VIP Copper Catalysis

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Enamide Synthesis by Copper-Catalyzed Cross-Coupling of Amides and Potassium Alkenyltrifluoroborate Salts**

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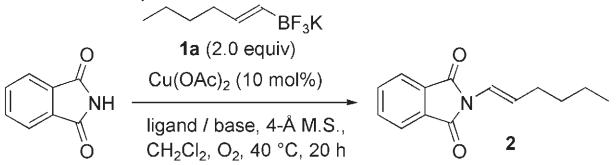
Dedicated to Professor William B. Motherwell on the occasion of his 60th birthday

Enamides are key structural motifs in various classes of natural products[1,2] and are also valuable synthetic intermediates.[3,4] In addition to a number of traditionally employed approaches,[5–9] several transition-metal-catalyzed methods for the synthesis of enamides have recently emerged.[10–12] Perhaps the most widely applicable metal-catalyzed method developed to date is the copper-catalyzed coupling[13] of alkenyl halides with amides,[14] a modern variant of the Goldberg reaction.[15] Porco, Buchwald, Ma, and others have shown that the coupling of amides and alkenyl bromides can be achieved using catalytic quantities of copper salts.[16] Despite these advances general methods are still needed for enamide formation, particularly since existing methods often have limited substrate scope and typically require elevated temperatures, rigorous exclusion of air and water, and the use of two or more equivalents of strong base. Lam et al. have reported the use of (*E*)-1-hexenylboronic acid as an alternative coupling partner.[17,18] Unfortunately, this method lacks generality, and only three examples of amide-like substrates (1-ethyl-1,3-dihydrobenzoimidazol-2-one, 2-hydroxypyridine, and phthalimide) were reported, which gave variable yields under five different sets of reaction conditions. One of the potential problems with this route, compared to similar reactions of arylboronic acids,[18,19] is the lower stability of alkenylboronic acids, particularly under oxidative conditions. We have previously demonstrated that the use of potassium organotrifluoroborate salts in copper-catalyzed cross-coupling reactions with alcohols[20] and amines[21] offer several advantages over the corresponding reactions of boronic acids. The tetracoordinate salts possess increased stability toward air and water, and are readily prepared.[22] Many are now commercially available,[23] and they are widely used for other classes of metal-catalyzed transformations.[23–25] Herein we report that potassium alkenyltrifluoroborate salts can be used in copper-catalyzed cross-coupling reactions with amides under mild base-free conditions.

Phthalimide was chosen as a test substrate in the initial experiments to optimize the reaction conditions, because it had been used by Lam et al.[17] in the coupling of hexenylboronic acid to give the corresponding enamide product **2** in good yield (79%) in the presence of stoichiometric amounts of Cu^{II} salts, but had provided poor yield (13%) under catalytic conditions ($Cu(OAc)_2$, 10 mol%). Coupling under the same catalytic conditions employed by Lam, except at 40 °C, using hexenyltrifluoroborate salt **1a** similarly gave **2** in low yield (Table 1, entry 1). The efficiency of the reaction improved on removal of the excess base (Et_3N) and was strongly dependant upon the choice of ligand (Table 1, entries 2–7). The highest yields were obtained in the presence of electron-rich monodentate amine ligands. Interestingly, the use of *N*-methylimidazole as ligand, which has not been used before in copper-catalyzed coupling reactions, gave the best results, affording **2** in quantitative yield (Table 1, entry 7). Attempted reaction of (*E*)-1-hexenylboronic acid under the same conditions was unsuccessful.

Table 1: Ligand optimization for cross-coupling of phthalimide with potassium hexenyltrifluoroborate **1a**.



Entry	Ligand	Amount [mol%]	Base (2 equiv)	Yield [%][a]
1	–	–	Et_3N	13
2	1,10-phenanthroline	10	Et_3N	12
3	1,10-phenanthroline	10	–	39
4	pyridine	20	–	51
5	DMAP	20	–	65
6	imidazole	20	–	85
7	*N*-methylimidazole	20	–	quant

[a] Yield of product isolated after silica gel chromatography. DMAP = 4-dimethylaminopyridine, M.S. = molecular sieves.

Unfortunately, attempts to expand the substrate scope, under the optimized conditions (Method A), gave mixed results with several classes of amides **3** (Table 2). While 2-hydroxypyridine and isatin exhibited good reactivity (Table 2, entries 1 and 2), 2-oxazolidinone and 2-pyrrolidinone

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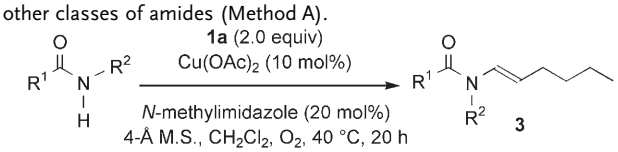
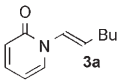
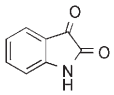
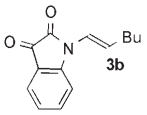
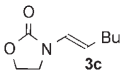
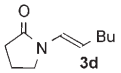
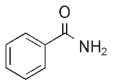
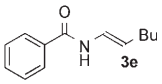
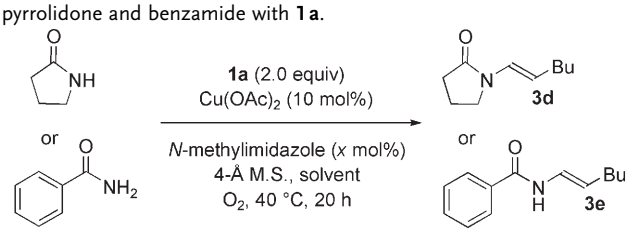
Table 2: Examination of the scope of the cross-coupling reaction with other classes of amides (Method A).



Entry	Substrate	Product	Yield [%][a]
1			78
2			82
3			40
4			22
5			0

[a] Yield of product isolated after silica gel chromatography.

Table 3: Optimization of the solvent and ligand for cross-couplings of 2-pyrrolidone and benzamide with **1a**.



Entry[a]	Substrate	DMSO/ CH_2Cl_2	Ligand [mol%]	Product	Yield [%][a]
1	2-pyrrolidinone	1:9	20	**3d**	68
2	2-pyrrolidinone	1:2	20	**3d**	78
3	2-pyrrolidinone	1:1	20	**3d**	84
4	2-pyrrolidinone	1:0	20	**3d**	24
5	benzamide	1:1	20	**3e**	62
6	benzamide	1:1	5	**3e**	70
7	benzamide	1:1	0	**3e**	81

[a] Yield of product isolated after silica gel chromatography.

afforded the corresponding enamides in only 40% and 22% yield, respectively (Table 2, entries 3 and 4). None of the desired enamide product was obtained in an attempted coupling using benzamide as a coupling partner (Table 2, entry 5).

The poor reactivity of 2-pyrrolidinone and benzamide may arise from a number of factors, including their coordination ability and their lower N–H acidity. In addition, these substrates are poorly soluble in CH_2Cl_2. Addition of a polar cosolvent, such as dimethyl sulfoxide (DMSO), was found to dramatically improve reaction yields (Table 3). Using $Cu(OAc)_2$ (10 mol%) and *N*-methylimidazole (20 mol%) gave the best result for the coupling of 2-pyrrolidinone with **1a** in CH_2Cl_2/DMSO (1:1, Table 3, entry 3). The use of either a higher or lower proportion of DMSO led to decreased yields of **3d** (Table 3, entries 1, 2, and 4). Similar results were obtained for the coupling of benzamide to give **3e** in 62% yield (Table 3, entry 5). Further optimization of these conditions revealed that changing the Cu/ligand ratio also resulted in improved product yields (Table 3, entries 5–7). Indeed, in sharp contrast to the results obtained for the coupling of phthalimide in CH_2Cl_2, where the presence of *N*-methylimidazole was essential, removal of the amine ligand led to the highest yields of product **3e** (Table 3, entry 7).

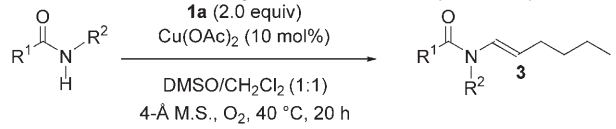
The "ligandless" protocol using the CH_2Cl_2/DMSO (1:1) solvent system (Method B) was evaluated with a range of amide substrates (Table 4). In general, good yields were obtained for both acyclic (Table 4, entries 1–8) and cyclic (Table 4, entries 9–12) amides. Notably, electron-deficient amides (Table 4, entries 2, 3, and 8) afforded the corresponding enamides **3** in higher yields than those obtained from the reactions of electron-rich amides (Table 4, entries 4, 5, and 7).

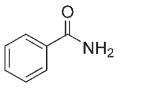
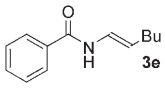
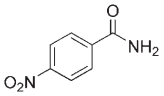
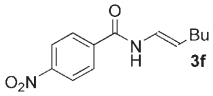
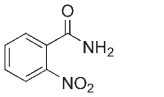
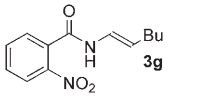
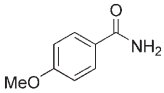
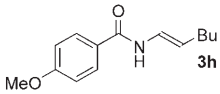
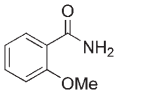
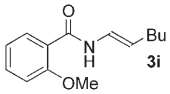
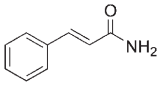
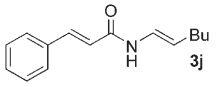
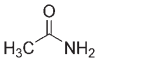
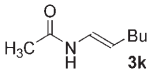
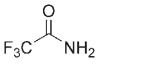
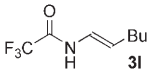
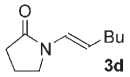
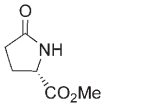
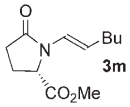
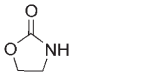
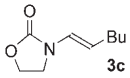
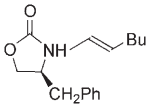
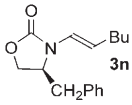
These results are in contrast to the findings of Altman and Buchwald, who observed that more electron-deficient hydroxypyridines gave lower yields than electron-rich examples in the copper-catalyzed coupling reaction with aryl halides.[26] In all cases the reactions were highly stereoselective, and only the *trans* enamides **3** were observed ($\geq$97:3 by ^{1}H NMR spectroscopy). Reaction of (*E*)-1-hexenylboronic acid with benzamide gave no detectable product with this protocol, and the reaction of oxazolidin-2-one gave **3c** in just 3% yield.

Other potassium alkenyltrifluoroborate salts could also be employed using the "ligandless" protocol (Method B) (Figure 1). Coupling of benzamide to give **4**, **5**, and **6** occurred in good yields from the corresponding *trans* alkenyltrifluoroborate salts. Reaction of potassium vinyltrifluoroborate with benzamide to give **7** occurred in lower yield. Coupling of *trans*-cinnamamide with potassium *trans*-styryltrifluoroborate gave a 56% yield of **9**, a precursor to the natural product lansamide I. Increasing the amount of alkenyltrifluoroborate salts used led to increased reaction yields. For example, the formation of **9** occurred in 70% and almost quantitative yields, respectively when three and five equivalents of the *trans* alkenyltrifluoroborate salts were used. Reaction of the *cis*-styryl trifluoroborate with benzamide afforded the *cis* enamide **8** in only 25% yield following chromatography on neutral alumina. The *cis* enamide **8** appeared to be unstable which is consistent with the observations of Fürstner and coworkers.[8b]

In conclusion, an efficient synthesis of enamides using a copper-catalyzed cross-coupling between potassium alkenyltrifluoroborate salts and amides has been described that occurs under an atmosphere of molecular oxygen in the absence of base at 40°C. The mechanism for the reaction is presumably analogous to those proposed for the coupling of arylboronic acids with phenols and other nucleophiles.[18] Further studies on the applications of this and related methods will be reported in due course.

Table 4: Expanding the substrate scope of the cross-coupling reactions of amides with **1a** under "ligandless" conditions (Method B).



Entry	Substrate	Product	Yield [%][a]
1		 **3e**	81
2		 **3f**	86
3		 **3g**	72
4		 **3h**	55
5		 **3i**	65
6		 **3j**	75
7		 **3k**	67
8		 **3l**	86
9		 **3d**	86
10		 **3m**	80
11		 **3c**	97
12		 **3n**	71

[a] Yield of product isolated after silica gel chromatography.

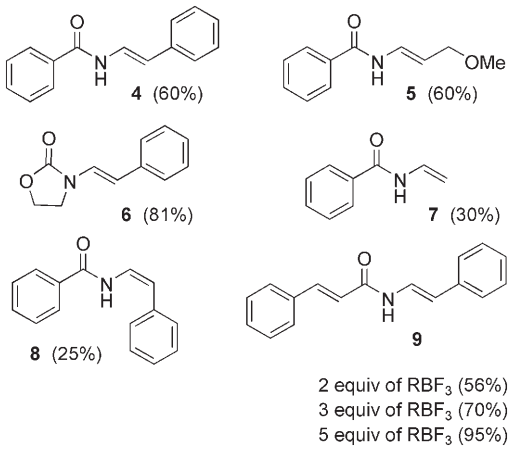


Figure 1. Examples of cross-couplings of various amides and potassium alkenyltrifluoroborate salts using a "ligandless" protocol (Method B).

Experimental Section

Method A: CH_2Cl_2 (2.0 mL) and *N*-methylimidazole (0.1 mmol) were added to $Cu(OAc)_2$ (0.05 mmol), amide (0.5 mmol), potassium alkenyltrifluoroborate salt (1.0 mmol), and 4-Å molecular sieves (0.375 g). The suspension was stirred for 20 h at 40 °C under an atmosphere of oxygen. Method B: CH_2Cl_2 (1.0 mL) and DMSO (1.0 mL) were added to $Cu(OAc)_2$ (0.05 mmol), amide (0.5 mmol), potassium alkenyltrifluoroborate salt (1.0 mmol), and 4-Å molecular sieves (0.375 g). The suspension was stirred for 20 h at 40 °C under an atmosphere of oxygen. For both methods the reaction mixture was then filtered through a plug of celite, which was then washed with EtOAc. The crude products were purified by silica gel chromatography using EtOAc/*n*-hexanes and 1% v/v Et_3N. The *cis* enamide **8** was purified by neutral alumina chromatography using EtOAc/hexanes (1:15).

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