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Direct Oxidative Coupling of Enamines and Electron-Deficient Amines: TBAI/TBHP-Mediated Synthesis of Substituted Diaminoalkenes under Metal-Free Conditions

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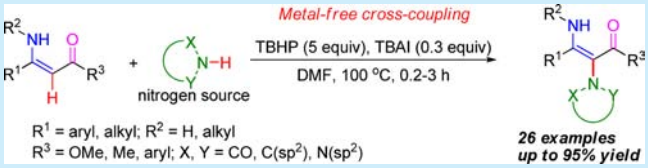
Supporting Information

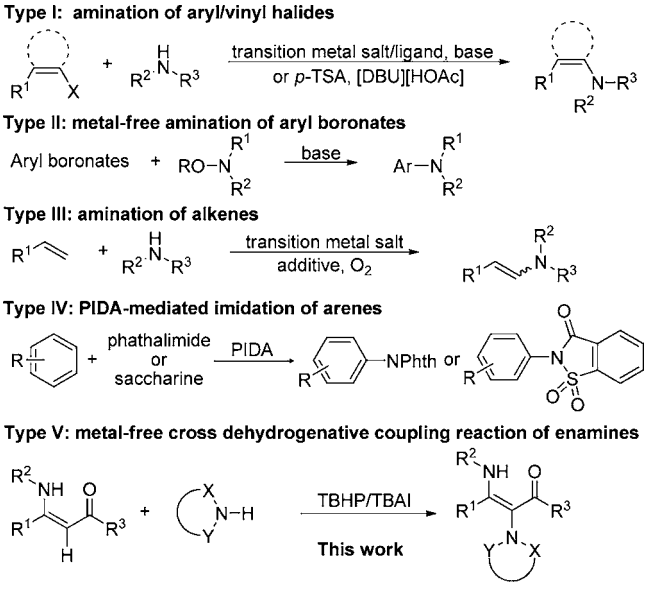
ABSTRACT: A metal-free cross-coupling of enamines and electron-deficient amines through oxidative C(sp^2)−N bond formation has been realized by using TBAI as catalyst and TBHP as oxidant. This novel strategy allows for an efficient organocatalytic synthesis of the synthetically useful diaminoalkene derivatives and is highlighted by appealing features such as readily available of the starting materials, wide substrate scope and transition-metal-free characteristics.



Cross-coupling reactions between an sp^2 carbon of an arene or alkene and an N-moiety represent the most adopted approach in building N-containing compounds in modern organic chemistry.[1] Fascinated by this powerful synthetic strategy, organic chemists have devoted a great deal of efforts to the development of notable C(sp^2)−N cross-coupling reactions. To date, the existing approaches generally fall into one of the following types. Type I is the cross-coupling reaction between aryl/vinyl halides and N-containing amines or amides, either in the presence of transition metals such as Cu,[2] Pd,[3] Co,[4] Rh,[5] Ni,[6] etc., including the well-known Goldberg reaction and Buchwald−Hartwig amination, or through the assistance of Brønsted acid/[DBU][HOAc] under metal-free conditions (Scheme 1, type I).[7] The second type involves aryl boronates reacting with aminating agents under basic conditions which give the cross-coupled products through C(sp^2)−N bond formation (Scheme 1, type II).[8] Significant progress in recent years has led to success in direct oxidative amination of olefins with amines catalyzed by Pd or Au (Scheme 1, type III).[9] It is evident that in these three types, prefunctionalization of the C(sp^2) of the arene/alkene and/or the presence of transition metals are/is indispensable for the coupling to occur. To our knowledge, there are few reports describing direct oxidative amination of an unfunctionalized arene/alkene under metal-free conditions. A literature search shows that the only existing such examples involve a hypervalent iodine-mediated intermolecular oxidative C(sp^2)−N coupling reaction between an arene and phthalimide or saccharine (Scheme 1, type IV),[10] but none with the more general alkene functionality. In this paper, we disclose an unprecedented cross-coupling reaction between the alkene moiety of enamines and electron-deficient amines through TBAI/TBHP-mediated oxidative C(sp^2)−N bond formation (Scheme 1, type V).

The combined use of TBAI as catalyst and TBHP as the terminal oxidant has been widely used as a powerful oxidation system in various oxidative coupling reactions.[11] For example, it has been applied to the syntheses of amide compounds from cross-couplings of aryl methyl ketones,[12a] alcohols,[12b,c] or aldehydes[12c−e] with dialkylformamides, amines, or ammonium salts. Meanwhile, TBAI/TBHP could also be used for the construction of heterocyclic imidazo[1,2-α]pyridines[13a] or oxazoles[13b] from β-keto esters with 2-aminopyridines or benzylamine, respectively, via C(sp^3)−H functionalization.

Scheme 1. Intermolecular C(sp^2)−N Cross-Coupling Reactions



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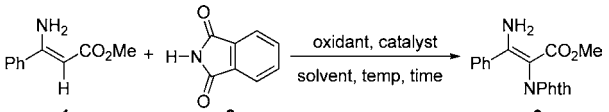
Furthermore, the TBAI/TBHP oxidative system has been successfully applied to the amination of heteroarenes,[14a] benzylic C−H bonds,[14b] and ketones.[14c] However, to our knowledge, it has never been used for the oxidative amination of enamine compounds. It is worth noting that such a direct amination of enamines through C(sp^2)−N bond formation provides a straightforward synthesis of a series of synthetically useful diaminoalkenes, which are not readily accessed through any of the known approaches.[15]

In our previous work, direct β-acyloxylation of enamine compounds was achieved via PhIO-mediated intermolecular oxidative C−O bond formation.[16] Inspired by this conversion, we anticipated the C−N cross-coupling between enamine and phthalimide using PhIO as oxidant.[17] Accordingly, enamine **1a** and phthalimide **2a** were used to test the feasibility of the transformation. However, the reaction of enamine **1a** with phthalimide **2a** under our previously optimized conditions for the coupling of enamines with carboxylic acids provided no desired product at all (Table 1, entry 1). Other hypervalent iodine reagents including PIDA and PIFA were also tested but found to be ineffective for the anticipated transformation (Table 1, entries 2−3).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**

entry	oxidant[b]	catalyst	solvent	temp (°C)	time (h)	yield[c] (%)
1	PhIO[d]		DCE	rt	0.5	ND[e]
2	PIDA[d]		DCE	rt	0.5	ND[e]
3	PIFA[d]		DCE	rt	0.5	ND[e]
4	TBHP	TBAI	DCE	100	2	20
5	TBHP	TBAI	EtOAc	100	1	40
6	TBHP	TBAI	EtOH	100	2	13
7	TBHP	TBAI	DMF	100	1	80
8	TBHP	TBAI	DMSO	100	1	65
9	TBHP	TBAI	MeCN	100	0.7	60
10	TBHP	TBAI	toluene	100	2	55
11	TBHP	NaI	DMF	100	2	50
12	TBHP	KI	DMF	100	2	53

[a]Reaction conditions: **1a** (1.0 mmol), oxidant (5.0 mmol), and catalyst (0.3 mmol) in solvent (5.0 mL), unless otherwise stated. [b]TBHP (70% in water) was extracted with petroleum ether and was evaporated for use. [c]Isolated yields. [d]1.2 equiv of oxidant was used. [e]No desired product.

Fortunately, when TBHP was used as the oxidant and TBAI as the catalyst, the desired cross-coupling product **3a** was obtained in 20% yield (Table 1, entry 4). Employing other oxidants such as $K_2S_2O_8$, O_2 and H_2O_2 (30% aq),[18] however, yielded no product in this reaction (not shown). Solvent screening showed that EtOAc, EtOH, DMF, DMSO, MeCN, and toluene were also effective for the reaction (Table 1, entries 5−10), with DMF proven the best choice, as the corresponding reaction gave the product in the highest observed yield of 80%. Our further control experiments indicated that TBAI was indispensable for the conversion since no reaction occurred if TBAI was not used (not shown). Instead of TBAI, the use of other catalysts, such as NaI and KI, significantly decreased the yield of **3a** (Table 1, entries 11−12), while TBAB, TBAC, I_2, and NIS resulted in no desired product (not shown). Increasing the temperature to 120 °C shortened the reaction time but was accompanied by decreased yield (48%, not shown) due to the formation of more byproducts. On the other hand, operating the reaction at 80 °C required increased reaction time without improving the yield (70%, not shown). On the basis of these results, the best conditions were concluded to be 5.0 equiv of TBHP with 0.3 equiv of TBAI in DMF at 100 °C for 1 h.[19]

To explore the generality and scope of the novel reaction, various enamines were examined as substrates to react with phthalimide (**2a**) under the optimized conditions. The aryl enamine substrates bearing either electron-donating or electron-withdrawing substituents on the aromatic ring were all converted to the corresponding products in satisfactory to good yields (Figure 1, **3a−e**). For substrates containing other heterocyclic rings in place of the aromatic ring, i.e., pyridyl and furyl, the reaction also conveniently afforded the desired products **3f** and **3g**, respectively, albeit in relatively lower yields. For substrates where the phenyl group was replaced by a methyl group or a more stericly hindered *tert*-butyl group, imidation products **3h** and **3i** were produced in 65% and 58% yield, respectively (Figure 1). These results indicated that the phenyl substituent in enamine **1a** was not indispensible for this transformation. The methoxycarbonyl group in the substrate could also be altered to the electron-withdrawing acyl group. Remarkably, when the methoxycarbonyl group in **3h** was displaced by an acetyl group, the reaction was completed within 10 min and the highest yield of 95% was achieved for the desired product **3j**. In the case where the electron-withdrawing group was a benzoyl group, **3k** was obtained with a 56% yield, possibly as a result of the hindrance of the phenyl groups. Further experiments showed that this method worked equally well for a broad range of enaminones containing a variety of R^1 and electron-withdrawing groups (E) (Figure 1, **3l−q**). To our delight, the method was also applicable to the N-substituted enamines. The N-substituted substrates **1r−u** were all converted to the corresponding coupled products to afford **3r−u** in moderate to good yields, respectively. To our disappointment, when the E substituent was a cyano group, the corresponding substrate failed to couple with **2a** (not shown).

To further probe the scope of the reaction, other nitrogenous compounds were examined. As illustrated in Figure 2, both succinimide and 4-nitrophthalimide successfully reacted with **1a** to afford **4a** and **4b** in moderate yields. In addition, 1*H*-benzimidazole and 1,2,4-1*H*-triazole also coupled with **1a** to give products **4c−d** in satisfactory yields. When benzotriazole was used, the reaction provided a mixture of **4e** and its regioisomeric compound **4e′**, with the former being the predominant product. Unfortunately, with saccharine or simple amines such as diphenylamine, dibenzylamine, or aniline as nitrogenous substrates, no desired product resulted in each case (not shown).

One useful application of the obtained diaminoalkene involves conversion to the 4-aminoisoxazole compound. Treating **3m** with PIDA in DCE at rt provided isoxazole **5** in 60% yield, together with the separable 2*H*-azirine **6** in 35% yield.[20] Upon treatment with $FeCl_2$ in 1,4-dioxane at reflux temperature, 2*H*-azirine **6** was converted smoothly to isoxazole **5** in an excellent 95% yield (Scheme 2).[21]

Our control experiment showed that the addition of TEMPO did not hamper the reaction, which indicated that the transformation may not involve a radical pathway. On the basis of this result and prior publications,[22] a plausible mechanism has been formulated and is presented in Scheme 3. Initially, tetra-*n*-butylammonium hypoiodite **A** was formed catalytically by the

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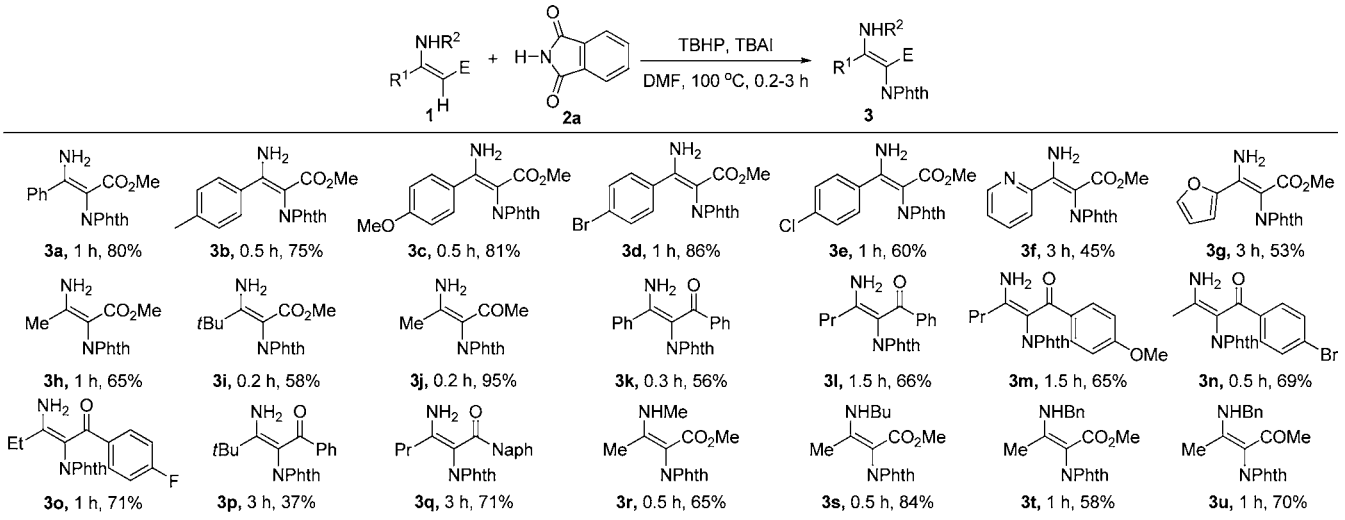


Figure 1. TBAI-catalyzed imidation of enamines with phthalimide. General conditions: substrate **1** (1.0 mmol), phthalimide **2a** (1.2 mmol), TBHP (5.0 mmol), and TBAI (0.3 mmol) in DMF (5 mL) at 100 °C.

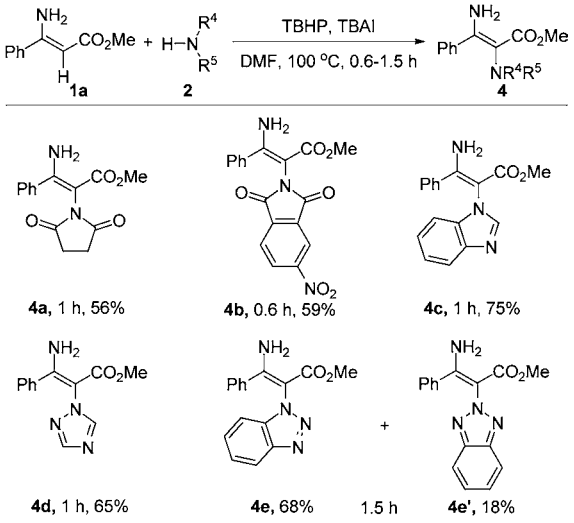
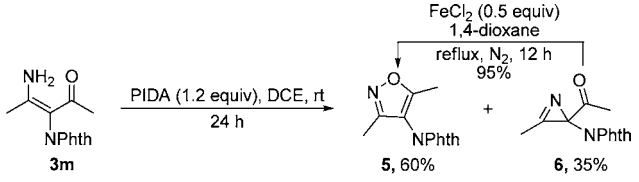


Figure 2. Oxidative C(sp^2)−N coupling of enamine **1a** with other nitrogenous compounds. General conditions: substrate **1a** (1.0 mmol), **2** (1.2 mmol), TBHP (5.0 mmol), and TBAI (0.3 mmol) in DMF (5 mL) at 100 °C.

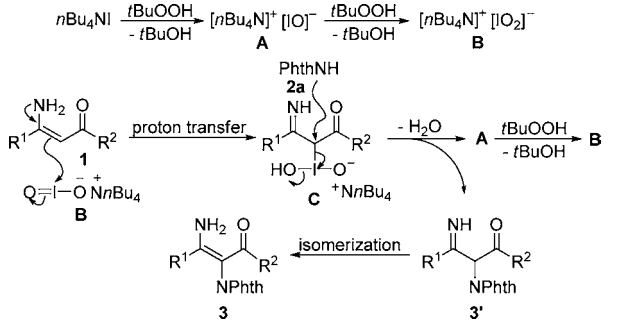
Scheme 2. Conversion of 3m to 5



peroxide *t*-BuOOH and was further oxidized in the same fashion to form tetra-*n*-butylammonium iodite **B**. Electrophilic addition reaction of enamine **1** by iodite **B** afforded intermediate **C**, which was then nucleophilically attacked by **2a** to give imine **3′**, while the released hypoiodite **A** was reoxidized by *t*-BuOOH to give **B**. Finally, imine **3′** isomerized into the more conjugated (therefore thermodynamically more stable) title product **3**.

In summary, we have disclosed an amination coupling reaction of enamines with electron-deficient amines including phthalimides, succinimide, and other nitrogenous compounds through

Scheme 3. Proposed Reaction Mechanism



the TBAI/TBHP-mediated intermolecular oxidative C(sp^2)−N bond formation. This novel method provides a convenient approach for the synthesis of diaminoalkene derivatives, which are not only synthetically useful but can be further converted to 4-aminoisoxazoles. The methodology features readily available starting materials, environmentally benign oxidant, and metal-free characteristics. Further studies on the reaction mechanism as well as its application are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral data for all new compounds, and X-ray structural data of **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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