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Cu(OAc)$_2$/TFA-Promoted Formal [3 + 3] Cycloaddition/Oxidation of Enamines and Enones for Synthesis of Multisubstituted Aromatic Amines

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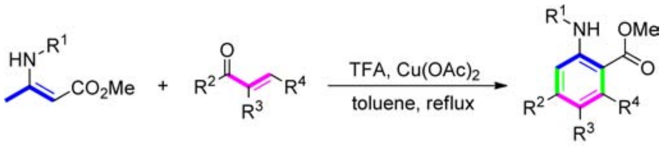
ABSTRACT



R^1 = aryl, alkyl; R^2 = aryl, alkyl; R^3 = H, CO_2Me, CO_2Et, COMe; R^4 = aryl

New strategies for the oxidative cycloaddition of enones with enamines are developed. These cycloaddition reactions directly afford substituted aromatic amines, which are important in organic chemistry, in moderate to good yield. Cu(OAc)$_2$/TFA is shown to be essential to achieve high reaction efficiency.

[3 + 3] Cycloaddition reactions are useful for the synthesis of six-membered cyclic compounds[1,2] and have been widely used in natural product synthesis.[3] However, this strategy is mainly limited to the synthesis of heterocycles[4] such as pyrans,[5] piperidine,[6] and pyridines.[7] The direct formation of multisubstituted arenes *via* formal [3 + 3] cycloaddition has rarely been reported. Although some methods to synthesize arene derivatives are available,[8−10] a direct methodology to generate substituted arenes that is compatible with various functional groups and uses readily available starting materials remains highly desirable.[11]

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Scheme 1. Construction of Arylamines by Formal [3 + 3] Strategy

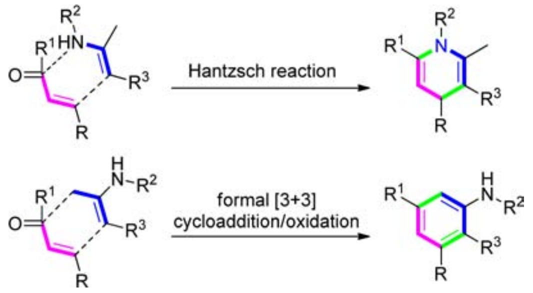
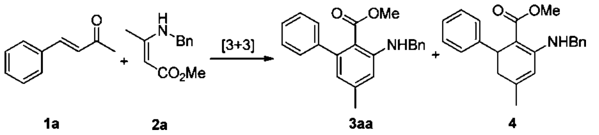


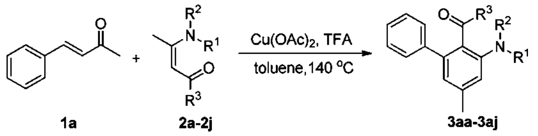
Table 1. Optimization of [3 + 3] Cycloaddition/Oxidation Reaction Conditions[a]



entry	oxidant	acid	solvent	t (h)	yield[b] (%)
1		AcOH	CH_3OH	10	trace (23)
2		TFA	CH_3OH	10	trace (42)
3		TFA	toluene	5	17 (40)
4		TFA	DMF	5	13 (10)
5	$CuSO_4$	TFA	toluene	5	18 (0)
6	$CuCl_2$	TFA	toluene	5	10 (0)
7	CuO	TFA	toluene	5	21 (0)
8	Oxone	TFA	toluene	7	11 (0)
9	(t-BuO)$_2$	TFA	toluene	5	10 (0)
10	Cu(OAc)$_2$	TFA	toluene	5	27 (0)
11[c]	Cu(OAc)$_2$	TFA	toluene	5	36 (0)
12[d]	Cu(OAc)$_2$	TFA	toluene	5	56 (0)
13[d,e]	Cu(OAc)$_2$	TFA	toluene	5	45 (0)

[a] Reactions were carried out using oxidant (1.0 equiv), acid (50 mol %), **1a** (0.3 mmol), and **2a** (0.36 mmol) in toluene (3 mL) at 120 °C under air. [b] The numbers in parentheses are the isolated yields of **4**. [c] TFA (1.0 equiv). [d] The reaction was refluxed in a 140 °C oil bath. [e] The reaction was carried out under Ar.

Table 2. Cu(OAc)$_2$/TFA-Promoted Formal [3 + 3] Cycloaddition/Oxidation with Different Enamines[a]



entry	substrate	product	yield (%)[b]
1	**2a** (R^1 = Bn; R^2 = H; R^3 = OMe)	**3aa**	56
2	**2b** (R^1 = Cy; R^2 = H; R^3 = OMe)	**3ab**	67
3	**2c** (R^1 = i-Pr; R^2 = H; R^3 = OMe)	**3ac**	63
4	**2d** (R^1 = Et; R^2 = H; R^3 = OMe)	**3ad**	43
5	**2e** (R^1 = Me; R^2 = H; R^3 = OMe)	**3ae**	42
6	**2f** (R^1 = Ph; R^2 = H; R^3 = OMe)	**3af**	24
7	**2g** (R^1 = H; R^2 = H; R^3 = OMe)	**3ag**	0
8	**2h** (R^1 = Et; R^2 = Et; R^3 = OMe)	**3ah**	0
9	**2i** (R^1 = Cy; R^2 = H; R^3 = OEt)	**3ai**	66
10	**2j** (R^1 = Cy; R^2 = H; R^3 = Me)	**3aj**	56

[a] Reactions were carried out using Cu(OAc)$_2$ (1.0 equiv), TFA (1.0 equiv), **1a** (0.3 mmol), and **2a**−**2j** (0.36 mmol) in toluene (3 mL) at reflux (in a 140 °C oil bath) under air, 4−7 h. [b] Isolated yields.

Enamines are powerful building blocks in organic synthesis. They are widely used in nucleophilic addition reactions for stereoselective construction of C−N[12] and C−C[13] bonds. Additionally, the high reactivity of the amino group and vinyl moiety of enamines makes it powerful for azaheterocycles synthesis, such as Hantzsch dihydropyridine (pyridine) synthesis and Nenitzescu indole synthesis.[14] There are a few examples of formal [3 + 3] cycloadditions of enamines and enones for the construction of cyclohexenes.[15,16] Although the reactions are still limited in substrate scope and low yields, a regioselective reaction on an allylic sp^3 C−H bond of enamines was achieved. We hypothesized that an oxidative [3 + 3] cycloaddition of prevalent enones and enamines may be used to construct multisubstituted aromatic amines directly (Scheme 1). In this communication, we report a novel cycloaddition reaction of enones and enamines to synthesize substituted aromatic amines.

Our investigation commenced with the cycloaddition/oxidation of benzylidene acetone **1a** and methyl 3-(benzylamino)but-2-enoate **2a** (Table 1). To our delight, when the reaction was performed under acidic conditions in CH_3OH at reflux (oil bath, 120 °C), cyclohexadiene **4** was isolated as a major product (Table 1, entries 1−2). The structure of **4** prompted us to optimize the reaction conditions. Screening of various parameters revealed that toluene and TFA were the most efficient solvent and acid, respectively, for this transformation although the main product was not what we desired (Table 1, entries 1−4). A series of oxidants were then screened, and it was found that Cu(OAc)$_2$ was the best oxidant for the selective formation of aromatic amine **3aa** (Table 1, entries 5−10; see the

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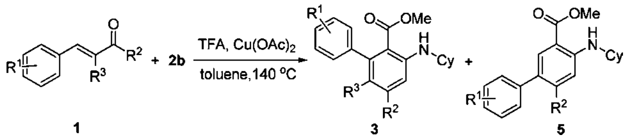
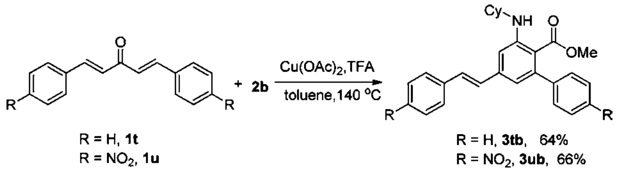
Table 3. Cu(OAc)$_2$/TFA-Promoted Formal [3 + 3] Cycloaddition/Oxidation of Various Enones with Enamine **2b**[a]



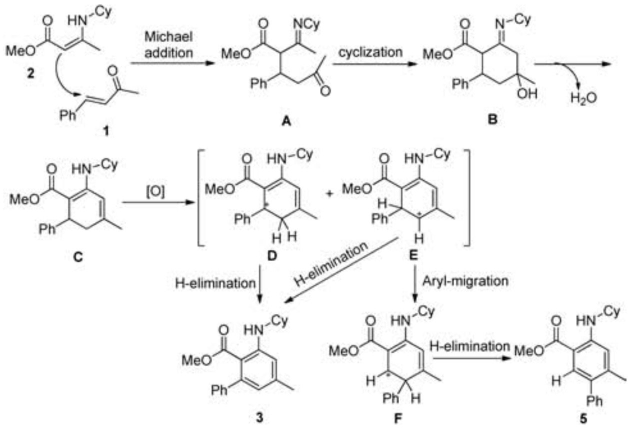
entry	substrate	product	yield (%)[b]
1	**1a** (R^1 = H; R^2 = Me; R^3 = H)	**3ab**	67
2	**1b** (R^1 = 4-Cl; R^2 = Me; R^3 = H)	**3bb**	66
3	**1c** (R^1 = 2-Cl; R^2 = Me; R^3 = H)	**3cb**	63
4	**1d** (R^1 = 2,4-Cl; R^2 = Me; R^3 = H)	**3db**	68
5	**1e** (R^1 = 4-F; R^2 = Me; R^3 = H))	**3eb**	56
6	**1f** (R^1 = 4-Br; R^2=Me; R^3 = H)	**3fb**	63
7	**1g** (R^1 = 4-NO$_2$; R^2 = Me; R^3 = H)	**3gb**	67
8	**1h** (R^1 = 3-NO$_2$; R^2 = Me; R^3 = H)	**3hb**	68
9	**1i** (R^1 = 4-Me; R^2 = Me; R^3 = H)	**3ib**	60
10	**1j** (R^1 = 3-Me; R^2 = Me; R^3 = H)	**3jb**	65
11	**1k** (R^1 = 4-Me$_2$N; R^2 = Me; R^3 = H)	**5k**	33
12	**1l** (R^1 = 2-MeO; R^2 = Me; R^3 = H)	**3 lb**	36
		5l	29
13	**1m** (R^1 = 4-MeO; R^2 = Me; R^3 = H)	**3mb**	37
		5m	28
14	**1n** (R^1 = H; R^2 = Et; R^3 = H)	**3nb**	63
15	**1o** (R^1 = H; R^2 = Ph; R^3 = H)	**3ob**	62
16	**1p** (R^1 = H; R^2 = Me; R^3 = CO$_2$Me)	**3pb**	73
17	**1p** (R^1 = H; R^2 = Me; R^3 = CO$_2$Et)	**3qb**	76
18	**1r** (R^1 = H; R^2 = Me; R^3 = COCH$_3$)	**3rb**	63
19	**1s** (R^1 = H; R^2 = H; R^3 = H)	**3sb**	34

[a] Reactions were carried out with Cu(OAc)$_2$ (1.0 equiv), TFA (1.0 equiv), **1a**–**1s** (0.3 mmol), and **2a** (0.36 mmol) in toluene (3 mL) at reflux (in a 140 °C oil bath) under air, 4–7 h. [b] Isolated yields.

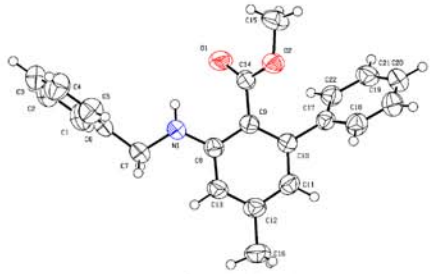
Scheme 2



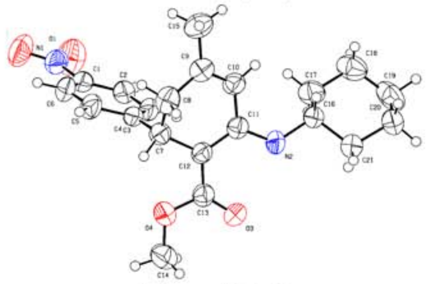
Scheme 3. Proposed Mechanism of Cu(OAc)$_2$/TFA-Promoted Formal [3 + 3] Cycloaddition/Oxidation



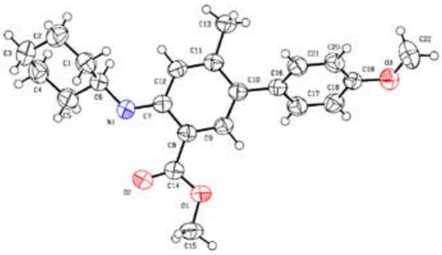
X-Ray Structures:



Product 3 (**3aa**)



Intermediate **C**



Pruduct 5 (**5m**)

Supporting Information for the X-ray structure of **3aa**). Furthermore, by optimizing the ratio of Cu(OAc)$_2$ and TFA, it was found that the reaction proceeded most effectively in Cu(OAc)$_2$ (1.0 equiv) and TFA (1.0 equiv) (Table 1, entry 11). The vigorous reflux was important for the reaction. A 140 °C oil bath was required to facilitate the reaction (Table 1, entry 12). Additionally, the product **3aa** was obtained in 45% yield when the reaction was performed under an argon atmosphere (Table 1, entry 13). This result indicated that the oxygen play a role for the reaction.

With the optimal parameters for this formal [3 + 3] cycloaddition/oxidation process established, its applicability to different enamines was investigated (Table 2). *N*-Substituted enamines with different aliphatic or aryl groups exhibited different reactivity. The degree of reactivity follows the sequence cyclohexyl > isopropyl > benzyl > ethyl > methyl > phenyl (Table 2, entries 1–6). Enamines with NH$_2$ or NEt$_2$ substituents (**2g** and **2h**, respectively) were unreactive (Table 2, entries 7 and 8). In addition, enaminone **2j** showed similar reactivity to enaminoester **2i**; both gave the desired amines **3ai** and **3aj**, respectively, in good yield (Table 2, entries 9–10).

Furthermore, the formal [3 + 3] cycloaddition/oxidation reaction proceeded smoothly with a series of enones **1a**–**1s** and enamine **2b** (Table 3). Benzalacetones with either electron-donating or -withdrawing groups on the phenyl groups reacted efficiently to give the corresponding arylamines in good yields (Table 3, entries 1–10). Overall, this transformation displays high functional group tolerance. It is worth noting that reaction with *o*-MeO- or *p*-MeO-substituted substrates not only gave the corresponding products **3lb** and **3mb** in 36 and 37% yield, respectively, but also afforded aryl-shift byproducts **5l** and **5m** in 29 and 28% yield, respectively (Table 3, entries 12–13; see the Supporting Information for the X-ray structure of **5m**). Only aryl-shift product **5k** was observed when **1k** was used as the substrate (Table 3, entry 11). When (*E*)-1-phenylpent-1-en-3-one **1n** and (*E*)-chalcone **1o** were employed as substrates, the corresponding arylamines **3nb** and **3ob**, respectively, were obtained in good yield (Table 3, entries 14–15). In addition, enones bearing an electron-withdrawing group at α-C, such as an ester and carbonyl moiety, also gave good results (Table 3, entries 16–18). Cinnamaldehyde **1s** was also converted into the corresponding arylamine **3sb** in 34% yield along with a mixture of byproducts (Table 3, entry 19).

To expand the applicability of the present method, the reaction of enones **1t** and **1u** with enamine **2b** was performed in the presence of $Cu(OAc)_2$ and TFA. The corresponding arylamine products **3tb** and **3ub** were obtained in 64 and 66% yield, respectively, as shown in Scheme 2.

A possible mechanism for the formal [3 + 3] cycloaddition/oxidation process is outlined in Scheme 3. The reaction commences with a Michael addition of enamine **2** to enone **1** yielding **A**, which undergoes an intramolecular cyclization reaction to form intermediate **B**. Subsequent dehydration and tautomerization gives intermediate **C** that is then oxidized by Cu^{2+} to form intermediates **D** and **E**. After elimination of a proton, **D** and **E** produce the energetically favored arylamine product **3**.[17] Alternatively, aryl migration of intermediate **E** followed by proton elimination would give product **5**.[18] Electron-rich arenes promote aryl migration,[19] which is consistent with the above results (Table 3, entries 11–13).

In conclusion, we have developed a novel $Cu(OAc)_2$/TFA-promoted formal [3 + 3] cycloaddition oxidation reaction for direct synthesis of multisubstituted aromatic amines. This novel method tolerates a wide range of functional groups and is a reliable procedure for rapid elaboration of readily available enamines and enones into a variety of substituted aromatic amines under mild conditions. Further scope and mechanistic studies of this reaction are underway in our laboratory.

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Supporting Information Available. Experimental procedures, spectral data for all products, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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