6,

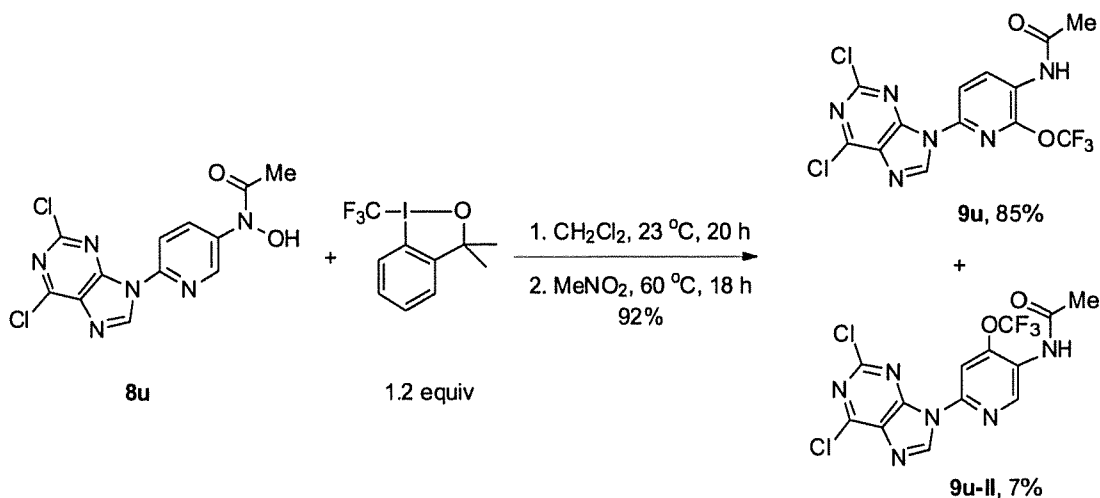
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112.7, 102.6, 24.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{15}\text{H}_{11}\text{BrF}_3\text{N}_4\text{O}_2$ ($[\text{M} + \text{H}]^+$), 415.0012, found, 415.0018.

5 ***N*-(6-(2-(Thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9t)**

A solution of *N*-hydroxy-*N*-(6-(2-(thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)pyridin-3-yl)acetamide (**8t**) (100 mg, 0.285 mmol) and Togni reagent I (113 mg, 0.188 mmol, 1.20 equiv) in CH_2Cl_2 (2.85 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 20 h. The reaction mixture was then stirred at 50 °C for 4h. The reaction mixture was concentrated *in vacuo* and the residue was triturated with hexanes. The purification afforded the title compound as a beige solid (113 mg, 0.270 mmol, 95% yield). $R_f = 0.42$ (EtOAc). ^1H NMR (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.00 (s, 1H), 9.05 (s, 1H), 8.64 (d, $J = 8.60$ Hz, 1H), 8.48 (s, 1H), 7.82 (d, $J = 7.31$ Hz, 1H), 7.55 (d, $J = 8.17$ Hz, 1H), 7.47 (d, $J = 7.31$ Hz, 1H), 7.40–7.30 (m, 2H), 2.18 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 169.5, 154.8, 146.6, 145.8, 145.0, 142.3, 141.2, 135.2, 135.1, 124.1, 123.5, 123.4, 122.7, 119.8, 119.6, 119.5 (q, $J = 260.0$ Hz), 110.8, 23.6. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): -57.2 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_5\text{O}_2\text{S}$ ($[\text{M} + \text{H}]^+$), 420.0737, found, 420.0738.

25 ***N*-(6-(2,6-Dichloro-9*H*-purin-9-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9u) and *N*-(6-(2,6-dichloro-9*H*-purin-9-yl)-4-(trifluoromethoxy)pyridin-3-yl)acetamide (9u-II)**



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A solution of *N*-(6-(2,6-dichloro-9*H*-purin-9-yl)pyridin-3-yl)-*N*-hydroxyacetamide (**8u**) (38.4 mg, 0.113 mmol) and Togni reagent I (44.9 mg, 0.136 mmol, 1.20 equiv) in CH₂Cl₂ (1.13 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 20 h. The reaction mixture
5 was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (1.13 mL, 0.100 M) and the reaction mixture was stirred at 60 °C for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (1:1 (v/v)) for development (prep TLC was developed three times). The
10 purification afforded **9u** (39.0 mg, 0.0968 mmol, 85% yield) and **9u-II** (3.3 mg, 0.0081 mmol, 7% yield). Data for **9u**: white solid; *R_f* = 0.44 (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.11 (d, *J* = 8.60 Hz, 1H), 8.94 (s, 1H), 8.47 (d, *J* = 8.60 Hz, 1H), 7.53 (s, 1H), 2.31 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C,
15 δ): 168.8, 153.9, 152.6, 151.7, 143.6, 143.5, 138.4, 133.1, 132.3, 123.2, 120.1 (q, *J* = 263.4 Hz), 113.1, 24.9. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₃H₈Cl₂F₃N₆O₂ ([M + H]⁺), 407.0032, found, 407.0037. Data for **9u-II**: white solid; *R_f* = 0.22 (EtOAc:hexanes 1:1 (v/v)). NMR
20 Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.60 (s, 1H), 9.20 (s, 1H), 8.67 (d, *J* = 1.72 Hz, 1H), 7.39 (br. s, 1H), 2.33 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.4, 153.9, 152.7, 151.6, 145.8, 143.9, 143.3, 142.9, 132.4, 126.2, 120.4 (q, *J* = 262.3 Hz), 104.6, 24.7. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.9 (s). Mass Spectrometry:
25 HRMS (ESI-TOF) (*m/z*): calcd for C₁₃H₈Cl₂F₃N₆O₂ ([M + H]⁺), 407.0032, found, 407.0035.

Ethyl (E)-3-(4-fluoro-3-(2-methoxy-5-((methoxycarbonyl)amino)-6-(trifluoromethoxy)pyridin-3-yl)phenyl)acrylate (9v)

30 A solution of ethyl (*E*)-3-(4-fluoro-3-(5-(hydroxy(methoxycarbonyl)amino)-2-methoxypyridin-3-yl)phenyl) acrylate (**8v**) (46.1 mg, 0.118 mmol) in CH₂Cl₂ (11.3 mL) was cooled to 4 °C. A solution of Togni reagent I (46.9 mg, 0.142 mmol, 1.20 equiv) in CH₂Cl₂ (0.500 mL) was then added dropwise and the reaction mixture was stirred at
35 4 °C for 29 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (9:1 (v/v)) for development (prep TLC was developed

four times). The purification afforded the title compound as a white solid (28.5 mg, 0.0622 mmol, 53% yield). $R_f = 0.62$ (EtOAc:hexanes 3:7 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.44 (br. s, 1H), 7.66 (d, $J = 15.92$ Hz, 1H), 7.57–7.50 (m, 2H), 7.15 (t, $J = 9.03$ Hz, 1H), 6.68 (br. s, 1H), 6.38 (d, $J = 15.92$ Hz, 1H), 4.26 (q, $J = 6.88$ Hz, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 1.33 (t, $J = 7.10$ Hz, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 166.9, 161.1 (d, $J = 252.7$ Hz), 154.6, 154.0, 143.2, 134.2, 131.7 (d, $J = 2.6$ Hz), 130.9 (d, $J = 3.3$ Hz), 129.6 (d, $J = 8.7$ Hz), 124.0 ($J = 15.6$ Hz), 120.3 (q, $J = 261.5$ Hz), 118.6 (d, $J = 1.8$ Hz), 116.7, 116.6, 116.3, 115.7, 60.7, 54.5, 52.9, 14.4. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s), -111.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{20}\text{H}_{19}\text{F}_4\text{N}_2\text{O}_6$ ($[\text{M} + \text{H}]^+$), 459.1174, found, 459.1184.

15 **Methyl 4-((4-(2-methoxy-5-(methoxycarbonyl)amino)-6-(trifluoromethoxy)pyridin-3-yl)phenyl)ethynyl)benzoate (9w)**

A solution of methyl 4-((4-(5-(hydroxy(methoxycarbonyl)amino)-2-methoxypyridin-3-yl)phenyl)ethynyl)benzoate (**8w**) (50.0 mg, 0.116 mmol) and Togni reagent I (45.9 mg, 0.139 mmol, 1.20 equiv) in CH_2Cl_2 (1.16 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 18 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using CH_2Cl_2 for development (prep TLC was developed twice). The purification afforded the title compound as a white solid (39.6 mg, 0.0791 mmol, 68% yield). $R_f = 0.27$ (CH_2Cl_2). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.51 (br. s, 1H), 8.03 (d, $J = 8.17$ Hz, 2H), 7.68–7.50 (m, 6H), 6.68 (br. s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 166.7, 154.1, 142.3, 135.8, 133.1, 131.8, 131.7, 129.7, 129.6, 129.3, 128.1, 122.2, 121.8 (q, $J = 260.8$ Hz), 121.3, 119.5, 116.7, 92.4, 89.5, 54.4, 52.9, 52.4. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{25}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_6$ ($[\text{M} + \text{H}]^+$), 501.1268, found, 501.1273.

35 **N-(6-(((8R,9S,13S,14S)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)oxy)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (9x)**: A solution of N-hydroxy-N-(6-(((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-

decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)pyridin-3-yl) acetamide (**8x**) (66.0 mg, 0.157 mmol) and Togni reagent I (62.1 mg, 0.188 mmol, 1.20 equiv) in CH₂Cl₂ (1.57 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 20 h. The reaction mixture was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed three times). The purification afforded the title compound as a white foamy solid (54.0 mg, 0.111 mmol, 71% yield). *R_f* = 0.49 (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.62 (d, *J* = 8.61 Hz, 1H), 7.37 (s, 1H), 7.27 (d, *J* = 8.37 Hz, 1H), 6.91 (dd, *J* = 8.39, 2.37 Hz, 1H), 6.88 (d, *J* = 2.15 Hz, 1H), 6.68 (d, *J* = 9.03 Hz, 1H), 2.92–2.86 (m, 2H), 2.51 (dd, *J* = 18.93, 8.60 Hz, 1H), 2.44–2.37 (m, 1H), 2.30 (td, *J* = 11.19, 3.44 Hz, 1H), 2.22 (s, 3H), 2.18–2.11 (m, 1H), 2.09–2.04 (m, 1H), 2.04–1.99 (m, 1H), 1.96 (dt, *J* = 12.48, 3.01 Hz, 1H), 1.67–1.59 (m, 2H), 1.59–1.42 (m, 4H), 0.92 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 221.0, 168.6, 156.9, 151.7, 143.5, 138.2, 136.5, 134.7, 126.6, 120.8, 120.1 (q, *J* = 261.5 Hz), 118.1, 118.0, 108.1, 50.6, 48.1, 44.2, 38.2, 36.0, 31.7, 29.5, 26.5, 25.9, 24.6, 21.7, 14.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.4 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₂₆H₂₈F₃N₂O₄ ([*M* + *H*]⁺), 489.1996, found, 489.2004.

***N*-(6-((6*R*,12*aR*)-6-(Benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1,4-dioxo-1,3,4,6,12,12*a*-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indol-7(2*H*)-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (**9y**)**

A solution of *N*-(6-((6*R*,12*aR*)-6-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-1,4-dioxo-1,3,4,6,12,12*a*-hexahydropyrazino[1',2':1,6]pyrido[3,4-*b*]indol-7(2*H*)-yl)-2-(trifluoromethoxy)pyridin-3-yl)acetamide (**8y**) (50.0 mg, 0.0927 mmol) in CH₂Cl₂ (8.77 mL) was cooled to 4 °C. A solution of Togni reagent I (39.3 mg, 0.119 mmol, 1.20 equiv) in CH₂Cl₂ (0.500 mL) was then added dropwise and the reaction mixture was stirred at 4 °C for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (1:4 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as a white solid (37.3 mg, 0.0614 mmol, 66% yield). *R_f* = 0.48 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 9.99 (s, 1H), 8.53

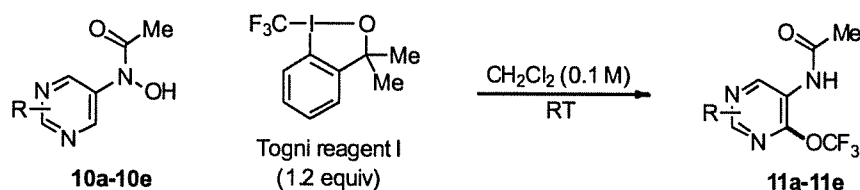
164

(d, $J = 8.53$ Hz, 1H), 7.80–7.72 (m, 1H), 7.42–7.36 (m, 1H), 7.34 (d, $J = 8.53$ Hz, 1H), 7.25–7.19 (m, 2H), 6.59 (s, 1H), 6.51 (d, $J = 8.03$ Hz, 1H), 6.32 (d, $J = 1.76$ Hz, 1H), 6.23 (dd, $J = 8.03, 1.76$ Hz, 1H), 5.83 (s, 2H), 4.55 (dd, $J = 11.54, 4.77$ Hz, 1H), 4.24–4.15 (m, 1H), 3.92 (d, $J = 17.32$ Hz, 1H), 3.65 (dd, $J = 16.19, 4.64$ Hz, 1H), 3.12 (dd, $J = 15.81, 12.30$ Hz, 1H), 2.90 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 169.4, 166.9, 166.3, 146.7, 146.0, 145.4, 141.7, 136.4, 136.0, 134.9, 134.2, 126.1, 123.4, 122.3, 121.3, 120.7, 119.7 (q, $J = 262.6$ Hz), 119.1, 118.4, 110.4, 109.9, 107.5, 107.4, 100.9, 54.7, 53.9, 51.4, 32.8, 23.6, 23.2. ^{19}F NMR (376 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{30}\text{H}_{25}\text{F}_3\text{N}_5\text{O}_6$ ($[\text{M} + \text{H}]^+$), 608.1751, found, 608.1761.

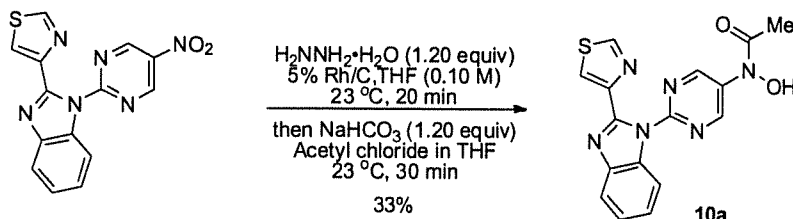
Example 8. Trifluoromethoxylation of Pyrimidine Substrates

To probe the applicability of the trifluoromethoxylation reaction to other heteroarenes, pyrimidines substituted with benzimidazolyl (10a), indolyl (10b), methoxy (10c), phenoxy (10d), or estronyl (10e) groups were examined (Scheme 8). These substrates were trifluoromethoxylated to afford the corresponding desired products (11a-11e) in good yields. Products 11a-11e are shown in Figure 3.

Scheme 8.



N-Hydroxy-*N*-(2-(2-(thiazol-4-yl)-1*H*-benzo[*d*]imidazol-1-yl)pyrimidin-5-yl)acetamide (10a)



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Under N_2 atmosphere, 4-(1*H*-benzo[*d*]imidazol-2-yl)thiazole (362 mg, 1.80 mmol, 1.20 equiv) was dissolved in THF (7.50 mL, 0.240 M) and stirred at 0 °C. NaH (72.0 mg, 1.80 mmol, 1.20 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, a solution of 2-chloro-5-nitropyrimidine (239 mg, 1.50 mmol, 1.00 equiv) in THF

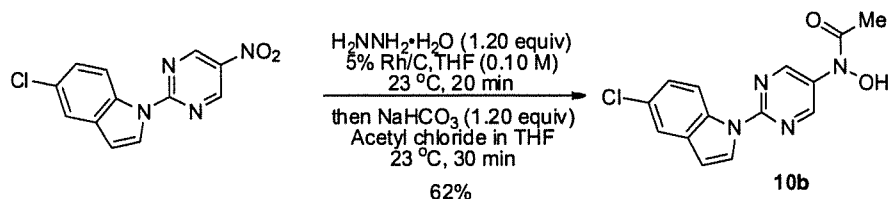
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(2.50 mL, 0.600 M) was added and then the reaction mixture was slowly warmed up to 50 °C for 12 h. The reaction mixture was poured to water (100 mL), extracted with EtOAc, washed with brine. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*.

5 The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (369 mg, 1.14 mmol, 76% yield). $R_f = 0.33$ (hexanes:EtOAc 2:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.46 (s, 2H), 8.70 (d, $J = 2.15$ Hz, 1H), 8.20 (s, 1H),
10 8.18–8.13 (m, 1H), 7.89 (dd, $J = 6.45, 2.58$ Hz, 1H), 7.48–7.43 (m, 2H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 159.0, 154.5, 154.4, 152.7, 147.6, 147.3, 143.0, 139.7, 134.1, 125.7, 125.2, 121.1, 120.6, 113.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₄H₉N₆O₂S ([M + H]⁺), 325.0502, found, 325.0506. Under N₂ atmosphere, a suspension of
15 4-(1-(5-nitropyrimidin-2-yl)-1*H*-benzo[d]imidazol-2-yl)thiazole (200 mg, 0.620 mmol, 1.00 equiv) and 5% Rh/C (7.12 mg, 0.60 mol% Rh) in THF (6.20 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (37.0 mg, 0.740 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (62.2 mg, 0.740 mmol,
20 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (58.1 mg, 0.740 mmol, 1.20 equiv) in THF (6.20 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then poured to water (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*.

25 The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 (v/v)), to afford the title compound as a yellow gum (72 mg, 0.204 mmol, 33% yield). $R_f = 0.13$ (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 11.23 (s, 1H), 9.21 (s, 2H), 9.00 (br. s., 1H), 8.49 (d, $J = 1.72$ Hz, 1H), 7.81 (dd,
30 $J = 6.45, 1.72$ Hz, 1H), 7.74–7.65 (m, 1H), 7.41–7.32 (m, 2H), 2.32 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, 25 °C, δ): 171.5, 154.5, 151.2, 148.0, 146.8, 146.3, 142.3, 135.4, 134.8, 124.3, 123.6, 122.0, 119.6, 111.9, 22.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₆H₁₃N₆O₂S ([M + H]⁺), 353.0815, found, 353.0817.

***N*-(2-(5-Chloro-1*H*-indol-1-yl)pyrimidin-5-yl)-*N*-hydroxyacetamide
(10b)**

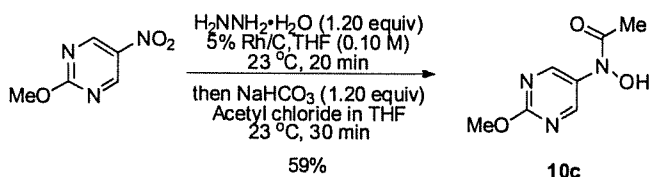


Under N_2 atmosphere, 5-chloro-1*H*-indole (0.570 g, 3.76 mmol, 1.20 equiv) was dissolved in DMF (10 mL, 0.376 M) and stirred at 0 °C. NaH (0.15g, 3.76 mmol, 1.20 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, a solution of 2-chloro-5-nitropyrimidine (0.500 g, 3.13 mmol, 1.00 equiv) in DMF (5.6 mL, 0.559 M) was added and then the reaction mixture was slowly warmed up to 50 °C for 12 h. The reaction mixture was poured to a solution of LiCl (100 mL), extracted with EtOAc. The combined organic layers washed with brine, dried (MgSO_4), filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (10:1 to 5:1 (v/v)), to afford the title compound as a yellow solid (0.710 g, 2.58 mmol, 83% yield). $R_f = 0.76$ (hexanes:EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.43 (s, 2H), 8.69 (d, $J = 8.60$ Hz, 1H), 8.27 (d, $J = 3.87$ Hz, 1H), 7.58 (d, $J = 1.72$ Hz, 1H), 7.33 (dd, $J = 8.82, 1.94$ Hz, 1H), 6.73 (d, $J = 3.01$ Hz, 1H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 158.7, 154.8, 138.2, 133.9, 133.3, 129.6, 127.5, 125.0, 121.0, 118.1, 109.7. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{12}\text{H}_{11}\text{ClN}_5\text{O}_2$ ($[\text{M} + \text{NH}_4]^+$), 292.0596, found, 292.0599. Under N_2 atmosphere, a suspension of 5-chloro-1-(5-nitropyrimidin-2-yl)-1*H*-indole (300 mg, 1.09 mmol, 1.00 equiv) and 5% Rh/C (12.6 mg, 0.60 mol% Rh) in THF (10.9 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (65.6 mg, 1.31 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO_3 (110 mg, 1.31 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (103 mg, 1.31 mmol, 1.20 equiv) in THF (10.9 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then poured to water (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was recrystallized from hexanes/EtOAc, to afford the title compound as a

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yellow solid (205 mg, 0.677 mmol, 62% yield). $R_f = 0.14$ (hexanes:EtOAc 2:1 (v/v)). $^1\text{H NMR}$ (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 11.10 (s, 1H), 9.13 (s, 2H), 8.69 (d, $J = 9.03$ Hz, 1H), 8.30 (d, $J = 3.87$ Hz, 1H), 7.72 (d, $J = 2.15$ Hz, 1H), 7.34 (dd, $J = 8.60, 2.15$ Hz, 1H), 6.78 (d, $J = 3.87$ Hz, 1H), 2.28 (s, 3H). $^{13}\text{C NMR}$ (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 171.0, 152.5, 148.9, 133.1, 133.0, 132.0, 127.3, 126.4, 123.4, 120.2, 117.0, 106.1, 21.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{14}\text{H}_{12}\text{ClN}_4\text{O}_2$ ($[\text{M} + \text{H}]^+$), 303.0643, found, 303.0645.

***N*-Hydroxy-*N*-(2-methoxypyrimidin-5-yl)acetamide (10c)**



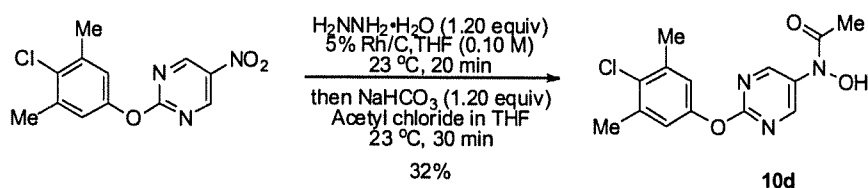
10

10c

Under N_2 atmosphere, a suspension of 2-methoxy-5-nitropyrimidine (180 mg, 1.16 mmol, 1.00 equiv) and 5% Rh/C (13.8 mg, 0.60 mol% Rh) in THF (11.6 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (69.7 mg, 1.39 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO_3 (117 mg, 1.39 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (109 mg, 1.39 mmol, 1.20 equiv) in THF (11.6 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then filtered through a short pad of celite. The celite was washed with EtOAc. The combined organic solution was concentrated in vacuo. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:1 to 0:1 (v/v)), to afford the title compound as a gray gum (125 mg, 0.682 mmol, 59% yield). $R_f = 0.33$ (EtOAc). NMR Spectroscopy: $^1\text{H NMR}$ (700 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 10.93 (br. s, 1H), 8.81 (s, 2H), 3.91 (s, 3H), 2.22 (br. s., 3H). $^{13}\text{C NMR}$ (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 170.7, 161.8, 151.0, 131.8, 54.9, 21.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_7\text{H}_{10}\text{N}_3\text{O}_3$ ($[\text{M} + \text{H}]^+$), 184.0717, found, 184.0718.

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***N*-(2-(4-Chloro-3,5-dimethylphenoxy)pyrimidin-5-yl)-*N*-hydroxyacetamide (10d)**

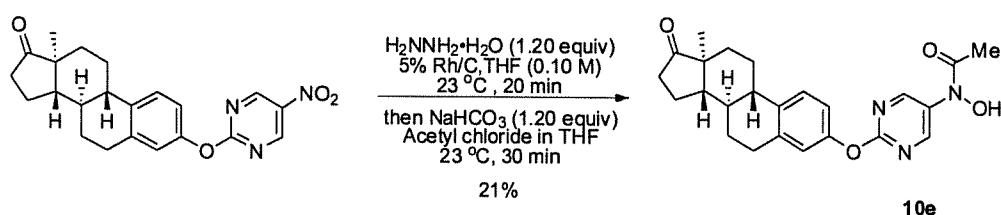


Under N₂ atmosphere, 4-chloro-3,5-dimethylphenol (240 mg, 1.52 mmol, 1.20 equiv) was dissolved in THF (8.40 mL, 0.181 M) and stirred at 0 °C. NaH (60.8 mg, 1.52 mmol, 1.20 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, a solution of 2-chloro-5-nitropyrimidine (200 mg, 1.24 mmol, 1.00 equiv) in THF (4.00 mL, 0.310 M) was added and then the reaction mixture was slowly warmed to 50 °C for 12h. The reaction mixture was poured to water (100 mL), extracted with EtOAc, washed with brine. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (20:1 to 1:1 (v/v)), to afford the title compound as a yellow solid (288 mg, 1.03 mmol, 83% yield). R_f = 0.61 (hexanes:EtOAc 10:1 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 9.32 (s, 2H), 6.94 (s, 2H), 2.41 (s, 6H). ¹³C NMR (125 MHz, CDCl₃, 25 °C, δ): 167.1, 156.5, 149.9, 139.1, 138.4, 132.7, 121.1, 21.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₂H₁₁ClN₃O₃ ([M + H]⁺), 280.0483, found, 280.0483. Under N₂ atmosphere, a suspension of 2-(4-chloro-3,5-dimethylphenoxy)-5-nitropyrimidine (140 mg, 0.500 mmol, 1.00 equiv) and 5% Rh/C (5.70 mg, 0.60 mol% Rh) in THF (5.00 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (30.0 mg, 0.60 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min. NaHCO₃ (50.4 mg, 0.600 mmol, 1.20 equiv) was added, followed by dropwise addition of a solution of acetyl chloride (47.1 mg, 0.600 mmol, 1.20 equiv) in THF (5.00 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then poured to water (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (1:1 to 0 :1(v/v)), to afford the title compound as a yellow solid (49.1 mg, 0.160 mmol, 32% yield). R_f = 0.53 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.99 (br. s., H), 8.86 (s, 2H),

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7.08 (s, 2H), 2.33 (s, 6H), 2.23 (br. s., 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 170.9, 161.0, 151.0, 137.1, 133.0, 129.9, 121.6, 21.6, 20.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{14}\text{H}_{15}\text{ClN}_3\text{O}_3$ ($[\text{M} + \text{H}]^+$), 308.0802, found, 308.0797.

5 ***N*-Hydroxy-*N*-(2-(((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)pyrimidin-5-yl)acetamide (10e)**



Under N_2 atmosphere, estrone (200 mg, 0.740 mmol, 1.00 equiv) was dissolved in THF (3.70 mL, 0.200 M) and stirred at 0 °C. NaH (29.6 mg, 0.740 mmol, 1.00 equiv, 60 % dispersion in mineral oil) was added in portionwise. After 30 min, a solution of 2-chloro-5-nitropyrimidine (130 mg, 0.81 mmol, 1.10 equiv) in THF (1.30 mL, 0.623 M) was added and then the reaction mixture was slowly warmed to 50 °C for 12 h. The reaction mixture was poured to water (100 mL), extracted with EtOAc, washed with brine. The combined organic layers was dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (5:1 to 2:1 (v/v)), to afford the title compound as a yellow solid (235 mg, 0.597 mmol, 81% yield). R_f = 0.33 (hexanes:EtOAc 4:1 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.32 (s, 2H), 7.38 (d, J = 8.60 Hz, 1H), 6.97 (dd, J = 8.60, 2.15 Hz, 1H), 6.92 (d, J = 2.15 Hz, 1H), 2.97–2.91 (m, 2H), 2.51 (dd, J = 19.36, 8.60 Hz, 1H), 2.46–2.40 (m, 1H), 2.34 (td, J = 11.08, 4.09 Hz, 1H), 2.19–2.11 (m, 1H), 2.10–2.02 (m, 2H), 1.98 (dt, J = 12.80, 2.85 Hz, 1H), 1.68–1.57 (m, 3H), 1.57–1.46 (m, 3H), 0.92 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 220.8, 167.3, 156.4, 150.2, 138.9, 138.3, 127.0, 121.2, 118.5, 50.5, 48.0, 44.3, 38.0, 35.9, 31.6, 29.6, 26.4, 25.8, 21.7, 13.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}_4$ ($[\text{M} + \text{H}]^+$), 394.1761, found, 394.1758.

Under N_2 atmosphere, a suspension of (8*R*,9*S*,13*S*,14*S*)-13-methyl-3-((5-nitropyrimidin-2-yl)oxy)-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-

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cyclopenta[a]phenanthren-17-one (170 mg, 0.430 mmol, 1.00 equiv) and 5% Rh/C (4.90 mg, 0.60 mol% Rh) in THF (4.30 mL, 0.100 M) was stirred at 23 °C. Hydrazine monohydrate (26.0 mg, 0.52 mmol, 1.20 equiv) was added dropwise. The reaction mixture was stirred at 23 °C for 20 min.

5 NaHCO₃ (43.7 mg, 0.520 mmol, 1.20 equiv) was added, followed by dropwise addition of acetyl chloride (40.8 mg, 0.520 mmol, 1.20 equiv) in THF (4.30 mL, 0.120 M). The reaction mixture was stirred at 23 °C for 30 min and then poured to water (100 mL), extracted with EtOAc. The combined organic layers was dried (MgSO₄), filtered and

10 concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes:EtOAc (2:1 (v/v)), to afford the title compound as a yellow solid (38 mg, 0.0902 mmol, 21% yield). R_f = 0.50 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, (CD₃)₂SO, 25 °C, δ): 10.98 (br. s., 1H), 8.83 (s, 1H), 7.33 (d, J = 8.17 Hz, 1H), 6.93 (dd, J = 8.60, 2.58 Hz, 1H), 6.89 (d, J = 2.58 Hz, 1H),

15 2.88–2.84 (m, 2H) 2.45 (dd, J = 19.15, 8.39 Hz, 1H), 2.42–2.38 (m, 1H), 2.30–2.25 (m, 1H), 2.23 (br. s., 3H), 2.11–2.05 (m, 1H), 2.00–1.93 (m, 2H) 1.80–1.76 (m, 1H), 1.62–1.36 (m, 6H), 0.86 (s, 3H). ¹³C NMR (175 MHz, (CD₃)₂SO, δ): 219.7, 170.8, 161.3, 150.8, 138.0, 136.6,

20 132.8, 126.6, 121.2, 118.7, 49.6, 47.3, 43.6, 37.6, 35.4, 31.4, 29.0, 25.9, 25.4, 21.6, 21.2, 13.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₂₄H₂₈N₃O₄ ([M + H]⁺), 422.2074, found, 422.2074.

N-(2-(2-(Thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)-4-

(trifluoromethoxy) pyrimidin-5-yl)acetamide (11a): A solution of *N*-hydroxy-*N*-(2-(2-(thiazol-4-yl)-1H-benzo[d]imidazol-1-yl)pyrimidin-

25 5-yl)acetamide (10a) (52.0 mg, 0.148 mmol) and Togni reagent I (58.8 mg, 0.178 mmol, 1.20 equiv) in CH₂Cl₂ (1.48 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 22 h. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeNO₂ (1.48

30 mL, 0.100 M) and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (1:4 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as an off-white solid (45.9

35 mg, 0.109 mmol, 74% yield). R_f = 0.59 (EtOAc). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.70 (s, 1H), 8.66 (d, J = 2.15 Hz, 1H), 8.14 (d, J = 2.15 Hz, 1H), 7.97 (dd, J = 6.24, 3.23 Hz, 1H),

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7.86–7.82 (m, 1H), 7.80 (s, 1H), 7.42–7.36 (m, 2H), 2.23 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.8, 152.7, 152.1, 151.5, 149.4, 147.3, 147.1, 142.7, 134.6, 125.1, 124.4, 120.8, 120.1, 119.6, 119.5 (q, *J* = 265.7 Hz), 112.8, 24.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.0 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₇H₁₂F₃N₆O₂S ([M + H]⁺), 421.0689, found, 421.0693.

***N*-(2-(5-Chloro-1*H*-indol-1-yl)-4-(trifluoromethoxy)pyrimidin-5-yl)acetamide (11b):** A solution of *N*-(2-(5-chloro-1*H*-indol-1-yl)pyrimidin-5-yl)-*N*-hydroxyacetamide (10b) (50.0 mg, 0.165 mmol) and Togni reagent I (65.4 mg, 0.198 mmol, 1.20 equiv) in CH₂Cl₂ (16.5 mL, 0.010 M) was stirred at 23 °C under N₂ atmosphere for 24 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as an off-white solid (42.8 mg, 0.115 mmol, 70% yield). *R_f* = 0.61 (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.55 (s, 1H), 8.54 (d, *J* = 9.03 Hz, 1H), 8.13 (d, *J* = 3.44 Hz, 1H), 7.56 (d, *J* = 2.15 Hz, 1H), 7.28 (dd, *J* = 8.60, 2.15 Hz, 1H), 7.18 (s, 1H), 6.62 (d, *J* = 3.44 Hz, 1H), 2.29 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.5, 152.6, 152.4, 151.1, 133.5, 132.5, 128.2, 127.1, 124.2, 120.6, 120.0 (q, *J* = 265.0 Hz), 116.8, 116.6, 107.0, 24.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (*m/z*): calcd for C₁₅H₁₁ClF₃N₄O₂ ([M + H]⁺), 371.0517, found, 371.0523.

***N*-(2-Methoxy-4-(trifluoromethoxy)pyrimidin-5-yl)acetamide (11c)**
A solution of *N*-hydroxy-*N*-(2-methoxypyrimidin-5-yl)acetamide (10c) (45.0 mg, 0.246 mmol) and Togni reagent I (97.4 mg, 0.295 mmol, 1.20 equiv) in CH₂Cl₂ (2.46 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 21 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (1:1 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as a white solid (48.7 mg, 0.194 mmol, 79% yield). *R_f* = 0.38 (EtOAc:hexanes 1:1 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 9.22 (s, 1H), 7.46 (br. s, 1H), 3.96 (s, 3H), 2.22 (s, 3H). ¹³C NMR (175

MHz, CDCl₃, 25 °C, δ): 168.8, 160.4, 154.5, 154.3, 119.7 (q, *J* = 264.3 Hz), 115.3, 55.6, 24.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₈H₉F₃N₃O₃ ([M + H]⁺), 252.0591, found, 252.0593.

5

***N*-(2-(4-Chloro-3,5-dimethylphenoxy)-4-(trifluoromethoxy)pyrimidin-5-yl)acetamide (11d)**

A solution of *N*-(2-(4-chloro-3,5-dimethylphenoxy)pyrimidin-5-yl)-*N*-hydroxyacetamide (**10d**) (30.5 mg, 0.0991 mmol) and Togni reagent I (39.3 mg, 0.119 mmol, 1.20 equiv) in CH₂Cl₂ (2.97 mL, 0.334 M) was stirred at 23 °C under N₂ atmosphere for 24 h. The reaction mixture was then stirred at 50 °C for 22 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed once). The purification afforded the title compound as a white solid (26.5 mg, 0.0705 mmol, 71% yield). R_f = 0.40 (EtOAc:hexanes 2:3 (v/v)). NMR Spectroscopy: ¹H NMR (400 MHz, CDCl₃, 25 °C, δ): 9.32 (s, 1H), 7.16 (br. s, 1H), 6.92 (s, 2H), 2.38 (s, 6H), 2.25 (s, 3H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 168.5, 159.3, 154.2, 153.5, 150.2, 137.8, 131.7, 121.3, 119.8 (q, *J* = 265.1 Hz), 116.7, 24.3, 21.0. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -56.7 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₅H₁₄ClF₃N₃O₃ ([M + H]⁺), 376.0670, found, 376.0677.

25 ***N*-(2-(((8*S*,9*R*,13*R*,14*R*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)-4-(trifluoromethoxy)pyrimidin-5-yl)acetamide (11e)**

A solution of *N*-hydroxy-*N*-(2-(((8*S*,9*R*,13*R*,14*R*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)pyrimidin-5-yl)acetamide (**10e**) (25.0 mg, 0.0593 mmol) and Togni reagent I (23.5 mg, 0.0712 mmol, 1.20 equiv) in CH₂Cl₂ (0.593 mL, 0.100 M) was stirred at 23 °C under N₂ atmosphere for 16 h. The reaction mixture was then stirred at 50 °C for 24 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (3:2 (v/v)) for development (prep TLC was developed twice). The purification afforded the title compound as a white solid (14.9 mg, 0.0304 mmol, 51% yield).

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$R_f = 0.47$ (EtOAc:hexanes 3:2 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.32 (s, 1H), 7.32 (d, $J = 8.60$ Hz, 1H), 7.14 (s, 1H), 6.96 (dd, $J = 8.39, 2.37$ Hz, 1H), 6.92 (d, $J = 2.58$ Hz, 1H), 2.95–2.90 (m, 2H), 2.51 (dd, $J = 18.93, 8.60$ Hz, 1H), 2.45–2.39 (m, 1H), 2.31 (td, $J = 11.19, 3.87$ Hz, 1H), 2.25 (s, 3H), 2.19–2.11 (m, 1H), 2.09–2.05 (m, 1H), 2.04–2.00 (m, 1H), 1.97 (dt, $J = 12.58, 3.17$ Hz, 1H), 1.67–1.60 (m, 2H), 1.58 (dd, $J = 12.48, 3.87$ Hz, 1H), 1.56–1.43 (m, 3H), 0.92 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 221.0, 168.4, 159.6, 154.3, 153.5, 150.5, 138.3, 137.4, 126.7, 121.5, 119.8 (q, $J = 265.1$ Hz), 118.7, 116.5, 50.6, 48.1, 44.3, 38.1, 36.0, 31.7, 29.6, 26.5, 25.8, 24.3, 21.7, 14.0. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.6 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{25}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_4$ ($[\text{M} + \text{H}]^+$), 490.1948, found, 490.1957.

15 **Example 9. Gram Scale Reaction of Pyridine Substrates and Further Functionalization**

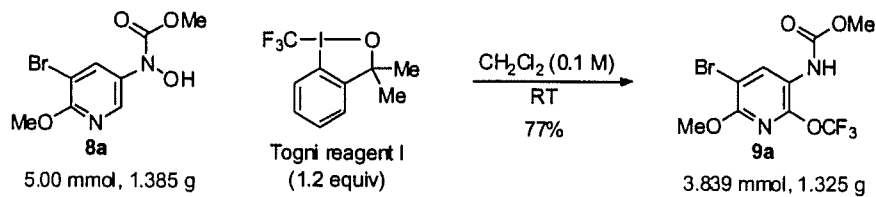
To ensure that the products disclosed herein can serve as useful building blocks for molecular screening, the protocol must be scalable and further functionalization of the trifluoromethoxylated products must be possible. To evaluate the reaction efficacy on preparative scale, a gram-scale reaction of **8a** (1.39 g, 5.00 mmol) was performed (Scheme 9a) and the efficiency of the small-scale reaction was retained upon scale-up. The trifluoromethoxylated products also proved to be versatile (Scheme 9). For examples, **9a** could be further elaborated through palladium-catalyzed Suzuki and Sonogashira couplings to afford the desired products (**13a**, **15a**) in good yields. In addition, deprotected amino-pyridine (**9a'**) could be efficiently incorporated into other molecules through amidation and palladium-catalyzed Buchwald-Hartwig coupling (**12a**, **14a**).

30

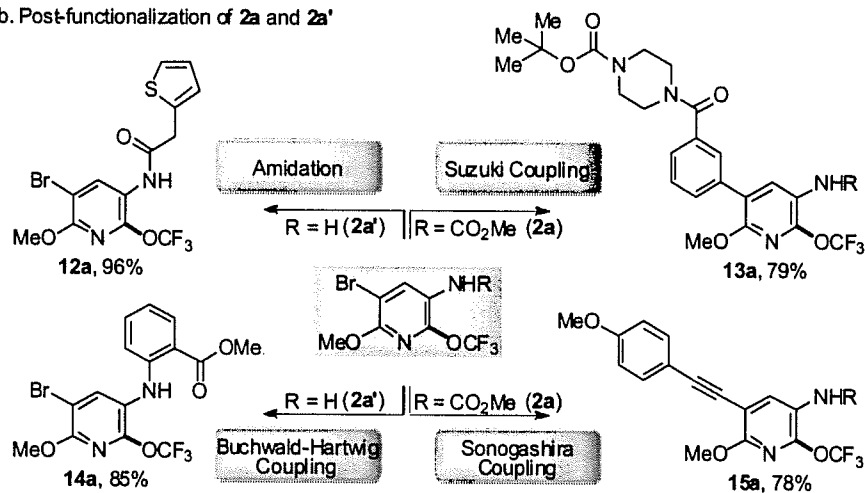
35

Scheme 9.

a. Gram-scale synthesis of 9a



b. Post-functionalization of 2a and 2a'

**Methyl (5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl) carbamate**

(9a): A solution of methyl (5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)carbamate (8a) (1.39 g, 5.00 mmol) and Togni reagent I (1.98 g, 6.00 mmol, 1.20 equiv) in CH_2Cl_2 (50.0 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 18 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography eluting with hexanes and then with EtOAc:hexanes (3:17 (v/v)). The purification afforded the title compound (2.51 g, 9.05 mmol, 95% yield), which was spectroscopically identical to the compound prepared according to the standard procedure (*vide supra*).

N-(5-Bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)-2-(thiophen-2-yl)acetamide (12a): To a solution of 2-(thiophen-2-yl)acetic acid (49.5 mg, 0.348 mmol, 2.0 equiv), DMF (1 drop) and DCM (3.50 mL, 0.100 M) at 0 °C under N_2 atmosphere was added dropwise oxalyl chloride (44.2 mg, 0.348 mmol, 2.0 equiv) via a syringe. The resulting mixture was stirred at 23 °C for 2 h, concentrated to afford crude acid chloride, which was used in the subsequent step without further purification. The above crude acid chloride was dissolved in CH_3CN (1.5 mL, 0.0232 M) and added to a solution of 5-bromo-6-methoxy-2-

(trifluoromethoxy)pyridin-3-amine (9a') (50 mg, 0.174 mmol, 1.0 equiv) in CH₃CN (3.5 mL, 0.0497 M) at 23 °C under N₂ atmosphere. The reaction mixture was stirred at 23 °C for another 2 h, concentrated *in vacuo* and purified by chromatography on silica gel, eluting with
5 hexanes:EtOAc (5:1 (v/v)), to afford the title compound as a yellow solid (69.0 mg, 0.167 mmol, 96% yield). R_f = 0.20 (EtOAc:hexanes 1:4 (v/v)). NMR Spectroscopy: ¹H NMR (500 MHz, CDCl₃, 25 °C, δ): 8.87 (s, 1H), 7.40 (br. s., 1H), 7.34 (dd, J = 5.04, 1.07 Hz, 1H), 7.09–7.03 (m, 2H), 3.97 (s, 2H), 3.92 (s, 3H). ¹³C NMR (125 MHz, CDCl₃, 25 °C,
10 δ): 168.1, 154.2, 142.2, 136.5, 134.8, 128.3, 127.9, 126.6, 119.9 (q, J = 261.8 Hz), 116.8, 102.6, 55.2, 38.4. ¹⁹F NMR (376 MHz, CDCl₃, 25 °C, δ): -57.1(s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for C₁₃H₁₁BrF₃N₂O₃S ([M + H]⁺), 412.9600, found, 412.9605.

15 **tert-Butyl 4-(3-(2-methoxy-5-((methoxycarbonyl)amino)-6-(trifluoromethoxy)pyridin-3-yl)benzoyl)piperazine-1-carboxylate**

(13a): Methyl (5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)carbamate (9a) (0.0600 g, 0.170 mmol, 1.00 equiv), methyl tert-butyl 4-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoyl)
20 piperazine-1-carboxylate (0.103 g, 0.240 mmol, 1.40 equiv), Na₂CO₃ (0.287 g, 0.430 mmol, 2.5 equiv), THF:H₂O 4:3 (1.01 mL, 0.200 M), and palladium-tetrakis(triphenylphosphine) (0.002 g, 0.020 mmol, 0.0500 equiv) were degassed via three freeze-pump-thaw cycles. The resulting mixture was heated at 60 °C for 72 hours and then allowed to cool to
25 room temperature after which water was added (twice the volume of THF:H₂O 4:3 used). The mixture was then extracted with ethyl acetate (twice the volume of THF:H₂O 4:3 used) and the organic extracts was dried with MgSO₄, filtered purified by preparative TLC (thickness: 1 mm) using EtOAc:hexanes (2:3 (v/v)) for development (prep TLC was
30 developed three times) to afford the pure cross-coupled product as a white solid (0.077 g, 0.14 mmol, 79% yield). R_f = 0.20 (EtOAc:hexanes 2:3 (v/v)). NMR Spectroscopy: ¹H NMR (700 MHz, CDCl₃, 25 °C, δ): 8.47 (br. s, 1H), 7.64–7.59 (m, 2H), 7.47 (t, J = 8.17 Hz, 1H), 7.40 (d, J = 7.31 Hz, 1H), 6.68 (br. s, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.76
35 (br. s., 2H), 3.60–3.34 (m, 6H), 1.47 (s, 9H). ¹³C NMR (175 MHz, CDCl₃, 25 °C, δ): 170.4, 154.7, 154.1, 142.5, 135.7, 135.5, 133.4, 130.7, 128.9, 127.9, 126.7, 121.0, 120.2 (q, J = 261.2 Hz), 116.7, 80.5,

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54.4, 52.9, 47.7, 43.8, 42.2, 28.5. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s).

Methyl 2-((5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl) amino)benzoate (14a): A mixture of 5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-amine (9a') (50.0 mg, 0.200 mmol, 1.20 equiv), methyl 2-iodobenzoate (44.5 mg, 0.170 mmol, 1.00 equiv), xantphos (10.0 mg, 0.0170 mmol, 0.100 equiv), NaO^tBu (2.30 mg, 0.238 mmol, 1.40 equiv), and $\text{Pd}_2(\text{dba})_3$ (7.80 mg, 0.00850 mmol, 0.05 equiv) in toluene (0.850 mL, 0.200 M) was stirred at 100 °C under N_2 for 40 hours and then allowed to cool to room temperature. The reaction was purified by preparative TLC (thickness: 1 mm) using EtOAc:hexanes (1:10 (v/v)) for development (prep TLC was developed two times) to afford title compound as a colorless liquid (61.0 mg, 0.145 mmol, 85% yield). R_f = 0.71 (EtOAc:hexanes 1:10 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 9.23 (s, 1H), 8.01-7.97 (m, 1H), 7.95 (s, 1H), 7.36 (t, J = 7.74 Hz, 1H), 6.87 (d, J = 8.60 Hz, 1H), 6.82- 6.79 (m, 1H), 3.99 (s, 3H), 3.92 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3 , 25 °C, δ): 168.9, 154.5, 147.2, 146.8, 139.7, 134.5, 131.9, 120.2 (q, J = 260.9 Hz), 119.7, 118.3, 113.4, 112.8, 102.1, 52.3, 52.1. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.5 (s). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $\text{C}_{15}\text{H}_{13}\text{BrF}_3\text{N}_2\text{O}_4$ ($[\text{M} + \text{H}]^+$), 421.0005, found, 421.0010.

Methyl (6-methoxy-5-((4-methoxyphenyl)ethynyl)-2-(trifluoromethoxy)pyridin-3-yl) carbamate (15a): Under N_2 atmosphere methyl (5-bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-yl)carbamate (15a) (0.0500 g, 0.140 mmol, 1.00 equiv), 1-ethynyl-4-methoxybenzene (0.0270 g, 0.200 mmol, 1.40 equiv), copper(I) iodide (0.550 mg, 2.90 μmol , 0.0200 equiv), and [1,1'-bis(diphenylphosphino) ferrocene] dichloropalladium(II), complex with dichloromethane (1.20 mg, 1.40 μmol , 0.0200 equiv in THF (0.72 mL, 0.200 M), was heated at 60 °C overnight and then allowed to cool to room temperature after which water was added (twice the volume of THF). The mixture was then extracted with ethyl acetate (twice the volume of THF:H₂O 4:3 used) and the organic extracts was dried with MgSO_4 , filtered purified by preparative TLC (thickness: 1 mm) using EtOAc:hexanes (1:9 (v/v)) for

development (prep TLC was developed three times) to afford the pure cross-coupled product as a white solid (0.045 g, 0.11 mmol, 78% yield). $R_f = 0.38$ (EtOAc:hexanes 3:16 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 , 25 °C, δ): 8.54 (br. s, 1H), 7.50–7.46 (m, 2H), 6.90–6.85 (m, 2H), 6.60 (br. s, 1H), 3.96 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 25 °C, δ): 160.0, 157.3, 153.9, 142.1, 135.4, 133.4, 120.3 (q, $J = 261.6$ Hz), 116.1, 115.0, 114.1, 105.3, 95.0, 81.7, 55.5, 54.8, 52.9. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.4 (s).

10

Example 10. Mechanistic studies and proposed reaction mechanism

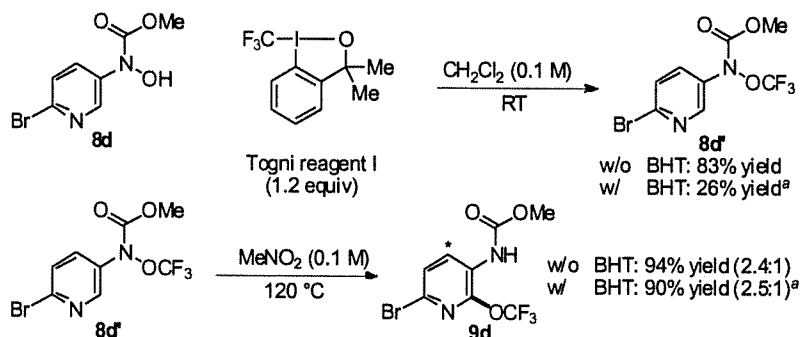
To gain some insight into the reaction mechanism, reactions in the presence of radical trap butylated hydroxytoluene (BHT) (Scheme 10a) were performed. We chose to use substrate **8d** because we could isolate the *O*-trifluoromethylated intermediate **8d'** and study each step (i.e. *O*-trifluoromethylation and OCF_3 -migration) separately. Addition of BHT (1 equiv) to a reaction mixture of **8d** and Togni reagent I had detrimental effect to the formation of *O*-trifluoromethylated *N*-hydroxylamine intermediate **8d'**. This result suggests the involvement of radical species in the reaction pathway, which is in agreement with literature precedent.^{14b, 17} On the other hand, BHT did not affect the reaction yield for the OCF_3 -migration process (step 2, Schem 10a). These experiments argue against the presence of long-lived radical species in the OCF_3 -migration process and are consistent with our previous finding.²⁸ Moreover, introduction of electron rich substituent *para* to the N-OCF_3 group facilitates the OCF_3 -migration process. These observations support the formation of nitrenium ion and trifluoromethoxide.^{24,28} On the basis of these results, a plausible mechanism for the trifluoromethoxylation reaction is illustrated in Scheme 10b. Deprotonation of **8d** forms *N*-hydroxyl an ion **I**, which undergoes single-electron transfer (SET) with Togni reagent I to generate *N*-hydroxyl radical **II**, trifluoromethyl radical, and alkoxide **III**. Recombination of *N*-hydroxyl radical and trifluoromethyl radical affords the *O*-trifluoromethylated hydroxylamine **1d'**, which could be isolated and characterized. This intermediate will then undergo thermally induced heterolytic cleavage of the N-O bond to form a tight ion pair of nitrenium ion **IV** and trifluoromethoxide.

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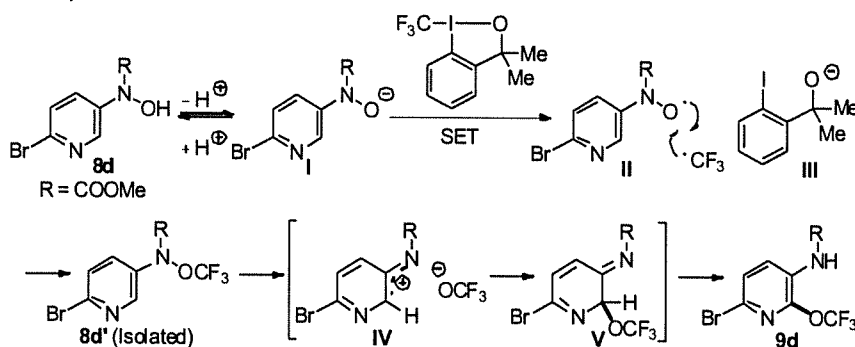
Recombination of this ion pair gives **V**, which upon tautomerization yields the desired product **9d**.

Scheme 10.

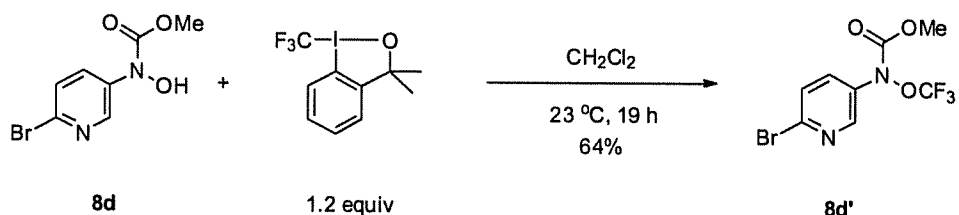
a. Mechanistic studies using radical inhibitor



b. Proposed reaction mechanism



5 Methyl-(6-bromopyridin-3-yl)(trifluoromethoxy)carbamate (8d')

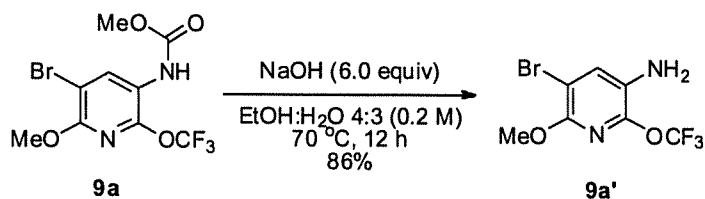


A solution of methyl (6-bromopyridin-3-yl)(hydroxy)carbamate (**8d**) (120.0 mg, 0.486 mmol) and Togni reagent I (192.4 mg, 0.583 mmol, 1.20 equiv) in CH_2Cl_2 (4.86 mL, 0.100 M) was stirred at 23 °C under N_2 atmosphere for 19 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparative TLC (thickness: 1 mm) using hexanes:EtOAc (97:3 (v/v)) for development (prep TLC was developed four times). The band corresponding to 2-(2-iodophenyl)propan-2-ol was on the bottom of the band corresponding to the product, so only top of the band corresponding to the product was scraped of the PLC plate. The purification afforded the title compound as a white solid (97.4 mg, 0.309 mmol, 64% yield). $R_f = 0.49$ (EtOAc:hexanes 1:9 (v/v)). NMR Spectroscopy: ^1H NMR (700 MHz, CDCl_3 ,

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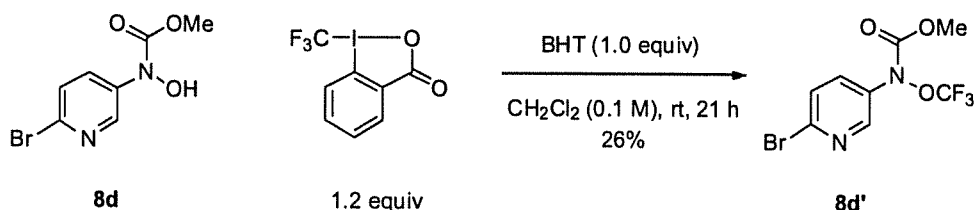
25 °C, δ): 8.45 (br. s, 1H), 7.60 (m, 1H), 7.56 (d, J = 8.60 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (175 MHz, CDCl_3 , 60 °C, δ): 155.2, 145.9, 141.2, 137.3, 133.9, 128.5, 122.7 (q, J = 263.7 Hz), 55.3. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -66.2(s). Mass Spectrometry: HRMS (ESI-TOF) (m/z):
 5 calcd for $\text{C}_8\text{H}_7\text{BrF}_3\text{N}_2\text{O}_3$ ($[\text{M} + \text{H}]^+$), 314.9587, found, 314.9592.

5-Bromo-6-methoxy-2-(trifluoromethoxy)pyridin-3-amine (9a')



To a stirred suspension of (5-bromo-6-methoxypyridin-3-yl)(hydroxy)carbamate (0.370 g, 1.07 mmol, 1.00 equiv) and sodium hydroxide (0.257 g, 6.43 mmol, 6.00 equiv) in EtOH:H₂O 4:3 (6.32 mL, 0.200 M) was heated at 70 °C overnight, cool to -20 °C, diluted with water and the crystals formed were filtered off to afford the deprotection of methyl carbamates as pure slightly light yellow solid
 10 (0.263 g, 0.92 mmol, 86% yield). R_f = 0.69 (EtOAc:hexanes 3:7 (v/v)). NMR Spectroscopy: ^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 7.55 (s, 1H), 5.17 (s, 2H), 3.77 (s, 3H). ^{13}C NMR (175 MHz, $(\text{CD}_3)_2\text{SO}$, 25 °C, δ): 147.73, 137.95, 131.06, 129.42, 120.01 (q, J = 257.3 Hz), 102.74, 54.17. ^{19}F NMR (376 MHz, CDCl_3 , 25 °C, δ): -56.9 (s). Mass Spectrometry:
 15 HRMS (ESI-TOF) (m/z): calcd for $\text{C}_7\text{H}_7\text{BrF}_3\text{N}_2\text{O}_2$ ($[\text{M} + \text{H}]^+$), 288.9618, found, 288.9629.

O-Trifluoromethylation in the presence of a radical trap



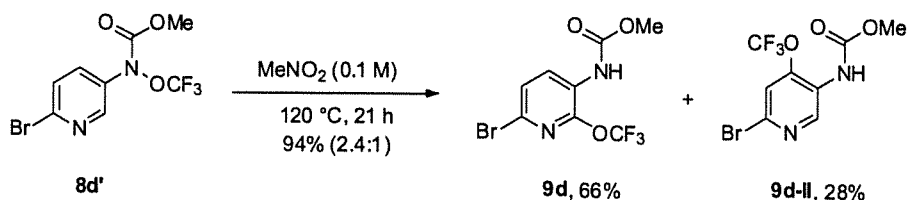
25 A solution of methyl (6-bromopyridin-3-yl)(hydroxy)carbamate (**8d**) (12.4 mg, 0.0502 mmol, 1.00 equiv), BHT (11.0 mg, 0.0500 mmol, 1.00 equiv) and Togni reagent I (19.8 mg, 0.0600 mmol, 1.2 equiv) in CH_2Cl_2 (0.500 mL) was stirred at 23 °C under N_2 atmosphere for 21 h. Trifluorotoluene (6.14 μL) and CDCl_3 (0.250 mL) were added and the
 30 reaction mixture was analyzed by ^{19}F NMR. The ^{19}F NMR analysis indicated

180

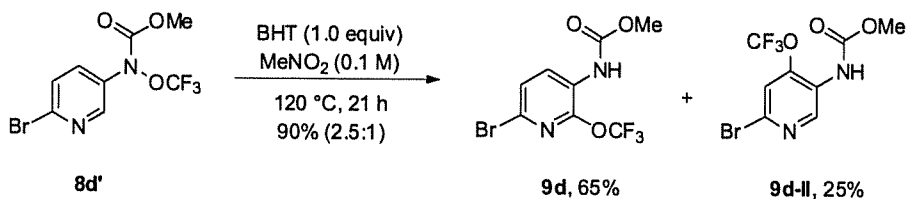
that the yield of *O*-trifluoromethylation of **8d** in the presence of BHT (26%) was much lower than in the absence of the radical trap (83%).

***O*-CF₃ Migration in the presence of a radical trap**

w/o BHT:



with BHT:



5

Reaction without BHT: Under N₂ atmosphere, a solution of methyl (6-bromopyridin-3-yl)(trifluoromethoxy)carbamate (9.45 mg, 30.0 μmol) (**8d'**) in MeNO₂ (0.300 mL, 0.100 M) was heated at 120 °C for 21 h. Trifluorotoluene (3.68 μL) and CDCl₃ (0.400 mL) were added and the reaction mixture was analyzed by ¹⁹F NMR. The ¹⁹F NMR analysis indicated that the yield of OCF₃-migration reaction was 94% (2.4:1).

10

Reaction with BHT: Under N₂ atmosphere, a solution of methyl (6-bromopyridin-3-yl)(trifluoromethoxy)carbamate (**8d'**) (9.45 mg, 30.0 μmol, 1.00 equiv) and BHT (11.0 mg, 50.0 μmol, 1.00 equiv) in MeNO₂ (0.300 mL, 0.100 M) was heated at 120 °C for 21 h. Trifluorotoluene (3.68 μL) and CDCl₃ (0.400 mL) were added and the reaction mixture was analyzed by ¹⁹F NMR. The ¹⁹F NMR analysis indicated that the yield of OCF₃-migration reaction was 90% (2.5:1).

20

Example 11. Additional Substrates

An additional aspect of the invention provides substituted or unsubstituted aryl and heteroaryl analogs of the compounds of Scheme 2 and Schemes 7-8 that readily undergo the two-step trifluoromethylation-migration sequence or the one-pot trifluoromethylation-migration reaction.

25

Discussion

Clearly, direct trifluoromethoxylation reactions that avoid use of highly toxic and thermally labile reagents are greatly desired. Therefore, we initiated a program to develop easily-handled and bench
5 stable trifluoromethoxylation reagents for direct introduction of the OCF₃ group into various organic molecules to facilitate studies of this functional group in the context of material, agricultural, and pharmaceutical regimes. In the course of the trifluoromethoxylation reagent development, we observed a thermally induced OCF₃-migration
10 to generate synthetically useful *ortho*-trifluoromethoxylated aniline derivatives (Scheme 1).^[13] Herein, we report the *first* synthesis, isolation, and characterization of protected *N*-aryl-*N*- (trifluoromethoxy)amines^[14] and their application in the synthesis of *ortho*-OCF₃ aniline derivatives.

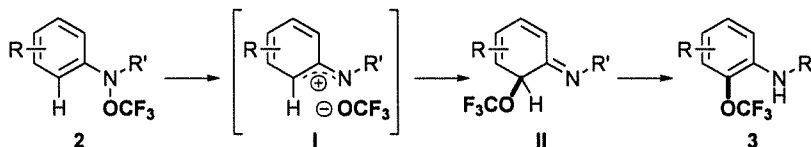
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A proposed mechanistic pathway for OCF₃-migration is depicted in Scheme 6A. The thermally induced heterolytic cleavage of the N-O bond of **2** liberates an ion pair of a nitrenium ion and trifluoromethoxide (**I**). Recombination of this ion pair affords intermediate **II**, which
20 then tautomerizes to restore the aromaticity and generate the desired product **3**. The proposed mechanism is supported by the following observations. First of all, comparable yields were obtained regardless of the presence or absence of the radical trap (BHT) in the reaction mixture (Scheme 11B). This indicates that formation of
25 long-lived radical species under the reaction conditions is unlikely. Secondly, we isolated benzoxazole **4r** from the rearrangement reaction of **2r** (Scheme 11C). Presumably, this side product can result from the competing reaction pathway **a** once the nitrenium ion **III** is generated. Finally, Kikugawa and coworkers reported an AlCl₃-mediated
30 regioselective OCH₃-migration of *N*-methoxy-*N*-phenylamides to produce *ortho*-OCH₃ aniline derivatives.^[13] A reaction mechanism involving a heterolytic cleavage of the N-O bond to furnish an ion pair was proposed (Scheme 11D).

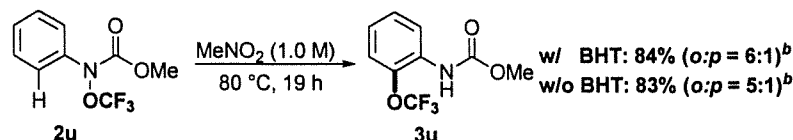
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Scheme 11. Evidences for the proposed reaction mechanism.

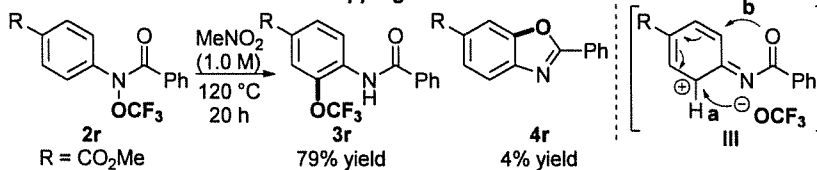
A: Proposed Reaction Mechanism: OCF₃-Migration via an Ion Pair Formation



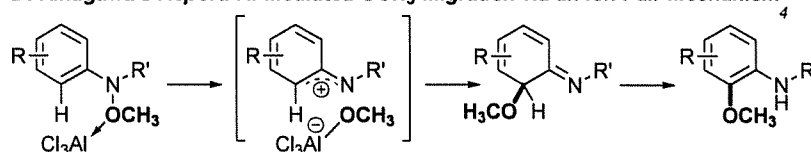
B: OCF₃-Migration in the Presence of Radical Trap



C: Benzoxazole Formation via Trapping of Carbocation Intermediate



D: Kikugawa's Report: Al-Mediated OCH₃-Migration via an Ion Pair Mechanism¹



[a] 1 equiv of BHT was used.

5 The *first* O-trifluoromethylation of a wide range of protected N-aryl-N-hydroxylamines and the *first* OCF₃-migration reaction to afford various *ortho*-OCF₃ aniline derivatives, which can be useful synthons for agrochemical and pharmaceutical development, as been developed.¹ 2a, b, 5g, 22] The OCF₃-migration reaction proceeds through the heterolytic cleavage of the N-O bond followed by recombination of the resulting ion pair. The arene trifluoromethoxylation protocol utilizes bench stable reagents, is amenable to gram-scale and one-pot synthesis, and displays high levels of *ortho*-selectivity as well as functional group tolerance.

15

Also, the *first* mild, general, and scalable protocol for the regioselective synthesis of trifluoromethoxylated pyridines and pyrimidines was been established. Several unique features distinguish our strategy from the existing approaches: (i) many substrates with complex skeleton could be trifluoromethoxylated at or below room temperature; (ii) a wide range of functional groups and substitution patterns are tolerated; (iii) this transformation could be amenable

20

to gram-scale synthesis; (iv) the halogen or amino group could be used as synthetic handles for further elaborations, and (v) the operational simplicity of our protocol would render trifluoromethoxylation available to broader synthetic community.

5 Since heteroarenes are ubiquitous in biologically active natural products, pharmaceuticals, and agrochemicals, OCF₃-containing heteroarenes will be invaluable for the discovery and development of new drugs, agrochemicals, and functional materials. Our current efforts are directed toward development of intermolecular

10 trifluoromethoxylation of hydrocarbons.

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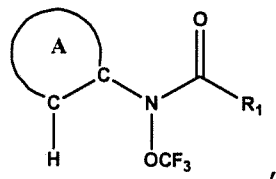
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What is claimed is:

1. A process of producing a compound having the structure:

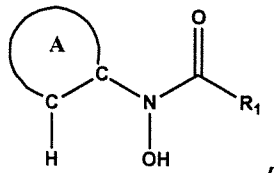


wherein

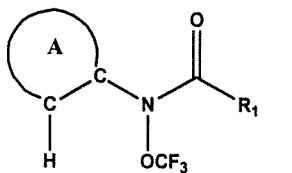
A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

comprising:

(a) reacting a compound having the structure:



with a trifluoromethylating agent in the presence of a base in a first suitable solvent under conditions sufficient to produce the compound having the structure:



2. The process of claim 1, wherein the first suitable solvent is chloroform, dichloromethane, nitromethane, dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, dichloroethane, or hexane.

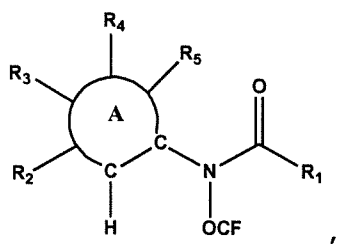
3. The process of claim 1, wherein the trifluoromethylating agent is Togni reagent I or Togni reagent II.

4. The process of any one of claims 1-3, wherein the base is cesium carbonate or sodium hydride.

5. The process of any one of claims 1-4, wherein A is a phenyl or pyridine.

6. The process of any one of claims 1-4, wherein A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

7. The process of claim 1, wherein the compound produced has the structure:

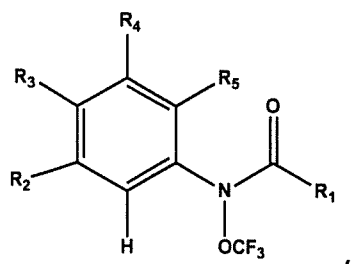


wherein

R_1 is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

R_2, R_3, R_4 and R_5 is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

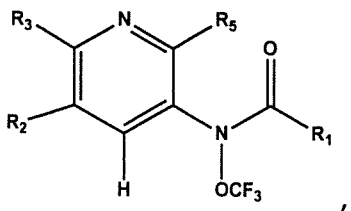
8. The process of claim 1, wherein the compound produced has the structure:



wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

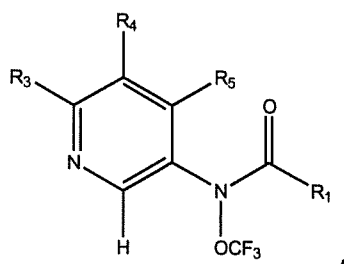
9. The process of claim 1, wherein the compound produced has the structure:



wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -

O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone; or the structure:

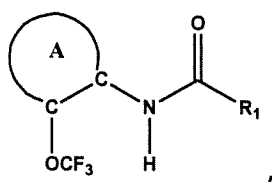


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene,

quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine..

10. A process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

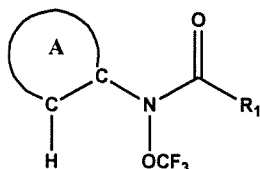


wherein

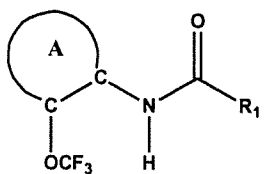
A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

comprising:

(b) maintaining the compound having the structure:



in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylatedtrifluoromethoxylated heteroaryl having the structure:



11. The process of claim 10, wherein the second suitable solvent is chloroform, dichloromethane, nitromethane, dimethylformamide, diethyl ether, tetrahydrofuran, dioxane, dichloroethane, or hexane.

12. The process of claim 10 or 11, wherein step (b) is carried out at room temperature.

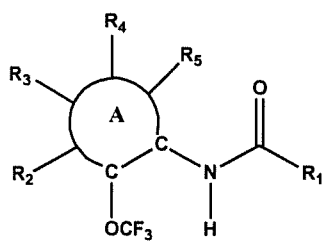
13. The process of any one of claims 10-12, wherein step (b) is carried out at a temperature of 50-140 °C.

14. The process of any one of claims 10-13, wherein the compound is maintained in the second suitable solvent for 10-50 hours.

15. The process of any one of claims 10-14, wherein A is a phenyl or pyridine.

16. The process of any one of claims 10-14, wherein A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

17. The process of claim 10, wherein the compound produced has the structure:

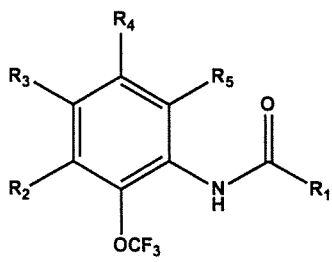


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-

(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

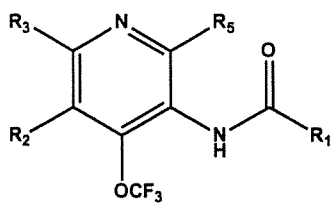
18. The process of claim 10, wherein the compound produced has the structure:



wherein

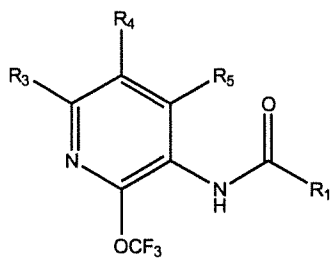
R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

19. The process of claim 10, wherein the compound produced has the structure:



wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone; or the structure:

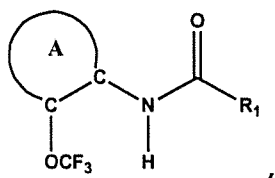


wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl),

-CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

20. A process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

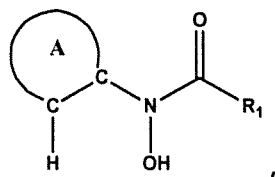


wherein

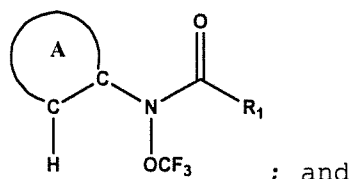
A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

comprising:

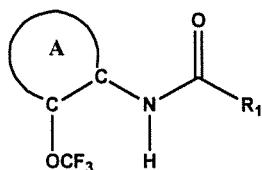
(a) reacting a compound having the structure:



with a trifluoromethylating agent in a first suitable solvent under conditions to produce a compound having the structure:

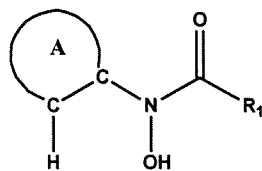


(b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

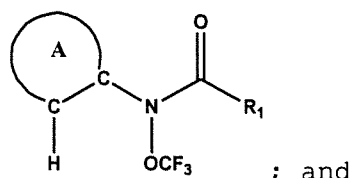


21. A process of claim 20 comprising:

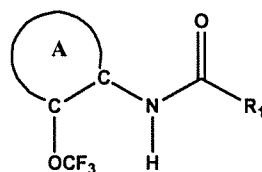
(a) reacting a compound having the structure:



with a trifluoromethylating agent in the presence of a base in a first suitable solvent under conditions to produce a compound having the structure:



(b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



22. The process of claim 20 or 21, wherein the first suitable solvent and second suitable solvent are identical.

23. The process of any one of claims 20-22, wherein step (a) and step (b) are performed by a sequential one-pot synthesis.

24. The process of any one of claims 20-22, wherein step (a) and step (b) are performed by a sequential one-pot synthesis without purification or work-up in between step (a) and step (b).

25. The process of any one of claims 20-24, wherein step (a) and (b) are each carried out at room temperature.

26. The process of any one of claims 20-24, wherein step (b) is carried out at a temperature of 50-140 °C.

27. The process of any one of claims 20-26, wherein trifluormethylating agent is Togni reagent I or Togni reagent II.

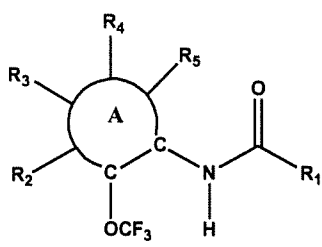
28. The process of any one of claims 20-27, wherein the base is sodium hydride or cesium carbonate.

29. The process of any one of claims 20-28, wherein A is a phenyl or pyridine.

30. The process of any one of claims 20-28, wherein A is a furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

31. The process of claim 20, wherein the compound produced has the structure:

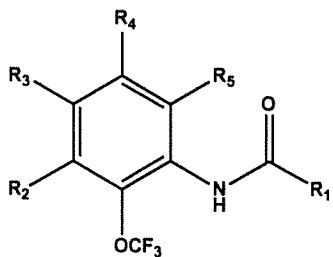
200



wherein

R_1 is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R_2 , R_3 , R_4 and R_5 is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

32. The process of claim 20, wherein the compound produced has the structure:



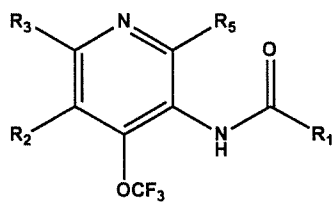
wherein

R_1 is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and

201

R₂, R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone.

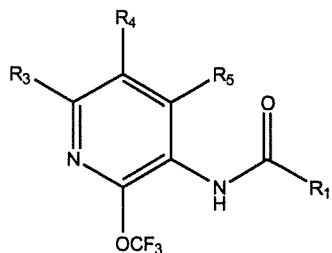
33. The process of claim 20, wherein the compound produced has the structure:



wherein

R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₂, R₃ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine,

pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, or quinolone; or the structure:

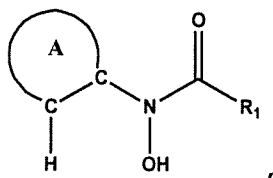


wherein

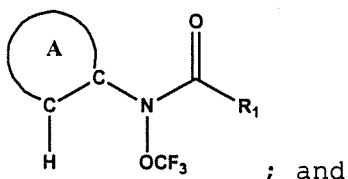
R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl); and R₃, R₄ and R₅ is each independently -H, halogen, -CN, -CF₃, -OCF₃, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -NH₂, -NH-(alkyl), -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -CO₂-(alkyl), -CO₂-(alkenyl), -CO₂-(alkynyl) -CO₂-(aryl), -C(-CO₂-(heteroaryl), -C(O)NH-(alkyl), -C(O)NH-(alkenyl), -C(O)NH-(alkynyl) -C(O)NH-(aryl), -C(O)NH-(heteroaryl), -C(O)N(alkyl)₂, -OH, -OAc, -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), -S-(heteroaryl), pyridine, furan, thiophene, pyrrole, thiazole, imidazole, pyrazole, isooxazole, isothiazole, naphthalene, anthracene, pyrimidine, pyrazine, pyridazine, indole, indoline, benzofuran, benzothiophene, quinolone, pyrazoline, triazole, benzimidazole, benzotriazole, azaindole, or purine.

34. The process of claim 20 comprising:

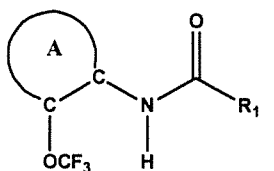
(a) reacting a compound having the structure:



with Togni reagent II in the presence of a base in a first suitable solvent under conditions sufficient to produce a compound having the structure:

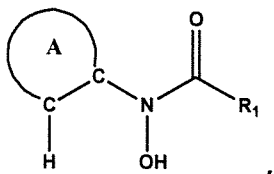


(b) maintaining the compound produced in step (a) in a second suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

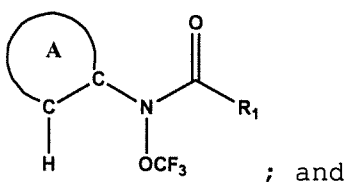


35. The process of claim 20 comprising:

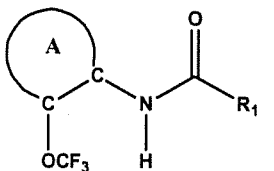
(a) reacting a compound having the structure:



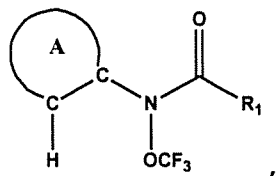
with Togni reagent II in the presence of cesium carbonate in chloroform or dichloromethane under conditions sufficient to produce a compound having the structure:



(b) maintaining the compound produced in step (a) in nitromethane under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:



36. A compound having the structure:

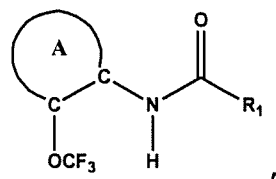


wherein

A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl),

or a salt or ester thereof.

37. A process of producing a trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

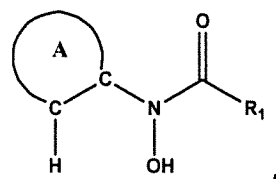


wherein

A is an aryl or heteroaryl, each with or without substitution; and R₁ is -H, -(alkyl), -(alkenyl), -(alkynyl), -(aryl), -(heteroaryl), -(alkylaryl), -(alkylheteroaryl), -NH-(alkyl), -N(alkyl)₂, -NH-(alkenyl), -NH-(alkynyl) -NH-(aryl), -NH-(heteroaryl), -O-(alkyl), -O-(alkenyl), -O-(alkynyl), -O-(aryl), -O-(heteroaryl), -S-(alkyl), -S-(alkenyl), -S-(alkynyl), -S-(aryl), or -S-(heteroaryl).

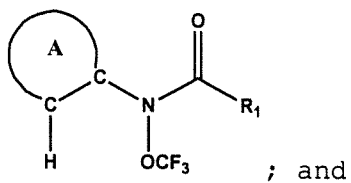
comprising:

(a) reacting a compound having the structure:

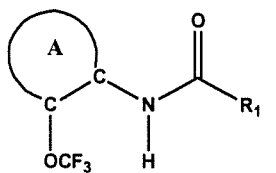


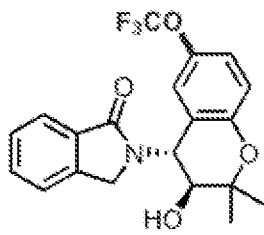
with a trifluoromethylating agent in a first suitable solvent under conditions to produce a compound having the structure:

205

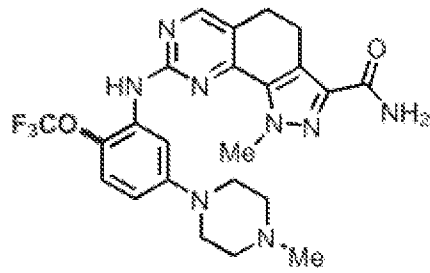


(b) maintaining the compound produced in step (a) in the first suitable solvent under conditions sufficient to produce the trifluoromethoxylated aryl or trifluoromethoxylated heteroaryl having the structure:

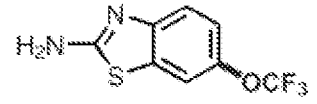




Celikalim



NMS-P937



Riluzole

Fig. 1A

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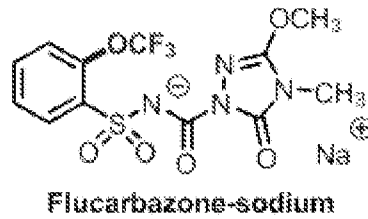
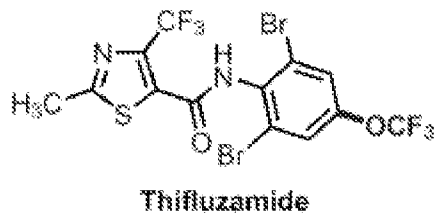
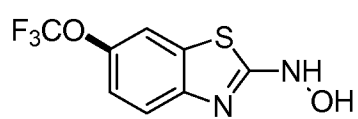
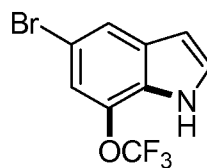


Fig. 1B

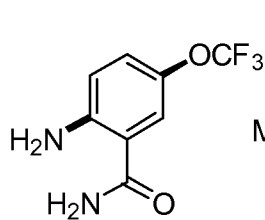
Sheet 3/5



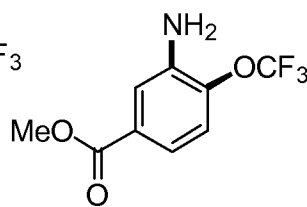
Toronto Research Chemicals
US\$120,000/g



Matrix Scientific
US\$15,680/g



Sigma-Aldrich
US\$10,000/g



Sigma-Aldrich
US\$10,000/g

Fig. 1C

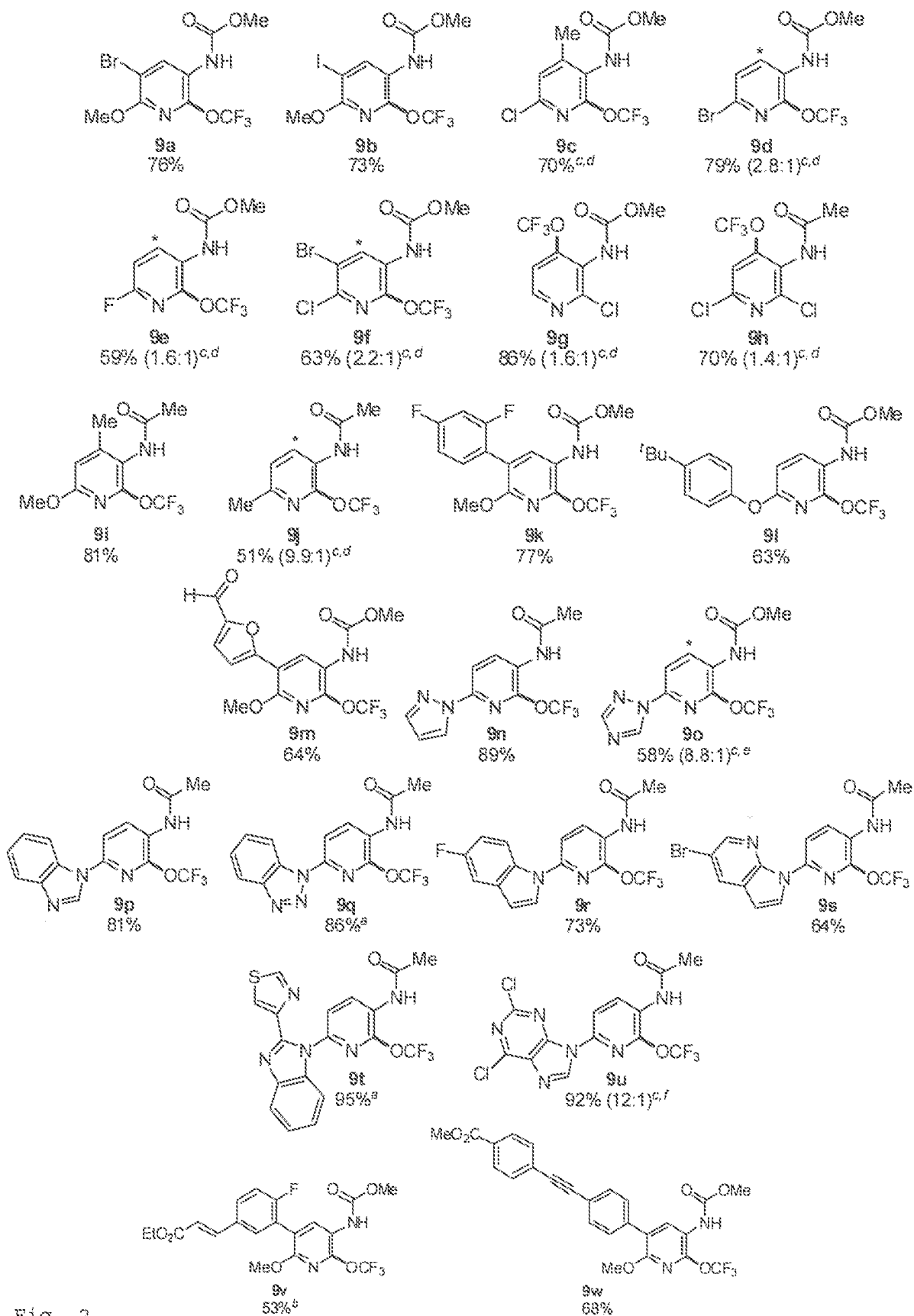


Fig. 2

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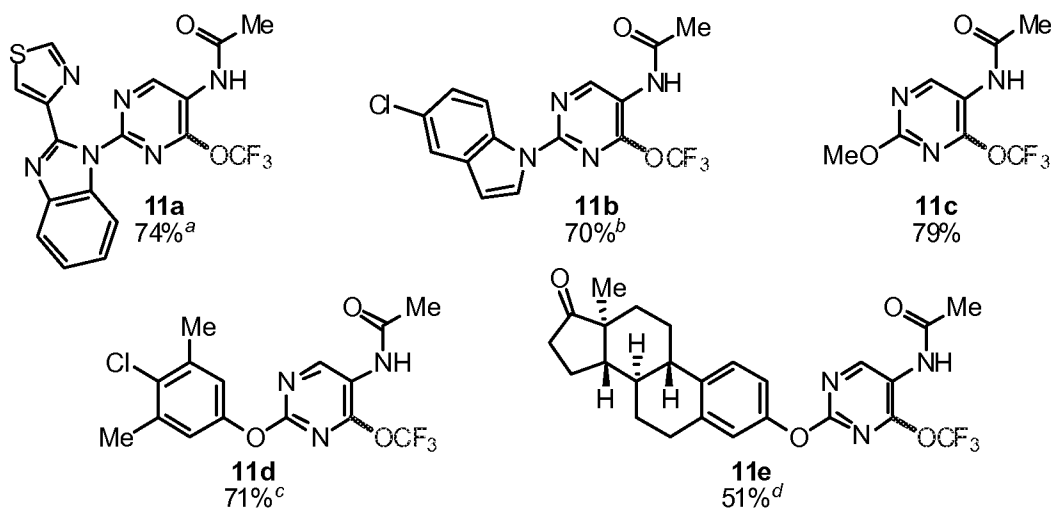


Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2015/054958

A. CLASSIFICATION OF SUBJECT MATTER (see extra sheet)		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
C07C 233/07, C07D 209/40, 213/42, 215/40, 239/88, 401/04, 417/04, 471/04, 471/14, C07J 43/00		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
PatSearch (RUPTO internal), USPTO, PAJ, Esp@cenet, DWPI, EAPATIS, PATENTSCOPE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	Katarzyna N. Hojczyk et al. Trifluoromethoxylation of Arenes: Synthesis of <i>ortho</i> -Trifluoromethoxylated Aniline Derivatives by OCF ₃ Migration. <i>Angewandte Chemie International Edition</i> , 30.10.2014, 53, 14559-14563	1-37
X A	MATOUSEK Vaclav et al. <i>O</i> -Trifluoromethylation of <i>N, N</i> -Disubstituted Hydroxylamines with Hypervalent Iodine Reagents. <i>European Journal of Organic Chemistry</i> , №15, 26.03.2014, 3087-3092	1-9 10-37
X A	XIN-YI Jiang et al. Copper-Catalyzed Three-Component Oxytrifluoromethylation of Alkenes with Sodium Trifluoromethanesulfinate and Hydroxamic Acid. <i>Angewandte Chemie International Edition</i> , 2013, 52, 14177-14180, table 1, compound 4	36 1-35, 37
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:		
“A”	document defining the general state of the art which is not considered to be of particular relevance	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“E”	earlier document but published on or after the international filing date	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“L”	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“O”	document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family
“P”	document published prior to the international filing date but later than the priority date claimed	
Date of the actual completion of the international search		Date of mailing of the international search report
25 December 2015 (25.12.2015)		11 February 2016 (11.02.2016)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37		Authorized officer S. Krylova Telephone No. 499-240-25-91

INTERNATIONAL SEARCH REPORT
Classification of subject matter

International application No.

PCT/US 2015/054958

C07C 233/07 (2006.01)
C07D 209/40 (2006.01)
C07D 213/42 (2006.01)
C07D 215/40 (2006.01)
C07D 239/88 (2006.01)
C07D 401/04 (2006.01)
C07D 417/04 (2006.01)
C07D 471/04 (2006.01)
C07D 471/14 (2006.01)
C07J 43/00 (2006.01)