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Aerobic Oxidation of Alkyl 2-Phenylhydrazinecarboxylates Catalyzed by CuCl and DMAP

Min Hye Kim and Jinho Kim*

Department of Chemistry, and Research Institute of Natural Sciences, Incheon National University, 119 Academy-ro, Yeonsu-gu, Incheon 22012, Republic of Korea

jinho@inu.ac.kr

Abstract

Recently, various fruitful organic reactions such as a catalytic Mitsunobu reaction were reported by virtue of alkyl 2-phenylazocarboxylates, however, the synthesis of alkyl 2-phenylazocarboxylates largely depended on the stoichiometric use of toxic oxidants. In this manuscript, an environment-friendly aerobic oxidative transformation of alkyl 2-phenylhydrazinecarboxylates to alkyl 2-phenylazocarboxylates was disclosed. The use of CuCl and DMAP system efficiently catalyzed the aerobic oxidation of alkyl 2-phenylhydrazinecarboxylates under mild conditions. The reaction rate of the present Cu-catalysis was much faster than that of the previously reported Fe-catalysis, and a variety of azo products were synthesized within 3 hours. The present protocol was effective on larger scale. It was observed that the produced azo compound could undergo various reactions without isolation through one-pot sequential protocols.

Azo compounds have been used in multifarious area due to their unique property and reactivity, which could be tuned by the substituent at nitrogen-nitrogen double bond.[1] Azobenzene derivatives, which contain phenyl groups at both nitrogens, have played an important role in dyes and pigments for a long

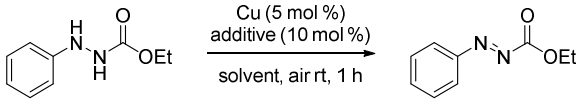
time.[2] In addition, their interesting E/Z isomerization by the light was utilized in the molecular switches and machines.[3] Dialkyl azodicarboxylates, which contain alkoxy carbonyl groups at both nitrogens, have been employed in the various organic reactions.[4] Mitsunobu reaction, the representative utilization of the dialkyl azodicarboxylates such as diethyl azodicarboxylate (DEAD), is widely used in pharmaceutical and synthetic chemistry, because the Mitsunobu reaction provides a facile route for the inversion of the chiral secondary alcohols.[5] Additionally, dialkyl azodicarboxylates have been employed in electrophilic aminations,[6] [4+2] cycloadditions,[7] oxidative couplings of tertiary amine,[8] hydrazination,[9] and dehydrations.[10]

Alkyl 2-phenylazocarboxylates are unsymmetrical azo compounds, which contain a phenyl group at one nitrogen and an alkoxy carbonyl group at the other. They recently received much attention from synthetic chemists, because these azo compounds showed distinct reactivity from symmetrical azo compounds. In C-N bond formation, they reacted with various organometallic reagents as well as enamines and showed the high regioselectivity at the phenyl substituted nitrogen position.[11] Heinrich et al. revealed that *para*-substituted alkyl 2-phenylazocarboxylates could be used in nucleophilic substitutions and radical reactions.[12] In addition, they reported that the treatment of alkyl 2-phenylazocarboxylates with tetrabutyl ammonium hydroxide (Bu_4NOH) generated phenylazocarboxylate salts and these salts could be utilized in cycloaddition and Mizoroki-Heck reaction.[13] They also achieved [3+2] cycloaddition of alkyl 2-phenylazocarboxylates for the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles.[14] Taniguchi group developed catalytic Mitsunobu reaction with the exquisite tunings of alkyl 2-phenylazocarboxylates in the Fe(Pc) catalyzed aerobic oxidation conditions.[15] It was reported that alkyl 2-phenylazocarboxylates reacted with acrylates to produce indoline derivatives through rhodium catalyzed C-H bond activation.[16]

The synthesis of alkyl 2-phenylazocarboxylates largely depends on the oxidations of the corresponding hydrazine compounds with stoichiometric oxidant such as MnO_2, ceric ammonium nitrate (CAN), $NaNO_2$, NBS, and $Pb(OAc)_4$.[11d,11g,12a,12b,17] In terms of green and sustainable chemistry, molecular oxygen is an attractive oxidant which is readily accessible and produces water as byproduct.[18] However, only few aerobic oxidation methods for alkyl 2-phenylazocarboxylates were reported.[19]

The oxidation potential of azo compound varied by the substituents at each nitrogen atom.[20] For example, the oxidation potential of di-*tert*-butyl hydrazodicarboxylate (DBAD-H_2), which have strong electron withdrawing groups at both nitrogen atoms, is 1.62 V and higher than that of 1,2-diphenylhydrazine (0.68 V). The oxidation potential of *tert*-butyl 2-phenyl hydrazinecarboxylate is between them (1.02 V). Recently, our group reported that the combination of Cu and DMAP could catalyze aerobic oxidation of DBAD-H_2.[21] On the basis of our observation and related references,[22] we envisioned that Cu/DAMP system would catalyze the aerobic oxidation of alkyl 2-phenylhydrazinecarboxylates efficiently due to their lower oxidation potential. Zhang et al. reported the preliminary result of the Cu-catalyzed aerobic oxidation of alkyl 2-phenylhydrazinecarboxylates.[23] However, they focused on the development of cross-coupling

Table 1. Optimization for Cu-catalyzed aerobic oxidation of ethyl 2-phenylhydrazinecarboxylate.[a]



1a **2a**

Entry	Cu	Additive	Solvent	Yield (%)[b]
1	CuI	DMAP	CH_2Cl_2	18
2	CuBr	DMAP	CH_2Cl_2	89
3	CuCl	DMAP	CH_2Cl_2	95
4	$CuBr_2$	DMAP	CH_2Cl_2	80
5	$CuCl_2$	DMAP	CH_2Cl_2	69
6	$Cu(OAc)_2$	DMAP	CH_2Cl_2	94
7	CuCl	pyridine	CH_2Cl_2	75
8	CuCl	DBU	CH_2Cl_2	84
9	CuCl	1,10-phen	CH_2Cl_2	16
10	CuCl	DMAP	CH_3CN	86
11	CuCl	DMAP	DMF	84

[a]Reaction conditions: **1a** (0.5 mmol), Cu (5 mol %), additive (10 mol %), and solvent (2 mL) in 50 mL round-bottom flask under air at room temperature for 1 h (stirring rate : 900 rpm). [b]Yield determined by ^{1}H NMR spectroscopy (internal standard: 1,1,2,2-tetrachloroethane).

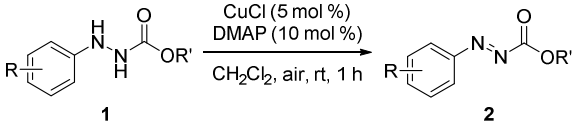
reaction using hydrazines such as *N*'-phenylbenzoylhydrazide and the reaction parameters as well as substrate scope for aerobic oxidation of alkyl 2-phenylhydrazinecarboxylates were not investigated sufficiently. Herein, we describe an efficient aerobic oxidative synthesis alkyl 2-phenylazocarboxylates catalyzed by CuCl/DMAP system.

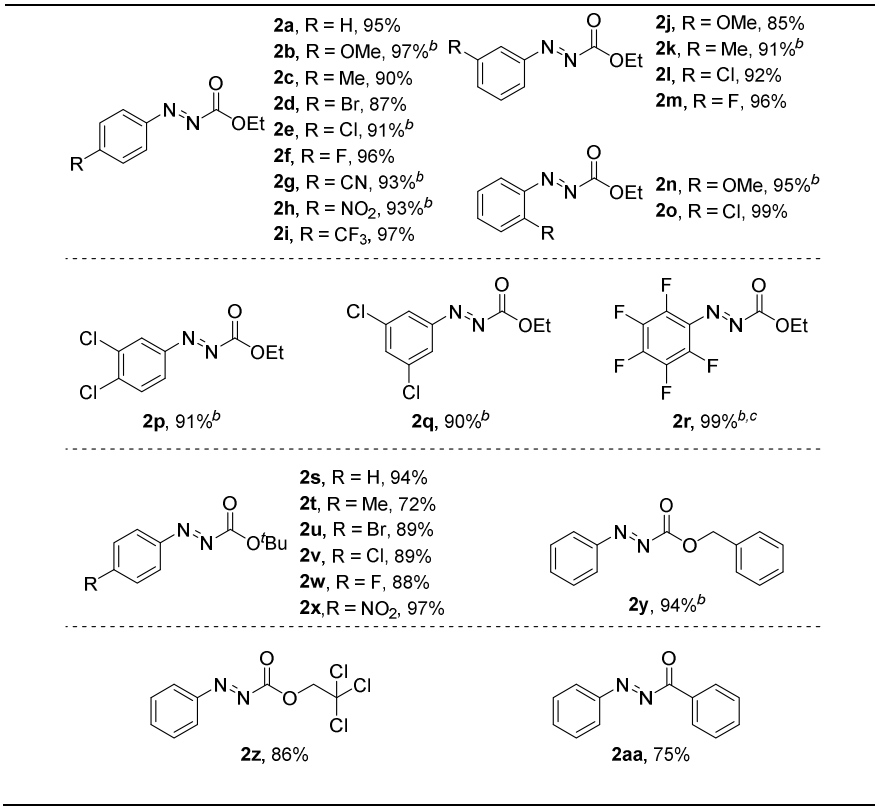
To prove our hypothesis, we screened copper catalyst with ethyl 2-phenylhydrazinecarboxylate **1a** as a model substrate (Table 1). The use of CuI/DMAP system, the optimized conditions in the aerobic oxidation of DBAD-H_2, gave poor conversion and yield in dichloromethane media (entry 1). It was revealed that several Cu sources such as CuCl, $Cu(CH_3CN)_4PF_6$, and $Cu(OAc)_2$, showed full conversion and excellent yield (entries 2–6).[24] However, we decided to choose CuCl for the optimal catalyst,[25] because it showed wide substrate scope. The use of pyridine, DBU, or 1,10-phenanthroline, instead of DMAP, produced ethyl 2-phenylazocarboxylate **2a** in lower yields (entries 7–9). It was revealed that the reactivity of the developed method was not affected by the choice of solvents, however, chlorinated solvents such as chloroform, dichloroethane, and dichloromethane exhibited better reactivities in general (entries 10 and 11). Control reactions revealed that CuCl, DMAP, and air are essential for oxidation of **1a**.[26] It was revealed that the reaction vessel size affected on the reactivity of the developed oxidation under air, however, the oxidation under oxygen showed better reactivity than under air as well as no significant difference of the reaction rate upon reaction vessel size. These observations indicated that mass transfer of oxygen is crucial for the present oxidation under air. In consideration of reactivity, reproducibility, and practicality, we decided to carry out the present oxidation in 50 mL round-bottom flask with a constant stirring rate (900 rpm) under air.

With the optimized conditions in hands (Table 1, entry 3), we investigated the substrate scope of the present aerobic oxidation (Table 2). Although good yields were generally obtained within 1 h, the prolonged reaction time increased the product yield above 90%.[27] Various *para*-substituted 2-phenylhydrazinecarboxylates underwent the present oxidation efficiently regardless of the electronic nature (**2a**–**2i**). The aerobic oxidation of *meta*-substituted as well as *ortho*-substituted 2-phenyl hydrazinecarboxylates produced the corresponding azo compound in good to excellent yields (**2j**–**2o**).

Disubstituted 2-phenylhydrazinecarboxylates such as **1p** and **1q** were employed and full conversions and high yields were observed in 3 h. The aerobic oxidation of **1r** was sluggish in the optimized conditions (45% conversion and 36% yield), however, the replacement of DMAP with 4-methoxypyridine gave a quantitative yield of **2r** in 3 h. It is presumably due to the facile coordination of electron deficient **2r** to Cu in 4-methoxypyridine, which has weaker interaction with Cu than DMAP.[28] Other alkyl 2-phenylhydrazinecarboxylates having *tert*-butyl (**2s**–**2x**), benzyl (**2y**), or trichloroethyl (**2z**), instead of ethyl group, were also tested in the present conditions, and good to high yields were observed. Interestingly, the aerobic oxidation of benzoyl-2-phenylhydrazine took place smoothly to provide benzoylazobenzene (**2aa**).

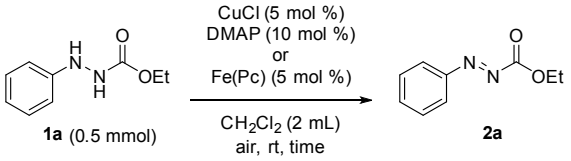
Table 2. Substrate scope of Cu-catalyzed aerobic oxidation of alkyl 2-phenylhydrazinecarboxylate.[a]





[a]Reaction conditions: **1** (0.5 mmol), CuCl (5 mol %), DMAP (10 mol %), and CH_2Cl_2 (2 mL) in 50 mL round-bottom flask under air at room temperature f or 1 h (stirring rate : 900 rpm). [b]For 3 h. [c]Instead of DMAP, 4-methoxypyridine was used.

We have compared the reaction rate of our developed Cu catalysis with that of Taniguchi's Fe(Pc) system,[19b] and observed that Cu catalysis is much faster than Fe(Pc) catalysis (Fig. 1). The present aerobic oxidation was effective on a larger scale (Scheme 1). Cu-catalyzed aerobic oxidation of **1a** (1.1 g, 6 mmol) was carried out in 200 mL beaker, the azo product **2a** was obtained in 87% yield.



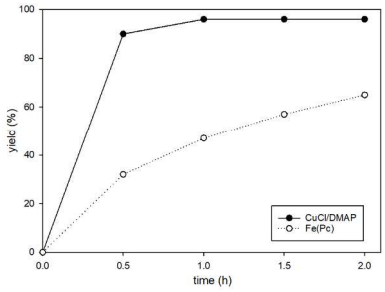
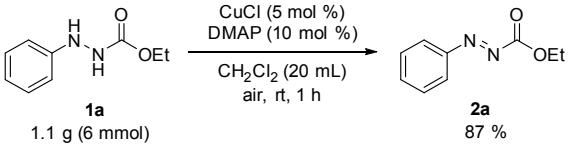
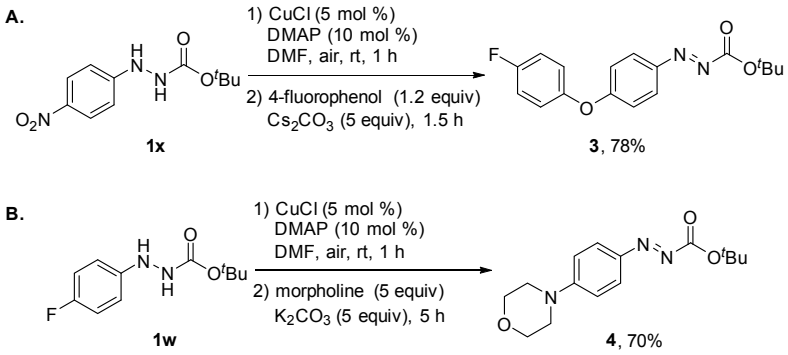


Figure 1. Comparison reaction rate of CuCl/DMAP catalysis with Fe(Pc) catalysis in the aerobic oxidation of **1a**.

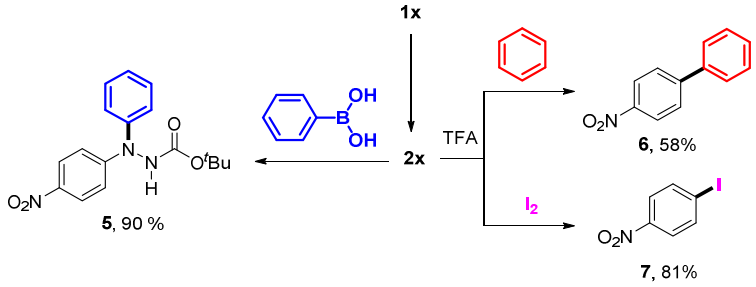


Scheme 1. The Cu-catalyzed aerobic oxidation on a gram scale.



Scheme 2. One-pot sequential aerobic oxidation and nucleophilic substitution.

Recently, Heinrich et al. demonstrated that **2x** underwent the nucleophilic substitution with phenol derivatives to generate diphenyl ethers.[12] We examined a domino reaction consisting of aerobic oxidation and nucleophilic substitution with **1x** in the presence of CuCl, DMAP, 4-fluorophenol, and Cs_2CO_3. However, the conversion of **1x** was poor and the desired product was obtained in only 38% yield without **2x**. The control experiment revealed that the nucleophilic substitution of **1x** with 4-fluorophenol did not occur. These results indicated that the poor yield of diphenyl ether was caused by the suppression of the aerobic oxidation of **1x** in the presence of 4-fluorophenol and Cs_2CO_3. To address this issue, we employed one-pot sequential strategy. After initial aerobic oxidation of **1x** in DMF for 1h, we added the solution of 4-fluorophenol and Cs_2CO_3 in DMF. After 1.5 h, the desired diphenyl ether **3** was isolated in 78% yield (Scheme 2, A). Similarly, **4** was synthesized by the addition of morpholine and K_2CO_3 after Cu-catalyzed aerobic oxidation of **1w** (Scheme 2, B).[29]



Scheme 3. Other one-pot sequential reactions with **1x**.

We also investigated other utilizations of **1x** using one-pot sequential strategy (Scheme 3). After the aerobic oxidation of **1x** with the developed Cu-catalysis, the addition of phenyl boronic acid gave hydrazine **5** in good yield,[11d,23a] or the addition of TFA generated aryl radical species.[12] We could utilized the in-situ generated aryl radical for the preparation of arylated (**6**, 58%) and iodinated compounds (**7**, 81%).

In summary, we demonstrated CuCl/DMAP was able to catalyze the aerobic oxidation of alkyl 2-phenylazocarboxylates efficiently. A variety of alkyl 2-phenylazocarboxylates were converted into the corresponding azo compounds in high to excellent yields within 3 h. The reaction rate of the developed

Cu catalysis was much faster than the previously reported Fe catalysis. The present method was effective even in larger scale. In addition, several one-pot sequential reactions consisting of Cu-catalyzed aerobic oxidation and other reactions were achieved.

Experimental Section

General considerations: All commercially available compounds and solvents were purchased and used as received, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with phosphomolybdic acid stain followed by heating. Flash chromatography was performed using Silica gel (particle size 40-63 um, 230-400 mesh). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 400 MHz NMR (400 MHz for ^{1}H, 101 MHz for ^{13}C, 376 MHz for ^{19}F). Chemical shift values are given in parts per million relative to internal TMS (0.00 ppm for ^{1}H) or $CDCl_3$ (77.06 ppm for ^{13}C). The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = double of doublet, dt = double of triplet, td = triple of doublet. Coupling constants, *J*, were reported in hertz unit (Hz). High resolution mass spectra were obtained from the Korea Basic Science Institute (Daegu) by using FAB method and magnetic sector mass analyzer.

Optimization for Cu-catalyzed aerobic oxidation of 1a (Table 1): To a 50 mL round bottom flask equipped with a magnetic stir bar, **1a** (0.5 mmol), copper catalyst (5 mol %, 0.025 mmol), additive (10 mol %, 0.05 mmol), and solvent (2.0 mL) were added. The reaction mixture was stirred at room temperature under air (stirring rate : 900 rpm). After 1 h, the reaction mixture was diluted by adding CH_2Cl_2 and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The ^{1}H NMR yield of the desired product was determined by integration using an internal standard (1,1,2,2-tetrachloroethane).

Preparation for alkyl 2-phenylhydrazinecarboxylates

Preparation for 1a-r, 1z, 1aa[17b]

To a 100 mL round bottom flask equipped with a magnetic stir bar, phenylhydrazine or appropriate phenylhydrazine hydrochloride (5.0 mmol), pyridine (1.1 equiv, 5.5 mmol, 0.45 mL), and CH_3CN (5.0 mL) were added. The solution was cooled to 0 ^oC and ethyl chloroformate (1.1 equiv, 5.5 mmol, 0.52 mL) was added dropwise. The reaction mixture was stirred for 1 h at room temperature. The reaction was diluted by adding CH_2Cl_2 and washed with 4 M HCl aqueous solution. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated on rotary evaporator. The residue was purified by recrystallization using CH_2Cl_2 and hexane to give alkyl 2-phenylhydrazinecarboxylates.

Preparation for 1s-x[30]

A 100 mL flame-dried round bottom flask, which was equipped with a magnetic stir bar and charged with phenylhydrazine or appropriate phenylhydrazine hydrochloride (5.0 mmol), was evacuated and back filled with N_2. After 3.0 mL of CH_3CN was added Et_3N (1.5 equiv, 7.5 mmol, 1.0 mL), di-*tert*-butyl dicarbonate (4.0 equiv, 20 mmol, 4.4 g), and CH_3CN (2.0 mL) were added in sequence. The reaction mixture was stirred for 1 h at room temperature. The reaction was diluted by adding CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated on rotary evaporator. The residue was purified by recrystallization using CH_2Cl_2 and hexane to give alkyl 2-phenylhydrazinecarboxylates. The hydrazine **1x** was purified by column chromatography and recrystallization.

Preparation for 1y[31]

To a 100 mL round bottom flask equipped with a magnetic stir bar, phenylhydrazine (5.0 mmol), pyridine (1.1 equiv, 5.5 mmol, 0.45 mL), and CH_2Cl_2 (5.0 mL) were added. The solution was cooled to 0 ^oC and benzoyl chloride (1.0 equiv, 5.0 mmol, 0.62 mL) was added dropwise. The reaction mixture was stirred for 5 h at room temperature. The reaction was diluted by adding CH_2Cl_2 and washed with 4 M HCl aqueous solution. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The

combined organic layer was dried over $MgSO_4$, filtered, and concentrated on rotary evaporator. The residue was purified by recrystallization using CH_2Cl_2 and hexane to give a benzoyl phenylhydrazine, **1y**.

General procedure for Cu-catalyzed aerobic oxidation of alkyl 2-phenylhydrazinecarboxylates (Table 2): To a 50 ml round bottom flask equipped with a magnetic stir bar, alkyl 2-phenylhydrazinecarboxylate (0.5 mmol), CuCl (5 mol %, 0.025 mmol, 2.5 mg), DMAP (10 mol %, 0.05 mmol, 6.2 mg), and CH_2Cl_2 (2.0 mL) were added. The reaction mixture was stirred for 1 or 3 h at room temperature under air (stirring rate : 900 rpm). The reaction was diluted by adding CH_2Cl_2 and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography to give azo products.

Ethyl 2-phenylazocarboxylate[19b] **(2a)**; 95% (85 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H), δ 7.61-7.49 (m, 3H), δ 4.52 (q, J = 7.1 Hz, 2H), δ 1.47 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.4, 152.8, 135.0, 130.4, 124.9, 65.6, 15.3.

Ethyl 2-(4-methoxyphenyl)azocarboxylate[19b] **(2b)**; 97% (110 mg), red oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 2H), δ 7.00 (d, J = 8.9 Hz, 2H), δ 4.50 (q, J = 7.1, Hz, 2H), δ 3.89 (s, 3H), δ 1.46 (t, J = 7.1 Hz 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 164.1, 161.6, 145.6, 125.9, 114.0, 63.7, 55.2, 13.7.

Ethyl 2-(4-methylphenyl)azocarboxylate[19b] **(2c)**; 90% (86 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.84 (d, J = 8.1 Hz, 2H), δ 7.32 (d, J = 8.0 Hz, 2H), δ 4.51 (q, J = 7.1 Hz, 2H), δ 2.44 (s, 3H), δ 1.46 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.7, 149.3, 144.7, 129.5, 123.4, 63.9, 21.2, 13.7.

Ethyl 2-(4-bromophenyl)azocarboxylate[19b] **(2d)**; 87% (112 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.6 Hz, 2H), δ 7.67 (d, J = 8.6 Hz, 2H), δ 4.52 (q, J = 7.1 Hz, 2H), δ 1.47 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.4, 149.8, 132.2, 128.4, 124.6, 64.1, 13.7.

Ethyl 2-(4-chlorophenyl)azocarboxylate[19b] **(2e)**; 91% (103 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7Hz, 2H), δ 7.47 (d, *J* = 8.7 Hz, 2H), δ 4.49 (q, *J* = 7.1 Hz, 2H), δ 1.44 (t, *J* = 7.1 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.4, 149.4, 139.7, 129.2, 154.5, 64.1, 13.7.

Ethyl 2-(4-fluorophenyl)azocarboxylate[19b] **(2f)**; 96% (94 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 5.3 Hz, 2H), δ 7.21 (t, *J* = 8.5 Hz, 2H), δ 4.52 (q, *J* = 7.1 Hz, 2H), δ 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 165.6 (d, *J* = 256.6 Hz), 161.5, 147.7 (d, *J* = 2.9 Hz), 125.7 (d, *J* = 9.6 Hz), 116.0 (d, *J* = 23.2 Hz), 64.0, 13.6.; ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.2.

Ethyl 2-(4-cyanophenyl)azocarboxylate[19b] **(2g)**; 93% (94 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), δ 7.81 (d, *J* = 8.4 Hz, 2H), δ 4.51 (q, *J* = 7.1 Hz, 2H), δ 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.2, 152.6, 132.9, 123.5, 117.3, 116.2, 64.5, 13.7.

Ethyl 2-(4-nitrophenyl)azocarboxylate[19b] **(2h)**; 93% (104 mg), red solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.9 Hz, 2H), δ 8.06 (d, *J* = 8.9 Hz, 2H), δ 4.56 (q, *J* = 7.1 Hz, 2H), δ 1.49 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.1, 153.8, 149.8, 124.3, 123.7, 64.5, 13.6.

Ethyl 2-(4-(trifluoromethyl)phenyl)azocarboxylate[11g] **(2i)**; 97% (119 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), δ 7.80 (d, *J* = 8.2 Hz, 2H), δ 4.54 (q, *J* = 7.1 Hz, 2H) , δ 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.0, 157.3, 138.8 (q, *J* = 32.8 Hz), 130.6 (q, *J* = 3.7 Hz), 127.9, 127.6 (q, *J* = 272.7 Hz), 68.9, 18.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.0.

Ethyl 2-(3-methoxyphenyl)azocarboxylate[19b] **(2j)**; 85% (88 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), δ 7.47-7.40 (m, 2H), δ 7.14 (d, *J* = 8.3 Hz, 1H), δ 4.52 (q, *J* = 7.1 Hz, 2H), δ 3.85 (s, 3H), δ 1.47 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 160.3, 152.7, 130.0, 121.0, 118.7, 105.3, 64.5, 55.5, 14.1.

Ethyl 2-(3-methylphenyl)azocarboxylate[19b] **(2k)**; 91% (87 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78-7.73 (m, 2H), δ 7.45-7.38 (m, 2H), δ 4.52 (q, *J* = 7.1, Hz 2H), δ 2.43 (s, 3H), δ

1.47 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 151.7, 139.3, 134.6, 129.1, 123.5, 121.7, 64.4, 21.2, 14.1.

Ethyl 2-(3-chlorophenyl)azocarboxylate[19b] **(2l)**; 92% (98 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.82 (m, 2H), δ 7.51 (dt, J = 15.8, 7.9 Hz, 2H), δ 7.48 (t, J = 7.9 Hz, 1H), δ 4.53 (q, J = 7.2 Hz, 2H), δ 1.47 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.3, 151.8, 135.0, 132.9, 129.9, 122.8, 121.8, 64.2, 13.7.

Ethyl 2-(3-fluorophenyl)azocarboxylate (2m); 96% (94 mg), red solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (m, 2H), δ 7.24-7.18 (m, 2H), δ 4.52 (q, 2H), δ 1.47 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.1 (d, J = 256.6 Hz), 161.9, 148.1 (d, J = 3.0 Hz), 126.2 (d, J = 9.6 Hz), 116.6, 116.3, 64.5, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –104.2; HRMS (FAB) m/z calcd. for $C_9H_{10}FN_2O_2$ $[M+H]^+$: 197.0726, found 197.0723.

Ethyl 2-(2-methoxyphenyl)azocarboxylate (2n); 95% (99 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.1 Hz, 1H), δ 7.55 (t, J = 7.8 Hz, 1H), δ 7.10 (d, J = 8.5 Hz, 1H), δ 6.98 (t, J = 7.7 Hz, 1H), δ 4.49 (q, J = 7.2 Hz, 2H), δ 4.02 (s, 3H), δ 1.45 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.8, 158.2, 140.4, 135.5, 120.1, 116.1, 112.5, 63.8, 55.7, 13.7; HRMS (FAB) m/z calcd. for $C_{10}H_{13}N_2O_3$ $[M+H]^+$: 209.0926, found 209.0929.

Ethyl 2-(2-chlorophenyl)azocarboxylate[19b] **(2o)**; 99% (105 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 12.4, 8.2 Hz, 2H), δ 7.49 (t, J = 7.6 Hz, 1H), δ 7.33 (t, J = 7.7 Hz, 1H), δ 4.52 (q, J = 7.1 Hz, 2H), δ 1.46 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.0, 147.8, 137.2, 134.4, 131.1, 127.3 , 117.1, 64.6, 14.1.

Ethyl 2-(3,4-dichlorophenyl)azocarboxylate[19b] **(2p)**; 91% (120 mg), red solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), δ 7.77 (d, J = 8.5 Hz, 1H), δ 7.59 (d, J = 8.5 Hz, 1H), δ 4.49 (q, J = 7.1 Hz, 2H), δ 1.44 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.1, 149.8, 137.6, 133.5, 130.7, 124.1, 123.0, 64.3, 13.9.

Ethyl 2-(3,5-dichlorophenyl)azocarboxylate[19b] **(2q)**; 90% (111 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 2H), δ 7.55 (s, 1H), δ 4.53 (q, *J* = 7.2 Hz, 2H), δ 1.47 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.0, 151.9, 135.5, 132.4, 121.6, 64.4, 13.6.

Ethyl 2-(2,3,4,5,6-pentafluorophenyl)azocarboxylate[19b] **(2r)**; 99% (133 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (q, *J* = 7.2 Hz, 2H), δ 1.49 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 160.7, 145.0–144.7 (m), 143.3–143.1 (m), 142.4–142.1 (m), 140.6–140.4 (m), 139.4–139.1 (m), 136.8–136.6 (m), 126.8–126.6 (m), 65.16, 13.96; ^{19}F NMR (376 MHz, $CDCl_3$) δ –146.7, –161.1.

***tert*-Butyl 2-phenylazocarboxylate**[19b] **(2s)**; 94% (97 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), δ 7.58-7.47 (m, 3H), δ 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 161.3, 151.6, 133.4, 129.2, 123.5, 85.0, 27.9.

***tert*-Butyl 2-(4-methylphenyl)azocarboxylate**[16] **(2t)**; 72% (79 mg), yellow solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), δ 7.30 (d, *J* = 8.0 Hz, 2H), δ 2.43 (s, 3H), δ 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.4, 150.9, 145.7, 131.0, 124.8, 75.3, 29.0, 22.8.

***tert*-Butyl 2-(4-bromophenyl)azocarboxylate**[16] **(2u)**; 89% (127 mg), yellow solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.6 Hz, 2H), δ 7.66 (d, *J* = 8.5 Hz, 2H), δ 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.1, 154.4, 136.7, 132.4, 129.1, 89.4, 31.9.

***tert*-Butyl 2-(4-chlorophenyl)azocarboxylate**[16] **(2v)**; 89% (107 mg), yellow solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 2H), δ 7.48 (d, *J* = 8.6 Hz, 2H), δ 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 151.1, 140.7, 130.7, 125.9, 75.3, 29.0.

***tert*-Butyl 2-(4-fluorophenyl)azocarboxylate**[16] **(2w)**; 88% (99 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.87 (m, 2H), δ 7.22-7.16 (m, 2H), δ 1.66 (s, 9H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 165.8 (d, *J* = 255.7 Hz), 160.98, 148.1 (d, *J* = 2.9 Hz), 125.9 (d, *J* = 9.5 Hz), 116.3 (d, *J* = 23.1 Hz), 85.0, 27.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –105.1.

***tert*-Butyl 2-(4-nitrophenyl)azocarboxylate**[12b] **(2x)**; 97% (122 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.9 Hz, 2H), δ 8.03 (d, *J* = 8.9 Hz, 2H), δ 1.68 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.5, 154.4, 150.1, 124.7, 124.1, 86.1, 27.8.

Benzyl 2-phenylazocarboxylate[19b] **(2y)**; 94% (113 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.2 Hz, 2H), δ 7.59-7.54 (m, 1H), δ 7.53-7.46 (m, 4H), δ 7.43-7.35 (m, 3H), δ 5.46 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.1, 151.6, 134.4, 134.0, 129.3, 128.9, 128.8, 128.7, 123.8, 69.9.

2,2,2,-Trichloroethyl 2-phenylazocarboxylate[19b] **(2z)**; 86%, (121 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2H), δ 7.64 (t, *J* = 7.3 Hz, 1H), δ 7.59-7.53 (m, 2H), δ 5.07 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 172.6, 160.6, 151.6, 134.5, 129.4, 124.1, 29.7

Benzoylazobenzene[19b] **(2aa)**; 75% (79 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.2 Hz, 2H), δ 7.99 (d, *J* = 7.4 Hz, 2H), δ 7.64 (t, *J* = 7.4 Hz, 1H), δ 7.57 (t, *J* = 7.7 Hz, 3H), δ 7.60-7.47 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.6, 106.6, 89.2, 88.0, 85.4, 85.1, 84.0, 83.5, 78.2.

Procedure for Cu-catalyzed aerobic oxidation of 1a on gram scale (Scheme 1): To a 200 mL beaker equipped with a magnetic stir bar, **1a** (6.0 mmol, 1.07 g), CuCl (5 mol %, 0.3 mmol, 30 mg), DMAP (10 mol %, 0.6 mmol, 73 mg), and CH_2Cl_2 (20 mL) were added. After covering the beaker with a perforated parafilm, reaction mixture was stirred for 1 h at room temperature under air (stirring rate : 900 rpm). The reaction was diluted by adding CH_2Cl_2 and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography to give **2a**.

Procedure for one-pot sequential nucleophilic substitution (Scheme 2): To a 50 mL round bottom flask equipped with a magnetic stir bar, **1x** (0.5 mmol), CuCl (5 mol %, 0.025 mmol, 2.5 mg), DMAP (10 mol %, 0.05 mmol, 6.2 mg), and DMF (2.0 mL) were added (stirring rate : 900 rpm). After 1 h, 4-fluorophenol (1.2 equiv, 0.6 mmol, 67 mg), Cs_2CO_3 (5.0 equiv, 2.5 mmol, 800 mg), and DMF (4.0 mL)

were added for **3** or morpholine (5 equiv, 2.5 mmol, 0.21 mL), K_2CO_3 (5.0 equiv, 2.5 mmol, 346 mg), and DMF (2.0 mL) were added for **4**. The reaction mixture was stirred for 1.5 h or 5 h for the synthesis of **3** or **4**, respectively. The reaction was diluted by adding EtOAc and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography to give **3** (EA/hexane=1:5) or **4** (EA/hexane=1:2)

***tert*-Butyl 2-(4-(4'-fluorophenoxy)phenyl)azocarboxylate**[12a] **(3)**; 78% (123 mg), orange oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), δ 7.14-7.04 (m, 4H), δ 7.02 (d, *J* = 8.9 Hz, 2H), δ 1.66 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6, 161.1, 159.6 (d, *J* = 243.7 Hz), 151.0 (d, *J* = 2.7 Hz), 147.0, 126.0, 121.9 (d, *J* = 8.4 Hz), 117.3, 116.7 (d, *J* = 23.4 Hz), 84.7, 27.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –117.8.

***tert*-Butyl 2-(*N*'-(4-Morpholin-4-yl-phenyl))azocarboxylate**[12a] **(4)**; 70% (102 mg), orange solid, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 2H), δ 6.90 (d, *J* = 9.0 Hz, 2H), δ 3.86 (dd, *J* = 6.4, 3.0 Hz, 4H), δ 3.39 (dd, *J* = 6.5, 2.9 Hz, 4H), δ 1.66 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.1, 154.9, 144.2, 126.5, 113.4, 83.8, 66.4, 47.2, 27.9.

Procedure for one-pot sequential arylation with boronic acid (Scheme 3): After 1 h of Cu-catalyzed aerobic oxidation of **1x** in the developed conditions, CH_2Cl_2 was evaporated and phenylboronic acid (1.8 equiv, 0.9 mmol, 110 mg) and MeOH (2.0 mL) was added. The reaction mixture was stirred for 40 min. The reaction was diluted by adding EtOAc and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography to give **5**. (EA/hexane=1:5)

***tert*-Butyl 2-(4-nitrophenyl)-2-phenylhydrazinecarboxylate**[11d] **(5)**; 90% (148 mg), yellow oil, EA/hexane=1:5, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.5 Hz, 2H), δ 7.48-7.25 (m, 6H), δ 6.91 (d, J = 7.2 Hz, 2H), δ 1.45/1.35 (s, 9H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.3, 152.5, 143.5, 140.4, 129.8, 125.6, 124.9, 113.3, 82.2, 28.2.

Procedure for the synthesis of 6 and 7 (Scheme 3): After 1 h of Cu-catalyzed aerobic oxidation of **1x** in the developed conditions, CH_2Cl_2 was evaporated and benzene (50 equiv, 25 mmol, 2.2 mL) and TFA (10 equiv, 5 mmol, 0.4 mL) were added for **6** or iodine (10 equiv, 5.0 mmol, 2.5 g), TFA (10 equiv, 5.0 mmol, 0.4 mL), and CH_3CN (2.0 mL) were added for **7**. The reaction mixture was stirred at 80 ^oC for 0.5 h (**6**) or 4 h (**7**). The reaction was diluted by adding EtOAc and quenched with a saturated aqueous solution of NH_4Cl. Two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The residue was purified by column chromatography to give **6** (EA/hexane=1:5) or **7** (hexane)

1-Phenyl-4-nitrobenzene[12a] **(6)**; 57% (57 mg), brown solid, EA/hexane=1:5, ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.9 Hz, 2H), δ 7.73 (d, J = 8.9 Hz, 2H), δ 7.62 (d, J = 8.0 Hz, 2H), δ 7.53-7.43 (m, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.6, 147.0, 138.7, 129.1, 128.9, 127.8, 127.4, 124.1.

1-Iodo-4-nitrobenzene[12a] **(7)**; 80% (100 mg), white solid, hexane, ^1H NMR (400 MHz, $CDCl_3$) δ 8.02-7.84 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 147.7, 138.6, 124.8, 102.7.

Author Information

Corresponding Authors

* E-mail: jinho@inu.ac.kr

Notes

The authors declare no competing financial interest.

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Associated Content

Supporting Information: Copies of ^1H, ^{13}C, and ^{19}F NMR spectra are included. This material is available free of charge via the Internet at http://pubs.acs.org/.

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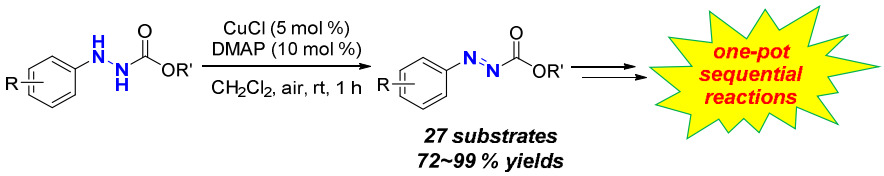
(31) (a) Cox, L. J.; Park, K.-H. *Tetrahedron Lett*. **2002**, *43*, 3899–3901; (b) Zhang, Y.; Tang, Q.; Luo, M. *Org. Biomol. Chem*. **2011**, *9*, 4977–4982.

TOC Graphic:


CuCl (5 mol %)
DMAP (10 mol %)
CH2Cl2, air, rt, 1 h
OR'
R
27 substrates
72~99 % yields
one-pot
sequential
reactions