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Copper-catalyzed cross-coupling of amides and potassium alkenyltrifluoroborate salts: a general approach to the synthesis of enamides

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ABSTRACT

Potassium alkenyltrifluoroborate salts undergo coupling with amides to give enamides using a catalytic amount of $Cu(OAc)_2$ under mild oxidative conditions. The air and water stable alkenyltrifluoroborate salts offer a practical alternative to the use of alkenyl halides and alkenylboronic acids as cross-coupling partners. A range of amides participate in the cross-coupling, including heterocyclic amides, imides, carbamates, benzamides, and acetamides. Optimization studies established two sets of conditions, best suited to either high pK_a or low pK_a amide substrates. Lower pK_a amide substrates worked best using a dichloromethane solvent system in the presence of 4 Å molecular sieves, 10 mol % $Cu(OAc)_2$, and 20 mol % *N*-methylimidazole. Higher pK_a amide substrates worked best using a 'ligandless' protocol using a 1:1 dichloromethane/DMSO solvent system in the presence of 4 Å molecular sieves and 10 mol % $Cu(OAc)_2$. The cross-coupling reactions occur stereospecifically with retention of alkene configuration from the alkenyltrifluoroborate salt. The mild reaction conditions employed are tolerant of various functionalities, including nitro, acetals, alkyl and aryl halides, and α,β-unsaturated carbonyls. Finally, the importance of copper sources and the presence of minor impurities were investigated.

1. Introduction

In contrast to the arylation of amides, originally reported by Goldberg,[1] the transition metal-catalyzed alkenylation of amides remained an unexplored area until the end of twentieth century. However, the utility of enamides as synthetic precursors,[2–4] and the discovery of several new families of enamide-containing natural products has sparked an interest in the development of new methodologies for the synthesis of the enamide functionality.[5,6] Representative enamide antitumor natural products include salicylihalamide A and B,[7] apicularen A and B,[8] aspergillamide A,[9] oximidine I and II,[10] TMC-95A,[11] and frangufoline[12] (Fig. 1).

There are a number of methods that have traditionally been employed for the synthesis of enamides, including acid-catalyzed condensation of amides and aldehydes,[13] Curtius rearrangement of α,β-unsaturated acyl azides,[14] acylation of imines,[15] elimination of β-hydroxy-α-silyl amides,[16] and condensation of aldehydes or ketones with nitriles.[17] More recently Re,[18] Ni,[19] Rh and Fe,[20,21] and Pd[22] catalyzed methods for the synthesis of enamides have emerged. Ru catalysis has been used for the amidation of alkynes to give both (*E*) and (*Z*)-enamides (Fig. 2a).[23]

Perhaps the most widely applicable metal-catalyzed method to have been developed to date is the copper-catalyzed coupling[24] of alkenyl halides with amides (Fig. 2b), a modern variant of the Goldberg reaction.[1] This approach has addressed some of the problems with other methods, since it permits good control of *E*/*Z* stereoselectivity, and does not require the use of expensive catalysts or harsh reaction conditions. Ogawa[25] originally reported the coupling of potassium amides and alkenyl bromides using stoichiometric amounts of copper, but Porco, Buchwald, Ma and others have since shown that the method can be rendered catalytic in copper.[26] Lam and co-workers also extended their studies on the amidation of arylboronic acids,[27] with a limited study on the use of (*E*)-1-hexenylboronic acid as an alternative coupling partner (Fig. 2c).[28,29] More recently, Liebeskind and co-workers showed that hydroxamic acid derivatives react with alkenylstannanes in the presence of a stoichiometric amount copper salt to afford enamides in moderate yields. Alkenylboronic acids, however, were unreactive under the same set of conditions.[30]

Despite these advances there is still a need for general methods 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.

Our interest in the use of organoboron compounds as reagents for organic synthesis, particularly organotrifluoroborate salts, led us to consider their utility for the cross-coupling with amides. The previous studies by Lam using hexenylboronic acid had lacked

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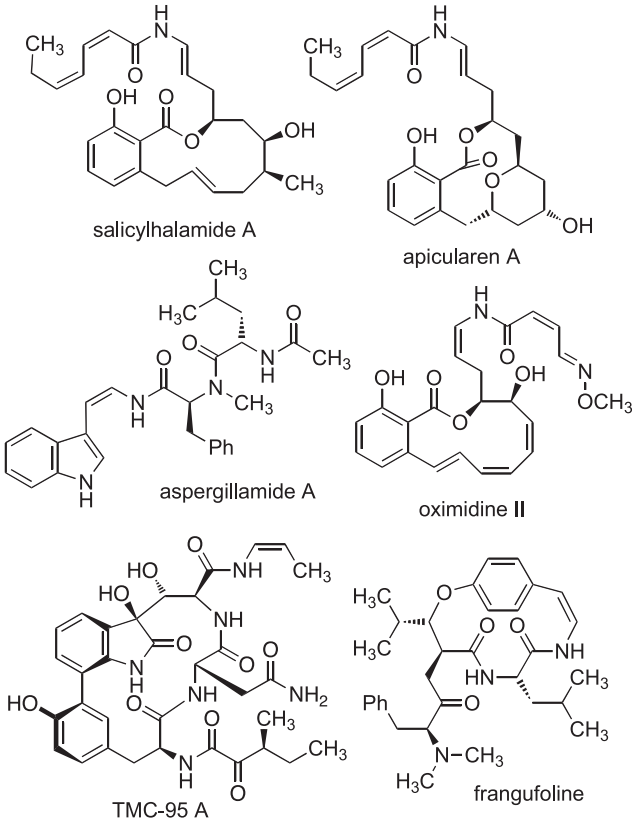


Figure 1. Enamide synthetic targets.

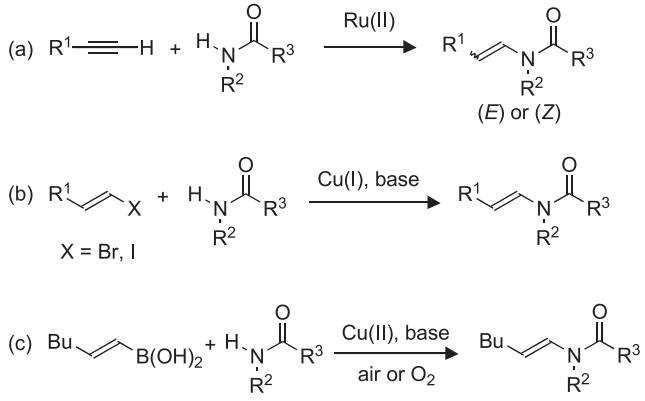
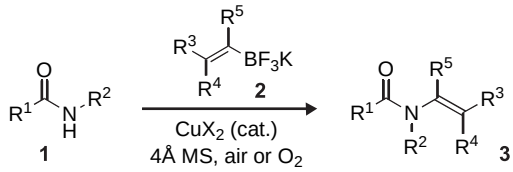


Figure 2. Metal-catalyzed cross-coupling approaches to the synthesis of enamides.

generality, and only three examples of amide-like substrates (1-ethyl-1,3-dihydro-benzoimidazol-2-one, 2-pyridone, and phthalimide) were reported, with variable yields under five different sets of reaction conditions.[28] We reasoned that one of the potential problems with this route, compared to similar chemistry employed with *aryl*boronic acids,[27,29] is the lower stability of alkenylboronic acids, particularly under oxidative conditions. Previous studies in our group have demonstrated that the use of potassium organotrifluoroborate salts in copper-catalyzed cross-couplings with alcohols[31] and amines[32] provides several advantages over the use of the boronic acids. The tetracoordinate organotrifluoroborate salts possess increased stability toward air and water, and are readily prepared.[33] Their commercial availability[34] and low toxicity[35] have contributed to growing recognition within the synthetic community of the value of these reagents for other classes of metal-catalyzed transformations.[34,36–38] We now report that potassium alkenyltrifluoroborate salts are effective coupling partners in copper-catalyzed cross-coupling reactions with a variety of amides under mild base-free conditions (Scheme 1).[39]

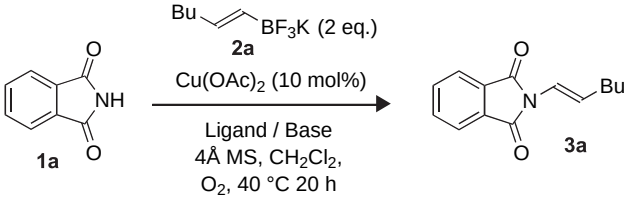


Scheme 1. Copper-catalyzed cross-coupling approach to the synthesis of enamides using alkenyltrifluoroborate salts.

2. Results and discussion

The previous investigations of Lam and co-workers had utilized phthalimide as one of the cross-coupling partners in couplings with hexenylboronic acid, giving a high product yield (79%) in the presence of a stoichiometric amount of $Cu(OAc)_2$, and a low yield (13%) in the presence of a catalytic amount (10 mol %) of $Cu(OAc)_2$ and 2 equiv of triethylamine.[28] Since our aim was to develop a robust *catalytic* method, phthalimide was chosen as the substrate of choice for an initial cross-coupling optimization study (Table 1). Initially, phthalimide was submitted to the reaction conditions developed by Lam and co-workers, except that potassium hexenyltrifluoroborate **2a** was used as the coupling partner, and an elevated temperature of 40 °C rather than room temperature was used. The desired product **3a** was obtained in a low yield (Table 1, entry 1). Reaction in the absence of external base and ligand resulted in no detectable product formation (Table 1, entry 2). The addition of the bidentate ligand 1,10-phenanthroline (10 mol %) did not improve the yield of **3a**, and further increasing the amount of 1,10-phenanthroline to 20 mol % (i.e., 2 equiv with respect to copper) inhibited the reaction (Table 1, entries 3 and 4). Reaction in the absence of triethylamine using 1,10-phenanthroline (10 mol %) as ligand led to a significant improvement in the yield of **3a** (Table 1, entry 5). Reaction using 2,2′-dipyridyl (10 mol %) was less successful (Table 1, entry 6). Further screening of a variety of monodentate ligands (20 mol %) led to good to excellent yields of **3a** (Table 1, entries 7–10). Thus, reaction yields increased along the series pyridine, dimethylaminopyridine (DMAP), imidazole, and *N*-methylimidazole, with the latter achieving quantitative formation of **3a**. To the best of our knowledge,

Table 1
Ligand optimization for the cross-coupling of phthalimide with potassium hexenyltrifluoroborate to yield enamide **3a**



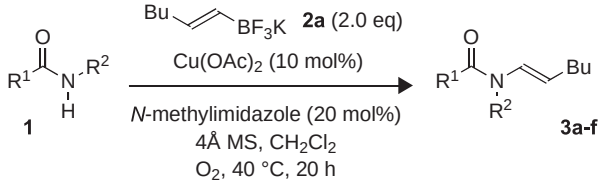
Entry	Additive	Ligand	Yield[a] (%)
1	Et_3N (2.0 equiv)	None	13
2	None	None	—
3	Et_3N (2.0 equiv)	1,10-Phenanthroline (10 mol %)	12
4	Et_3N (2.0 equiv)	1,10-Phenanthroline (20 mol %)	3
5	None	1,10-Phenanthroline (10 mol %)	39
6	None	2,2′-Dipyridyl (10 mol %)	10
7	None	Pyridine (20 mol %)	51
8	None	DMAP (20 mol %)	65
9	None	Imidazole (20 mol %)	85
10	None	1-Methylimidazole (20 mol %)	Quant.

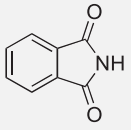
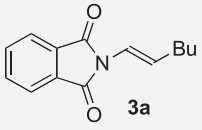
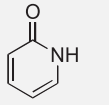
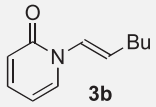
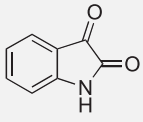
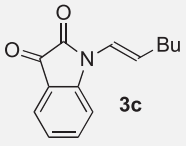
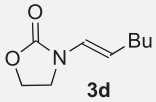
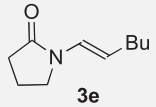
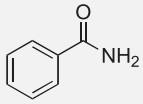
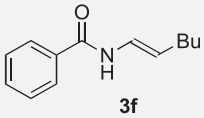
[a] Isolated product after column chromatography.

this is the first time *N*-methylimidazole has been used as a ligand for a copper-catalyzed reaction, and its success may be due to its high affinity for binding to copper[40] and potentially for stabilization of copper at higher oxidation state.[41]

A diverse set of amides were screened using the optimized conditions (method A) of $Cu(OAc)_2$ (10 mol %), *N*-methylimidazole (20 mol %), 4 Å molecular sieves, in dichloromethane under an atmosphere of oxygen at 40 °C (Table 2). Unfortunately, the reaction scope was not general. Thus, while 2-hydroxypyridine and isatin gave the desired enamides in 78% and 82%, respectively, lower yields were obtained for the couplings of oxazolidinone and pyrrolidinone, and only starting material was recovered when benzamide was submitted to the optimized reaction conditions. Two factors may be responsible for this behavior. Firstly, the lower solubility of the latter amides in dichloromethane may be problematic. Secondly, there was a rough correlation of lower yields with the amides having higher pK_a values. Thus, good yields were obtained with the more acidic amides, such as phthalimide (pK_a=13.4 in DMSO),[42] isatin, and hydroxypyridine (pK_a=17.0 in DMSO).[43] Whereas, lower yields of the enamide products **3** were obtained with the less acidic amides, oxazolidinone (pK_a=20.8 in DMSO), pyrrolidinone (pK_a=24.2 in DMSO),[43] and benzamide (pK_a=23.3 in DMSO).[44] The unsatisfactory results obtained with these amides, required a re-examination of reaction conditions in order to achieve the goal of a more generally applicable method.

Table 2
Examination of the scope of the optimized copper-catalyzed cross-coupling reaction using *N*-methylimidazole as a ligand (method A)

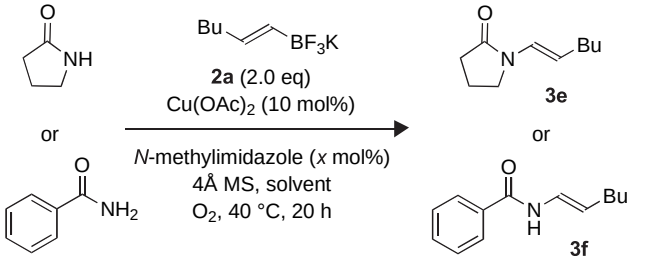


Entry	Amide	pK_a	Product	Yield[a] (%)
1		13.4	 **3a**	Quant.
2		17.0	 **3b**	78
3		—	 **3c**	82
4		20.8	 **3d**	40
5		24.2	 **3e**	22
6		23.3	 **3f**	0[b]

[a] Isolated product after column chromatography.
[b] Only starting material was recovered.

Benzamide was chosen as an appropriate starting point for reaction optimization, since this prototypical amide had failed to give any of the desired product under the initial conditions (method A). An initial optimization screen of solvents (DMSO, acetonitrile, and dichloromethane) and ligands (monodentate and bidentate), using benzamide as a starting material with $Cu(OAc)_2$ (10 mol %), 4 Å molecular sieves, in dichloromethane under an atmosphere of oxygen at 40 °C, was unsatisfactory giving low yields (0–14%) of **3f**. Similar observations were made with couplings using 2-pyrrolidinone, although reaction using either dichloromethane or DMSO as solvent, gave modest yields of **3e**, of 22% and 24%, respectively (Table 3, entries 1 and 7). The use of DMSO alone improved reactant solubility, but we were concerned that DMSO may be too strongly coordinating with copper. Therefore, the use of varying dichloromethane/DMSO co-solvent mixtures was investigated (Table 3, entries 2–6). The yield of **3e** improved in each case, with the highest yield occurring with a 1:1 ratio of dichloromethane/DMSO (Table 3, entry 6). Reaction of benzamide with potassium hexenyltrifluoroborate under the same conditions led to **3f** in 62% yield, a substantial improvement over the 14% yield obtained in pure DMSO (Table 3, entries 10 and 9).

Table 3
Optimization of the solvent and ligand for the cross-couplings of 2-pyrrolidinone and benzamide with potassium hexenyltrifluoroborate



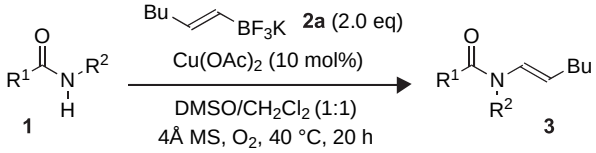
Entry	Substrate	DMSO/CH_2Cl_2	Ligand (mol %)	Product	Yield[a] (%)
1	2-Pyrrolidinone	0:1	20	**3e**	22
2	2-Pyrrolidinone	1:9	20	**3e**	68
3	2-Pyrrolidinone	1:4	20	**3e**	69
4	2-Pyrrolidinone	1:3	20	**3e**	71
5	2-Pyrrolidinone	1:2	20	**3e**	78
6	2-Pyrrolidinone	1:1	20	**3e**	84
7	2-Pyrrolidinone	1:0	20	**3e**	24
8	2-Pyrrolidinone	1:1	0	**3e**	86
9	Benzamide	1:0	20	**3f**	14
10	Benzamide	1:1	20	**3f**	62
11	Benzamide	1:1	5	**3f**	70
12	Benzamide	1:1	0	**3f**	80

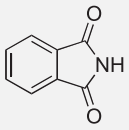
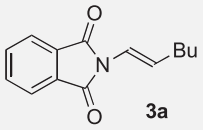
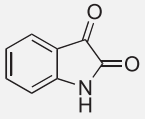
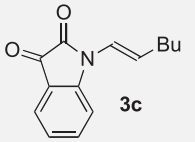
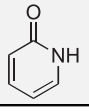
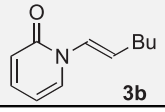
[a] Isolated product after column chromatography.

Finally, a further iteration of the ligand to copper ratio was attempted using the 1:1 ratio of dichloromethane/DMSO (Table 3, entries 11 and 12). Surprisingly, it appeared that not only was the *N*-methylimidazole ligand not necessary for the reaction, but that the highest yield of **3f** was observed in its absence. This was completely unexpected based upon the preliminary optimization studies using phthalimide, for which 20 mol % of *N*-methylimidazole was optimal (Table 1). The 'ligandless' set of conditions (i.e., in the absence of *N*-methylimidazole) using a 1:1 solvent ratio of dichloromethane/DMSO (method B) was similarly applied to pyrrolidinone, and led to **3e** in 86% yield (Table 3, entry 8).

Application of the 'ligandless' method B using phthalimide and isatin, afforded the corresponding products **3a** and **3c** in much lower yields than were obtained using method A (Table 4, entries 1 and 2). Moreover, 2-hydroxypyridine did not react at all using method B (Table 4, entry 3). The two methods thus complement each other, with method A appearing to work better for lower pK_a substrates, while method B is better suited for the higher pK_a substrates.

Table 4
Application of method B to low pK_a substrates



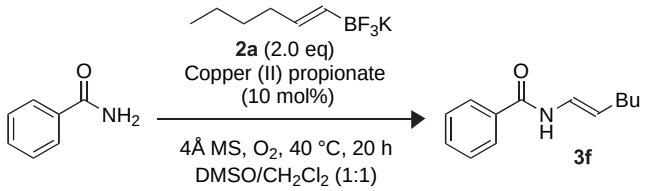
Entry	Amide	Product	Yield[a] (%)
1		 **3a**	35
2		 **3c**	56
3		 **3b**	0

[a] Isolated product after column chromatography.

The origin of the difference in success of the two sets of conditions, 'ligand-based' method A and 'ligandless' method B, is not clear. The poor performance of method B with lower pK_a substrates may occur because of their decreased ability to stabilize copper at a higher oxidation state, presumably Cu(III). For method A it is possible that *N*-methylimidazole also serves as a base, leading to deprotonation of the lower pK_a substrates and coordination of the deprotonated cross-coupling partner to copper. With higher pK_a substrates the *N*-methylimidazole may not serve this role, and instead its direct coordination to copper may have a deleterious role. The strikingly different results obtained on variation of the dichloromethane/DMSO ratio using 20 mol % of *N*-methylimidazole (Table 3, entries 1–7, 9, and 10) are not easily rationalized. The solubility of substrate **1** may be less important, since although benzamide has much lower solubility than either phthalimide or pyridin-2(1*H*)-one at room temperature, it was found to be completely soluble at 40 °C in dichloromethane at the concentrations being employed for method A (approximately 0.25 M). With increasing amounts of DMSO, the benzamide substrates were found to have higher solubility. The solubility of the copper salts or organotrifluoroborate salts **2** may be more important. Salts **2** were found to be only partially soluble in dichloromethane at 40 °C, but completely soluble in DMSO at 40 °C. The copper salts were also only partially soluble in dichloromethane, but completely soluble in the dichloromethane/DMSO solvent mixtures. Perhaps, the success of the 1:1 dichloromethane/DMSO solvent ratio can be attributed to achieving an appropriate 'Goldilocks' modulation of organotrifluoroborate salt solubility, i.e., not too low (as for dichloromethane) and not too high (as for DMSO). Of course, DMSO may also serve as a ligand to copper.[45]

Further attempts at improving the reaction conditions (method B) focused upon the influence of the copper catalyst on the cross-coupling of benzamide (Table 5). Copper(II) acetate (97% or 99.999% purity) and copper(II) propionate (98%) reproducibly gave **3f** in 80%, 60%, and 49% yields, respectively (Table 5, entries 1–3). The wide variation in these results was unexpected, and showed that the purity of the copper source was playing a role. The lower yield obtained with copper(II) propionate compared to copper(II) acetate was particularly surprising, given their similar solubilities and the very similar steric and electronic properties of the acetate and propionate counter ions. Other copper(II) salts showed inferior catalytic activity to copper acetate, with $Cu(OTf)_2$ achieving the closest result, giving **3f** in 70% yield (Table 5, entry 4). $Cu(acac)_2$ was completely inactive, presumably due to the strong coordinating character of the bidentate acac ligand (Table 5, entry 5). Copper(I) and copper(II) chloride also gave modest yields of **3f** (Table 5, entries 6 and 7). It is worth mentioning that all of these salts were soluble under the reaction conditions. Although not unexpected, it is clear that the nature of the counter ion plays a key role in the ability of the complexes to catalyze the reaction.

Table 5
The influence of copper salts for the cross-couplings of benzamide with potassium hexenyltrifluoroborate



Entry	Cu(II) source	Purity (%)	Yield[a] (%)
1	$Cu(OAc)_2$	97	80
2	$Cu(OAc)_2$	99.999	60
3	$Cu(O_2C_3H_5)_2$	98	49
4	$Cu(OTf)_2$	98	70
5	$Cu(acac)_2$	97	—
6	$CuCl_2$	≥99	54
7	CuCl	≥99	30

[a] Isolated product after column chromatography.

The interesting differences achieved for the reactions using copper(II) propionate and copper(II) acetate, and the effect of purity, inspired us to look more carefully at the copper salts. An analysis using Inductively Coupled Plasma Atomic Emission Spectrometry (ICP AES) for the presence of 28 different metal ions was run on both anhydrous copper(II) acetate (97% purity, Strem Chemicals) and copper(II) propionate (98% purity, Alfa Aesar) (Table 6). The results showed that the sample of anhydrous copper(II) acetate contained approximately 10 mg of chromium, 0.8 mg of iron. and 0.6 mg of calcium per gram of sample. The sample of anhydrous copper(II) propionate on the other hand did not contain any detectable amounts of other metal ions.

Table 6
Metal analysis of copper(II) acetate and copper(II) propionate

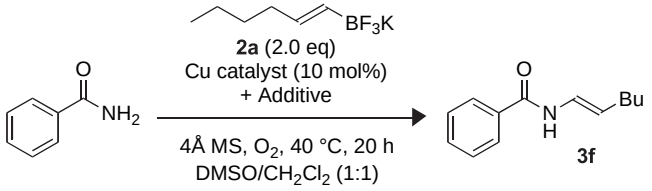
Entry	Element	Copper(II) acetate	Copper(II) propionate
1	Ca	0.574[a]	BDL[b]
2	Cr	9.96	BDL
3	Cu	402	360
4	Fe	0.789	BDL
5	Other metals[c]	BDL	BDL

[a] Numbers are milligram per gram of sample.
[b] BDL—below detection limit.
[c] Ag, Al, As, B, Ba, Be, Cd, Co, K, Li, Mg, Mn, Mo, Na, Ni, Pb, Sb, Se, Si, Sr, Ti, Tl, V, Zn.

For the sample of copper(II) acetate (97% purity), which gave the best results in the cross-coupling reactions, the presence of calcium ions is unlikely to exert a significant effect on the reaction, although the presence of iron and chromium metal ions may influence the reaction, especially considering the oxidative reaction conditions and the redox active nature of these two metals. The presence of chromium was of particular interest, because of its high concentration in the copper(II) acetate (97% purity) sample and its absence in the copper(II) propionate or copper(II) acetate (99.999% purity) sample. According to the ICP AES analysis of copper(II) acetate (97% purity), the addition of 10 mol % of Cu is accompanied by 0.35 mol %

of Cr, with respect to the starting material. To test whether chromium or iron had an effect on the reactions, reactions were run with copper(II) propionate doped with Cr(II) or Fe(II) (Table 7). Reactions with copper(II) propionate (10 mol %) doped with chromium(II) chloride in small amounts (0.175 or 0.35 mol % relative to starting material) led to a modest improvement in the yields of **3f** (Table 7, entries 3 and 4). However, lower yields of **3f** were obtained with a higher amount of chromium(II) chloride (0.60 mol %) dopant (Table 7, entry 5). The use of a chromium(II) chloride doped sample of $Cu(OAc)_2$ (99.999% purity) increased the yield of the reaction, beyond that obtained with $Cu(OAc)_2$ (99.999% purity) alone (Table 7, entry 6). The use of an iron(II) acetate (0.028 mol %) doped sample of copper(II) propionate led to a modest decrease in yield (Table 7, entry 7). Finally, the use of catalytic quantities of $CrCl_2$ alone afforded no product. These results suggest that the presence of a chromium impurity may have a modest effect on the reaction, but further investigation is required before this can be confirmed, and an understanding of these observations made.

Table 7
The influence of metal ion additives on the cross-coupling reaction of benzamide and **2a** catalyzed by copper(II) propionate and copper(II) acetate

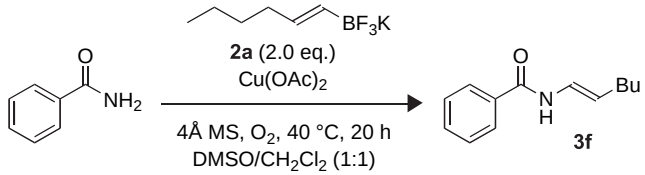


Entry	Cu (II) source (purity)	Additive	Added metal ion (mol %)	Yield[a] (%)
1	$Cu(OAc)_2$ (97%)	—	—	80
2	$Cu(O_2C_3H_5)_2$ (98%)	—	—	49
3	$Cu(O_2C_3H_5)_2$ (98%)	$CrCl_2$	0.175	55
4	$Cu(O_2C_3H_5)_2$ (98%)	$CrCl_2$	0.350	64
5	$Cu(O_2C_3H_5)_2$ (98%)	$CrCl_2$	0.600	40
6	$Cu(OAc)_2$ (99.999%)	$CrCl_2$	0.350	69
7	$Cu(O_2C_3H_5)_2$ (98%)	$Fe(OAc)_2$	0.028	40

[a] Isolated product after column chromatography.

As a final optimization step, the effect of temperature, catalyst loading, and the amount of potassium hexenyltrifluoroborate and myristic acid was probed (Table 8). The catalyst loading of 10 mol % copper(II) acetate (97% purity) was found to be optimal, since lower (5 mol %) and higher (20 mol %) catalyst loadings led to 46% and 16% yields of **3f**, respectively (Table 8, entries 1–3). It is particularly interesting that a higher catalyst loading leads to lower product yields. The addition of myristic acid has been reported to improve the yields in oxidative cross-couplings of amines and arylboronic acids.[46] It was proposed that the role of the myristate carboxylate side-chain (a long aliphatic chain) was to improve the solubility of the copper salt in the aprotic non polar solvent (toluene). In our case, however, the yield of **3f** decreased to 47% when myristic acid (20 mol %) was added to the reaction, probably, due to the fact that the copper salt is soluble in dimethylsulfoxide and the myristate only acted as a ligand to copper, thus inhibiting the coordination of an amide and transmetalation of organotrifluoroborate (Table 8, entry 4). Elevating the reaction temperature to 50 °C did not cause an improvement in the yield of **3f** (Table 8, entry 5). A slightly lower yield was observed when the temperature was lowered to 30 °C, and no product was observed when the reaction was run at ambient temperature (Table 8, entries 6 and 7). The use of just 1.2 equiv of trifluoroborate salt **2a**, rather than the 2.0 equiv usually employed, resulted in significantly lower amounts of isolated product **3f** (Table 8, entry 8). Finally, it should be noted that all of the reactions described in this manuscript were conducted under a slightly positive oxygen pressure using a gas manifold equipped

Table 8
Re-examination of temperature, copper, and potassium hexenyltrifluoroborate salt **2a** stoichiometry



Entry	Copper source	Temperature	Yield[a] (%)
1	$Cu(OAc)_2$ (10 mol %)	40 °C	80
2	$Cu(OAc)_2$ (5 mol %)	40 °C	46
3	$Cu(OAc)_2$ (20 mol %)	40 °C	16
4	$Cu(OAc)_2$ (10 mol %)/myristic acid (20 mol %)	40 °C	47
5	$Cu(OAc)_2$ (10 mol %)	50 °C	78
6	$Cu(OAc)_2$ (10 mol %)	30 °C	69
7	$Cu(OAc)_2$ (10 mol %)	rt	—
8	$Cu(OAc)_2$ (10 mol %) using **2a** (1.2 equiv)	40 °C	16

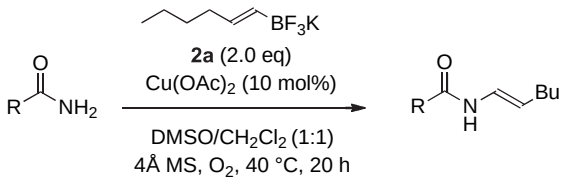
[a] Isolated product after column chromatography.

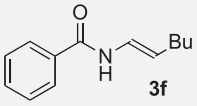
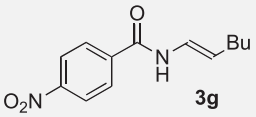
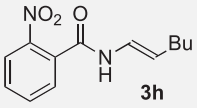
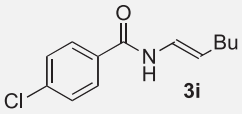
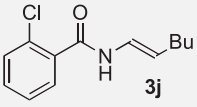
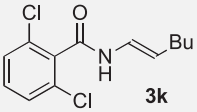
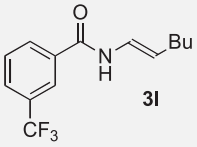
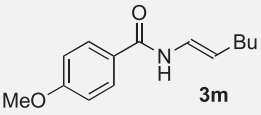
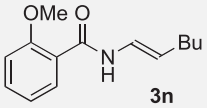
with an oil bubbler, with the oxygen gas supplied from a cylinder passed through a gas drying unit filled with DRIERITE desiccant. Attempts to utilize a balloon filled with oxygen or air led to lower yields of **3f**.

With an optimized 'ligandless' protocol developed, the next step was to evaluate its effectiveness with a range of amide substrates. In general, the resultant enamides **3** are of particular interest since they provide easy excess to functionalized systems that can further undergo transition metal[47] and organocatalyzed transformations.[48] In general, various benzamide derivatives participated in the reaction to afford enamides **3** in good yields using method B (Table 9). In all cases the reactions were highly stereoselective, and only the *trans*-enamides **3** were observed ($\geq$97:3 by ^{1}H NMR spectroscopy). Electron-deficient benzamides afforded the corresponding enamides **3g–l** (Table 9, entries 2–7) in higher yields than was for the case with the electron-rich amides (Table 9, entries 8 and 9). Chlorosubstituted benzamides reacted well, regardless of the position of the chloride on the ring (Table 9, entries 4–6), with even the di-*ortho*-chloro substituted product **3k** being formed in good yield. The difference in yield between the electron-rich and electron-deficient benzamides is quite different to the observations of Buchwald and Altman,[49] who noted that while pyridin-2(1*H*)-one underwent a copper(I) catalyzed coupling with aryl iodide under mild conditions, the more electron-deficient nitro-substituted pyridin-2(1*H*)-one was unreactive, even at 150 °C.

In addition to benzamides, acetamide underwent cross-coupling in good yield to give enamide **3o** (Table 10, entry 1). As for the cross-coupling reactions of benzamides, more electron-deficient acetamides afforded the corresponding enamides **3p–r** in higher yields (Table 10, entries 2–4). These results are in agreement with Ogawa's results where trifluoroacetamide gave a much higher yield of the enamide than was observed for the cross-coupling of acetamide with *trans*-β-bromostyrene.[25] In the case of (*S*)-(−)-lactamide an interesting example of chemoselective coupling was observed, with the alcohol group undergoing selective O-alkenylation in the presence of the amide, to give the corresponding enol ether **4** (Table 10, entry 5). Acrylamide and cinnamamide were also effective cross-coupling partners giving **3s** and **3t**, respectively (Table 10, entries 6 and 7). Reaction of heteroaromatic substituted substrates gave mixed results with 2-thiophenecarboxamide affording **3u** in good yield (Table 10, entry 8), whereas coupling of nicotinamide was unsuccessful. The reaction of pyrrolidinone gave **3e** in 86% yield, and the reaction of methyl (*S*)-(+)-2-pyrrolidone-5-carboxylate gave **3v** in 80% yield (Table 10, entries 9 and 10). Reaction of cyclic oxazolidinones occurred in good yields to give **3d** and **3w** (Table 10, entries 11 and 12). Again in

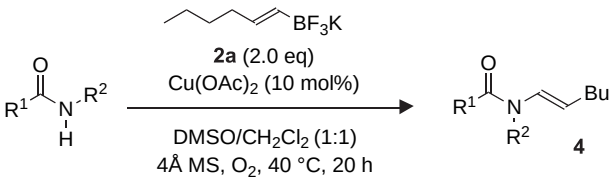
Table 9
Substrate scope of the cross-coupling reactions of primary amides with **2a** under 'ligandless' conditions (method B)

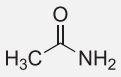
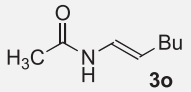
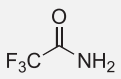
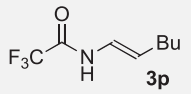
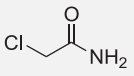
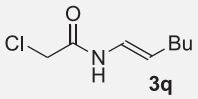
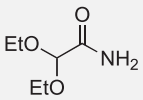
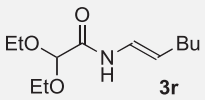
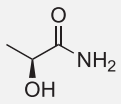
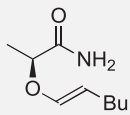
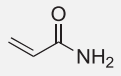
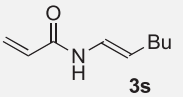
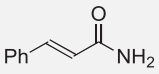
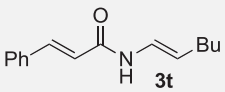
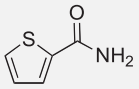
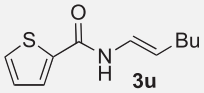
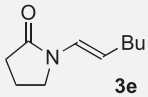
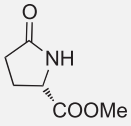
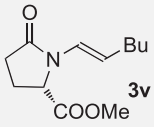
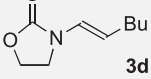
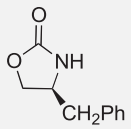
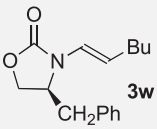


Entry	Product	Yield[a] (%)
1	 **3f**	81
2	 **3g**	86
3	 **3h**	72
4	 **3i**	66
5	 **3j**	71
6	 **3k**	70
7	 **3l**	66
8	 **3m**	55
9	 **3n**	65

[a] Isolated product after column chromatography.

Table 10
Substrate scope of the cross-coupling reactions of amides, lactams, and oxazolidinones with **2a** under 'Ligandless' conditions (method B)



Entry	Amide	Product	Yield[a] (%)
1		 **3o**	67
2		 **3p**	86
3		 **3q**	88
4		 **3r**	79
5		 **4**	68
6		 **3s**	74
7		 **3t**	75
8		 **3u**	76
9		 **3e**	86
10		 **3v**	80
11		 **3d**	97
12		 **3w**	71

[a] Isolated product after column chromatography.

all cases the reactions were highly diastereoselective, and only the *trans*-enamides **3** were observed (≥97:3 by ^{1}H NMR spectroscopy).

Other potassium alkenyltrifluoroborate salts can also be employed using the ligand-free protocol to give enamides **5** (Fig. 3). For example, reactions of benzamide, a substituted acetamide and oxazolidinone with potassium *trans*-styryltrifluoroborate **2b,** afforded the products **5a**, **5b**, and **5c** in good yields. In the case of reactions with potassium *cis*-styryltrifluoroborate salt **2c**, however, the isolation of the *cis*-enamide **5d** proved to be difficult. Even though the product was observed by TLC, the enamide decomposed on the silica gel column. These observations are in agreement with observations by Fürstner and co-workers.[16c] The product was isolated by employing alumina column chromatography. Reaction of potassium vinyltrifluoroborate **2d** with benzamide was similarly problematic, giving **5e** in low yield. Several attempts to improve the yield by increasing the amount of vinyltrifluoroborate were fruitless.

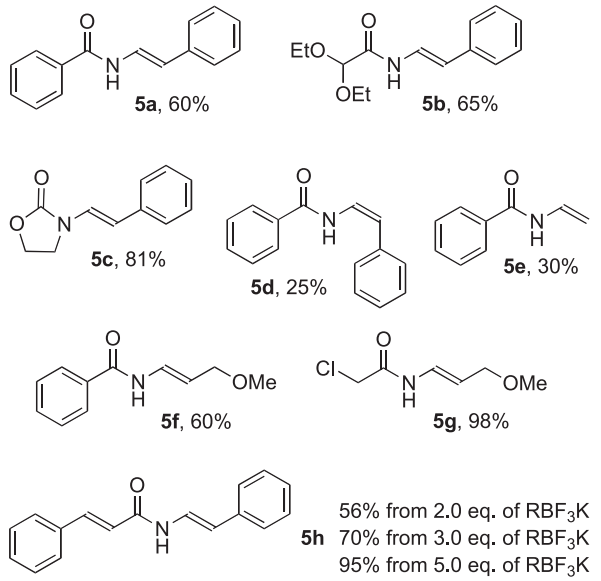
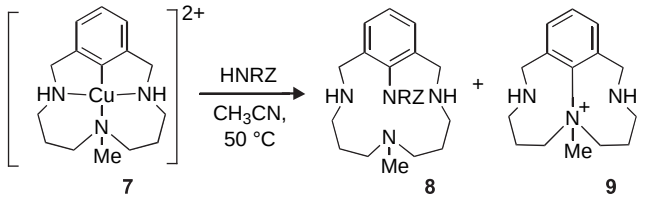


Figure 3. Substrate scope of the cross-coupling reactions of amides and oxazolidinones with potassium alkenyltrifluoroborate salts under 'ligandless' conditions (method B).

Coupling of potassium *trans*-3-methoxy-1-propenyltrifluoroborate salt **2e** with benzamide and chloroacetamide gave the products **5f** and **5g** in good and excellent yields. Coupling of *trans*-cinnamamide with potassium *trans*-styryltrifluoroborate gave a 56% yield of **5h**. Increasing the amount of the alkenyltrifluoroborate salt used led to improved yields of **5h**, with almost quantitative formation when using 5 equiv of the potassium *trans*-styryltrifluoroborate salt. Enamide **5h** has been reported to be the key intermediate in the synthesis of a natural product lansamide I, which was prepared in three steps in 42% yield using an alternative route.[50]

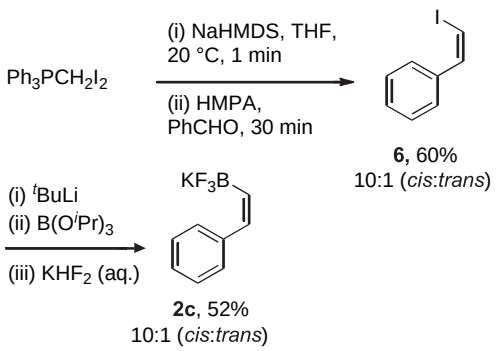
The developed methodology relies upon ready access to potassium alkenyltrifluoroborate salts **2**. The salts can be synthesized from the corresponding boronic acids and potassium hydrogen fluoride using the standard procedure developed by Vedejs and co-workers.[33] Potassium *trans*-styryltrifluoroborate **2b** was prepared from commercially available *trans*-styrylboronic acid. The corresponding *cis*-styryltrifuoroborate salt **2c** was prepared using a metalation approach, which was initially used for the synthesis of boronic acids, and later adopted for the synthesis of organotrifluoroborate salts (Scheme 2). Thus, *cis*-styryliodide **6** was formed in 60% yield in a 10:1 diastereomeric ratio (cis/trans), from the reaction of benzaldehyde with an in situ preformed phosphonium ylid, according to the protocol of Stork and Zhao.[51] Lithium–halogen exchange of **6** in the presence of *tert*-butyllithium, and trapping of the resultant organolithium species with triisopropylborate, followed by reaction of the boronate ester intermediate with potassium hydrogen fluoride afforded *cis*-styryltrifluoroborate salt **2c** in 52% yield without any loss of stereochemical fidelity.

There are several proposed mechanisms concerning the couplings of alkenyl and arylboronic acids that have appeared in the literature. Evans and co-workers proposed a mechanism for the cross-coupling of arylboronic acids and phenols.[52] They suggested that tetracoordinated Cu(II) intermediate, which resulted after the coordination and deprotonation of phenol, and transmetalation of arylboronic acid, can either undergo reductive elimination directly or be initially oxidized to Cu(III) and then proceed to reductive elimination. Lam and co-workers proposed a similar pathway for the arylation and alkenylation of nitrogen nucleophiles, where oxidation of a Cu(II) to a Cu(III) intermediate and reductive elimination are fast compared to slow reductive elimination of Cu(II) species.[38] Collman and Zhong proposed a similar mechanism in more detail for the arylation of imidazoles in the presence of $[Cu(OH)\cdot TMEDA]_2Cl_2$ complex.[53] Collman also outlined the importance of ligands on copper as a means of reducing oxidation potential. More recently, Stahl and co-workers have reported the reactions of a defined copper(III) complex **7** with various amides affording coupling product **8** (Scheme 3).[42] A byproduct **9** was observed when complex **7** was heated in the absence of external nucleophile and when less reactive amides were employed. After performing kinetic studies for different amides it was observed that amides with lower pK_a values reacted more rapidly than those with high pK_a values. As a result, Stahl and co-workers suggested that this trend was a result of an amide being deprotonated prior to or in the rate-determining step. The C–N bond formation event was suggested to proceed via a three-centered Cu(III) intermediate, which was not observed, or by the bimolecular attack of an amidate on the *ipso* carbon of the aryl ligand. Stahl has subsequently proposed a Cu(I)/Cu(II)/Cu(III) mechanistic scheme for the coupling of boronic esters with methanol, where transmetalation is the rate-determining step.[54]



Scheme 3. Stahl's studies on the reactivity of copper(III) complex **7**.

It is clear that enamide formation is very sensitive to changes in the ligand, solvent, and the structures of the substrate amides and alkenyltrifluoroborate salts. While the specific copper oxidation states, spatial orientation of the complexes, and the sequence of events in a catalytic cycle are not known, a general mechanistic scheme can be made (Fig. 4), based upon some of the generally



Scheme 2. Synthesis of potassium *cis*-styryltrifluoroborate salt **2c**.

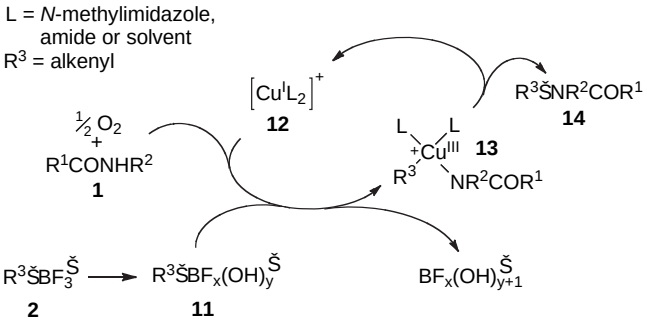


Figure 4. Mechanistic overview for the copper-catalyzed cross-coupling between amides and potassium alkenyltrifluoroborate salts.

accepted speculations outlined above, and the recent studies of Stahl and co-workers. The transmetalation step probably does not occur directly on the organotrifluoroborate salt **2**. Instead replacement of at least one of the fluoride ions from **2** must occur to give the boron intermediate **11**, which contains a hydroxyl group(s). The presence of the hydroxy group on **11** allows the formation of a bridging M–O–B species that is required for transmetalation, as for palladium[55] and rhodium[56] catalyzed reactions. Oxidation by molecular oxygen of Cu(I) species **12** to Cu(III) is believed to occur in a stepwise fashion via Cu(II).[56] Transmetalation by **11** and coordination of **1** may occur either at the Cu(II) or Cu(III) oxidation states, leading to intermediate **13**. Rapid reductive elimination of **13** then gives the product enamide **14** and regenerates Cu(I) complex **12**. It is also possible that dinuclear Cu complexes may be involved in the catalytic cycle. The role of 4 Å molecular sieves is not clear, but they may serve as a catalyst for hydrogen peroxide decomposition, or aid in the re-oxidation of copper by oxygen, perhaps through the generation of a peroxo-copper species.[57] In addition, they may facilitate ligand exchange on boron (as for the conversion of **2** to **11**).

3. Conclusions

In conclusion, two protocols for the cross-coupling reaction of potassium alkenyltrifluoroborate salts with amides to give enamides have been developed. The existing methods for the synthesis of enamides 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. In contrast, this protocol occurs at low temperature under neutral conditions, providing an attractive alternative for the synthesis of the enamide moiety. The cross-coupling reactions occur under an atmosphere of molecular oxygen at 40 °C in the presence of a copper catalyst (10 mol %). For amide substrates with lower pK_a values, such as phthalimide, isatin, and 2-hydroxypyridine, the presence of *N*-methylimidazole (20 mol %), was essential for the reaction to take place, possibly due to the ability of *N*-methylimidazole to act as a stabilizing ligand for higher oxidation states of copper, and/or to facilitate deprotonation of the amides bound to copper. For less acidic amide substrates (higher pK_a's), reaction in a DMSO/CH_2Cl_2 co-solvent mix occurred in the absence of *N*-methylimidazole or other added external ligand. Under these conditions we speculate that DMSO may serve as a ligand for copper, and that deprotonation of the copper bound amide may not be necessary for reductive elimination to occur. Further investigations on the applications of this reaction and of the utility of organotrifluoroborate salts in metal-catalyzed couplings will be reported in due course.

4. Experimental section

4.1. General

The following general experimental applies for all experiments described in this paper. Unless otherwise stated, all reactions were performed under oxygen. All reagents, unless otherwise stated were used as received. Reaction solvents were distilled under an inert atmosphere before use and transferred via syringe using standard techniques unless otherwise stated. Dichloromethane was distilled from CaH_2 under nitrogen. DMSO was purchased as anhydrous grade from Aldrich. All other solvents were obtained as ACS grade (or better). All reagents, unless otherwise stated, were used as received (Aldrich, Fischer Scientific Ltd., or Lancaster). *cis*-Styryl iodide,[53] potassium hexenyltrifluoroborate,[58] and potassium *trans*-styryl trifluoroborate[37,59] were prepared according to the literature procedures. FTIR spectra were obtained on a Perkin–Elmer Spectrum 1000, with samples loaded as films on NaCl plates or as KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained on Varian Mercury 300 or Unity 400 as solutions in deuterated solvents ($CDCl_3$, DMSO-d_6, and acetone-d_6, obtained from Cambridge Isotope Labs) and referenced to their corresponding solvent peaks (i.e., $CHCl_3$ 7.26 ppm; DMSO 2.54 ppm; acetone 2.09 ppm for proton resonances, and $CHCl_3$, 77.23 ppm; DMSO 40.45; acetone 205.87 ppm for carbon resonances). Chemical Shifts are expressed in parts per million values. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; *J*, coupling constant in hertz. Low-resolution mass spectra (MS) were recorded on a Bell and Howell 21-490 spectrometer. High-resolution mass spectra (HRMS) were recorded on an AEI MS3074 spectrometer. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230–400 mesh, low acidity, obtained from Silicycle Inc.) and aluminum oxide (activated, neutral, Brockmann I, standard grade, ~150 mesh, 58 Å, obtained from Aldrich) was performed on reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminum-backed silica gel plates (Alugram SIL/G/UV254 purchased from Silicycle Inc.), visualized with an UV lamp (254 nm) and potassium permanganate (Aldrich). Spectral data are provided for all new compounds and for compounds that lack full characterization in the literature. Spectral data for compounds **3e**,[23b] **3v**,[23b] **5a**,[26a] **5c**,[60] **5d**,[23c] **5e**,[61] and **5h**[62] were in agreement with literature values.

4.2. Method A

To $Cu(OAc)_2$ (0.05 mmol), amide (0.5 mmol), potassium alkenyltrifluoroborate salt (1.0 mmol), and 4 Å molecular sieves (0.38 g) were added CH_2Cl_2 (2.0 ml) and *N*-methylimidazole (0.1 mmol). The suspension was stirred for 20 h at 40 °C under positive atmosphere of oxygen (oxygen from a cylinder was passed through a gas drying unit filled with DRIERITE), then through a manifold equipped with an oil bubbler. The reaction flask was attached to the manifold. The reaction mixture was then filtered through a plug of Celite, which was washed with EtOAc (50 mL). The crude products were purified by silica gel chromatography using EtOAc/hexanes/Et_3N.

4.3. Method B

To $Cu(OAc)_2$ (0.05 mmol), amide (0.5 mmol), potassium alkenyltrifluoroborate salt (1.0 mmol), and 4 Å molecular sieves (0.38 g) were added CH_2Cl_2 (1.0 ml) and DMSO (1.0 ml). The suspension was stirred for 20 h at 40 °C under an atmosphere of oxygen (see method A). The reaction mixture was then filtered through a plug of Celite, which was washed with EtOAc (50 mL). The crude products were purified by silica gel chromatography using EtOAc/hexanes/Et_3N.

4.4. Characterization data

*4.4.1. trans-2-Hex-1-enyl-isoindole-1,3-dione (**3a**)[28].* Synthesized by method A. Isolated as yellow crystals (114 mg, quantitative); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 33:66:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, J=5.5, 3.0 Hz, 2H), 7.72 (dd, J=5.5, 3.0 Hz, 2H), 6.57–6.63 (m, 2H), 2.11–2.20 (m, 2H), 1.41–1.51 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 134.5, 131.9, 123.6, 123.1, 117.7, 31.8, 31.1, 22.4, 14.1.

*4.4.2. trans-1-Hex-1-enyl-1H-pyridin-2-one (**3b**)[28].* Synthesized by method A. Isolated as colorless crystals (89 mg, 78%); crude product was purified by silica gel column chromatography (eluting with

EtOAc/hexanes/Et_3N 33:66:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, J=7.0, 2.0 Hz, 1H), 7.31 (ddd, J=9.0, 6.5, 2.0 Hz, 1H), 7.24 (d, J=4.5 Hz, 1H), 6.55 (d, J=9.0 Hz, 1H), 6.19 (dd, J=6.0, 6.0 Hz, 1H), 5.79 (dt, J=14.5, 7.0 Hz, 1H), 2.18–2.25 (m, 2H), 1.41–1.51 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.7, 140.0, 134.0, 126.9, 123.6, 121.4, 106.5, 31.6, 29.9, 22.4, 14.0.

*4.4.3. trans-1-Hex-1-enyl-1H-indole-2,3-dione (**3c**)*[28]. Synthesized by method A. Isolated as red crystals (94 mg, 82%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 25:75:1); IR (KBr pellet) ν 3454, 2923, 1732, 1608, 1470, 1362, 1324, 1181, 1095, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59–7.63 (m, 2H), 7.12–7.18 (m, 2H), 6.31–6.42 (m, 2H), 2.20–2.25 (m, 2H), 1.40–1.50 (m, 4H), 0.94 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 157.2, 150.6, 138.5, 126.1, 125.6, 124.4, 118.7, 117.9, 111.1, 31.7, 30.7, 22.4, 14.1; MS (EI) m/z (rel intensity) 77 (28), 130 (19), 145 (100), 158 (70), 229 (46); HRMS (EI) m/z calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1102, found 229.1105.

*4.4.4. trans-3-Hex-1-enyl-oxazolidin-2-one (**3d**).* Synthesized by method B. Isolated as a colorless oil (82 mg, 97%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 50:50:1); IR (thin film) ν 2924, 2362, 1751, 1669, 1416, 1247, 1289, 1082, 943, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J=14.5 Hz, 1H), 4.82 (dt, J=14.5, 7.0 Hz, 1H), 4.42 (t, J=8.0 Hz, 2H), 3.69 (t, J=8.0 Hz, 2H), 2.03–2.10 (m, 2H), 1.23–1.43 (m, 4H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 124.0, 111.6, 62.3, 42.8, 32.4, 29.6, 22.2, 14.1; MS (EI) m/z (rel intensity) 100 (100), 126 (29), 170 (70), 192 (49); HRMS (EI) m/z calcd for $C_9H_{15}NO_2$ (M^+) 189.0793, found 189.0793.

*4.4.5. trans-N-Hex-1-enyl-benzamide (**3f**).* Synthesized by method B. Isolated as colorless crystals (83 mg, 81%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (thin film) ν 3278, 3025, 2923, 1651, 1543, 1423, 1323, 1024, 946, 707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–7.88 (m, 1H; NH), 7.79–7.84 (m, 2H), 7.50 (t, J=7.5 Hz, 1H), 7.41 (dd, J=7.5, 7.5 Hz, 2H), 6.90–6.99 (m, 1H), 5.32 (dt, J=14.5, 7.0 Hz, 1H), 2.04–2.10 (m, 2H), 1.29–1.42 (m, 4H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 134.1, 131.9, 128.8, 127.2, 123.0, 114.6, 32.2, 29.7, 22.3, 14.1; MS (EI) m/z (rel intensity) 105 (100), 106 (7), 204 (4), 226 (17); HRMS (EI) m/z calcd for $C_{13}H_{18}NO$ (M^++1) 204.1382, found 204.1374.

*4.4.6. trans-N-Hex-1-enyl-4-nitro-benzamide (**3g**).* Synthesized by method B. Isolated as yellow crystals (106 mg, 85%): mp=124–125 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (KBr pellet) ν 3296, 2928, 2420, 1641, 1599, 1515, 1297, 953, 866, 844, 708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J=8.5 Hz, 2H), 8.07 (d, J=10.0 Hz, 1H; NH), 7.98 (d, J=8.5 Hz, 2H), 6.91 (dd, J=14.0, 10.0 Hz, 1H), 5.43 (dt, 1H, J=14.0, 7.0 Hz, 1H), 2.05–2.12 (m, 2H), 1.26–1.43 (m, 4H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5, 149.9, 139.7, 128.5, 124.1, 122.5, 116.6, 32.1, 29.7, 22.3, 14.1; MS (EI) m/z (rel intensity) 104 (25), 150 (100), 167 (25), 205 (34), 248 (12); HRMS (EI) m/z calcd for $C_{13}H_{16}N_2O_3$ (M^+) 248.1161, found 248.1167.

*4.4.7. trans-N-Hex-1-enyl-2-nitro-benzamide (**3h**).* Synthesized by method B. Isolated as yellow crystals (89 mg, 72%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 50:50:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, J=10.0 Hz, 1H, NH), 7.91 (d, J=8.0 Hz, 1H), 7.57 (dd, J=7.5, 7.5 Hz, 1H), 7.47 (dd, J=7.5, 7.5 Hz, 1H), 7.39 (d, J=7.0 Hz, 1H), 6.68 (dd, J=14.0, 10.0 Hz, 1H), 5.21 (dt, J=14.0, 7.0 Hz, 1H), 1.29–2.00 (m, 2H), 1.31 (s, 4H), 0.89 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 146.6, 133.8, 132.2, 130.8, 128.9, 124.6, 122.1, 116.1, 32.0, 29.7, 22.4, 14.1; MS (EI) m/z (rel intensity) 76 (27), 104 (17), 150 (100), 205 (18), 248 (14); HRMS (EI) m/z calcd for $C_{13}H_{16}N_2O_3$ (M^+) 248.1161, found 248.1155.

*4.4.8. 4-Chloro-trans-N-hex-1-enyl-benzamide (**3i**).* Synthesized by method B. Isolated as colorless crystals (79 mg, 66%): mp=110–111 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (neat) ν 3318, 2967, 2928, 2473, 1679, 1631, 1594, 1529, 1486, 954 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.47 (d, J=7.0 Hz, NH), 7.94 (m, 2H), 7.49 (m, 2H), 6.94 (ddt, J=14.5, 10.0, 1.5 Hz), 5.45 (dt, J=14.5, 7.5 Hz), 2.07 (m, 2H), 1.34 (m, 4H), 0.90 (J=7.5 Hz); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.6, 137.0, 132.9, 129.1, 128.5, 123.5, 113.5, 32.1, 29.5, 21.9, 13.3; MS (EI) m/z (rel intensity) 111 (20), 139 (100), 141 (30), 237 (18), 239 (6); HRMS (EI) m/z calcd for $C_{13}H_{16}NOCl$ (M^+) 237.0920, found 237.0925.

*4.4.9. 2-Chloro-trans-N-hex-1-enyl-benzamide (**3j**).* Synthesized by method B. Isolated as colorless crystals (85 mg, 71%): mp=54–56 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 25:75:1); IR (neat) ν 3277, 3081, 2965, 2934, 1650, 1592, 1530, 1430, 953, 744 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.24 (d, J=6.0 Hz, NH), 7.50–7.36 (m, 4H), 6.89 (ddt, J=14.5, 10.0, 1.5 Hz, 1H), 5.42 (dt, J=14.5, 7.0 Hz, 1H), 2.12–2.05 (m, 2H), 1.41–1.33 (m, 4H), 0.92 (t, J=3.5 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.4, 136.4, 130.7, 129.8, 129.1, 127.0, 122.9, 122.8, 113.6, 32.0, 29.4, 21.9, 13.3; MS (EI) m/z (rel intensity) 111 (18), 139 (100), 141 (30), 237 (12), 239 (4); HRMS (EI) m/z calcd for $C_{13}H_{16}NOCl$ (M^+) 237.0920, found 237.0920.

*4.4.10. 2,6-Dichloro-trans-N-hex-1-enyl-benzamide (**3k**).* Synthesized by method B. Isolated as colorless crystals (95 mg, 70%): mp=178–179 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 25:75:1); IR (neat) ν 3252, 2928, 1652, 1548, 1432, 1317, 1119, 962, 800, 773 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.39 (d, J=7.0 Hz, NH), 7.44–7.42 (m, 3H), 6.88 (ddt, J=14.5, 10.0, 1.5 Hz), 5.41 (dt, J=14.5, 7.0 Hz), 2.12–2.05 (m, 2H), 1.42–1.35 (m, 4H), 0.94–0.90 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 160.8, 136.3, 131.9, 131.0, 128.0, 122.5, 114.2, 32.0, 29.4, 22.0, 13.3; MS (EI) m/z (rel intensity) 173 (100), 175 (70), 190 (28), 271 (12), 273 (7); HRMS (EI) m/z calcd for $C_{13}H_{15}NOCl_2$ (M^+) 271.0531, found 271.0534.

*4.4.11. trans-N-Hex-1-enyl-3-trifluoromethyl-benzamide (**3l**).* Synthesized by method B. Isolated as colorless crystals (90 mg, 66%): mp=43–44 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (neat) ν 3259, 3202, 2963, 1644, 1544, 1348, 1320, 1163, 1120, 920 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 9.67 (d, J=7.5 Hz, NH), 8.24–8.21 (m, 2H), 7.88 (d, J=8.0 Hz, 1H), 7.73 (t, J=8.0 Hz, 1H), 7.0 (ddt, J=14.5, 10.0, 1.5 Hz, 1H), 5.5 (dt, J=14.5, 7.0 Hz, 1H), 2.11–2.04 (m, 2H), 1.40–1.28 (m, 4H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 162.2, 135.2, 131.2, 129.9 (q, J=32.5 Hz), 129.5, 127.9 (q, J=3.5 Hz), 124.1 (q, J=271.5 Hz), 124.0 (q, J=4.0 Hz), 123.4, 114.1, 32.1, 29.5, 21.9 ,13.1; MS (EI) m/z (rel intensity) 145 (28), 173 (100), 190 (18), 228 (15), 271 (9); HRMS (EI) m/z calcd for $C_{14}H_{16}F_3NO$ (M^+) 271.1195, found 271.1184.

*4.4.12. trans-N-Hex-1-enyl-4-methoxy-benzamide (**3m**).* Synthesized by method B. Isolated as colorless crystals (65 mg, 56%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 25:75:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J=10.0 Hz, 1H; NH), 7.76 (d, J=9.0 Hz, 2H), 6.94 (dd, J=14.0, 10.0 Hz, 1H), 6.87 (d, J=9.0 Hz, 2H), 5.29 (dt, J=14.0, 7.0 Hz, 1H), 3.81 (s, 3H), 2.00–2.07 (m, 2H), 1.32–1.39 (m, 4H), 0.88 (t, J=7.0 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 162.6, 129.2, 126.3, 123.2, 114.1, 114.0, 55.6, 32.3, 29.7, 22.3, 14.1; MS (EI) *m*/*z* (rel intensity) 77 (7), 92 (6), 135 (100), 233 (18); HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1416, found 233.1419.

*4.4.13. trans-N-Hex-1-enyl-2-methoxy-benzamide (**3n**).* Synthesized by method B. Isolated as a colorless oil (76 mg, 65%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (thin film) ν 3374, 2954, 2356, 1644, 1519, 1298, 1248, 1021, 952, 755 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (d, *J*=9.5 Hz, 1H; NH), 8.20 (dd, *J*=8.0, 2.0 Hz, 1H), 7.40–7.45 (m, 1H), 7.00–7.08 (m, 3H), 5.25 (dt, *J*=14.5, 7.0 Hz, 1H), 3.96 (s, 3H), 2.03–2.10 (m, 2H), 1.29–1.40 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 157.6, 133.3, 132.7, 123.1, 121.6, 121.1, 114.4, 111.6, 56.2, 32.3, 29.8, 22.3, 14.1; MS (EI) *m*/*z* (rel intensity) 57 (14), 77 (20), 92 (12), 135 (100), 233 (29); HRMS (EI) *m*/*z* calcd for $C_{14}H_{19}NO_2$ (M^+) 233.1416, found 233.1420.

*4.4.14. trans-N-Hex-1-enyl-acetamide (**3o**).* Synthesized by method B. Isolated as a colorless oil (47 mg, 67%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 75:25:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, *J*=11.0 Hz, 1H; NH), 6.69 (m, 1H), 5.12 (dt, *J*=14.5, 7.0 Hz, 1H), 1.94–2.00 (m, 5H), 1.24–1.35 (m, 4H), 0.85 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 122.6, 113.4, 32.2, 29.5, 23.3, 22.3, 14.1; MS (EI) *m*/*z* (rel intensity) 56 (100), 60 (17), 70 (11), 98 (23), 141 (20); HRMS (EI) *m*/*z* calcd for $C_8H_{15}NO$ (M^+) 141.1151, found 141.1154.

*4.4.15. 2,2,2-Trifluoro-trans-N-hex-1-enyl-acetamide (**3p**).* Synthesized by method B. Isolated as a yellow oil (84 mg, 86%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 10:100:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 6.61 (dd, *J*=14.0, 10.0 Hz, 1H), 5.51 (dt, *J*=14.5, 7.0 Hz, 1H), 2.02–2.09 (m, 2H), 1.24–1.41 (m, 4H), 0.88 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4 (q, ^2J(C,F)=38.0 Hz), 120.2, 120.0, 116 (q, ^1J(C,F)=287.0 Hz), 31.6, 29.5, 22.2, 14.0; MS (EI) *m*/*z* (rel intensity) 57 (32), 69 (17), 82 (17), 152 (100), 195 (14); HRMS (EI) *m*/*z* calcd for $C_8H_{12}F_3NO$ (M^+) 195.0871, found 195.0871.

*4.4.16. 2-Chloro-trans-N-hex-1-enyl-acetamide (**3q**).* Synthesized by method B. Isolated as colorless crystals (77 mg, 88%): mp=34–35 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 33:66:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 9.11 (s, NH), 6.68 (ddt, *J*=14.0, 10.0, 1.5 Hz, 1H), 5.38 (dt, *J*=14.0, 7.5 Hz, 1H), 2.06–2.00 (m, 2H), 1.37–1.29 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.2, 122.6, 113.9, 42.3, 31.9, 29.3, 21.8, 13.3; MS (EI) *m*/*z* (rel intensity) 56 (45), 132 (100), 140 (30), 175 (20), 177 (7); HRMS (EI) *m*/*z* calcd for $C_8H_{14}NOCl$ (M^+) 175.0764, found 175.0769.

*4.4.17. trans-2,2-Diethoxy-N-hex-1-enyl-acetamide (**3r**).* Synthesized by method B. Isolated as colorless oil (90 mg, 79%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 33:66:1); IR (thin film) ν 3300, 2976, 2958, 2874, 1670, 1514, 1166, 1128, 1064, 956 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.80 (d, *J*=5.5 Hz, NH), 6.67 (ddt, *J*=14.5, 10.5, 1.5 Hz, 1H), 5.42 (dt, *J*=14.5, 7.0 Hz, 1H), 4.78 (s, 1H), 3.68–3.55 (m, 4H), 2.09–1.99 (m, 2H), 1.36–1.31 (m, 4H), 1.18 (t, *J*=7.0 Hz, 6H), 0.91–0.87 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 164.9, 122.3, 114.0, 98.9, 62.3, 32.3, 29.6, 22.1, 14.7, 13.5; MS (EI) *m*/*z* (rel intensity) 37 (75), 103 (100), 229 (5); HRMS (EI) *m*/*z* calcd for $C_{12}H_{23}NO_3$ (M^+) 229.1678, found 229.1676.

*4.4.18. trans-2-Hex-1-enyloxy-propionamide (**4**).* Synthesized by method B. Isolated as colorless crystals (58 mg, 68%): mp=44–46 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 66:33:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 6.79–6.64 (m, NH_2), 6.21 (dt, *J*=12.5, 1.0 Hz, 1H), 4.91 (dt, *J*=12.5, 7.5 Hz, 1H), 4.15(q, *J*=7.0 Hz, 1H), 1.96–1.88 (m, 2H), 1.35 (d, *J*=7.0 Hz, 3H), 1.33–1.28 (m, 4H), 0.89–0.86 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.0, 144.6, 106.7, 75.9, 32.5, 26.9, 21.7, 17.8, 13.3; MS (EI) *m*/*z* (rel intensity) 55 (55), 57 (28), 72 (100), 73 (90), 171 (10); HRMS (EI) *m*/*z* calcd for $C_9H_{17}NO_2$ (M^+) 171.1259, found 171.1266.

*4.4.19. trans-N-Hex-1-enyl-acrylamide (**3s**).* Synthesized by method B. Isolated as colorless oil (57 mg, 74%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 50:50:1); IR (thin film) ν 3267, 3194, 2957, 2928, 1658, 1626, 1533, 1236, 954, 800 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.07 (s, NH), 6.81 (ddt, *J*=14.5, 10.5, 1.5 Hz, 1H), 6.26 (d, *J*=2.0 Hz, 1H), 6.25 (s, 1H), 5.63 (dd, *J*=7.0, 5.5 Hz, 1H), 5.27 (dt, *J*=14.5, 7.0 Hz, 1H), 2.06–2.00 (m, 2H), 1.39–1.28 (m, 4H), 0.92–0.87 (m, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 161.8, 131.1, 125.8, 123.2, 112.8, 32.1, 29.4, 21.8, 13.3; MS (EI) *m*/*z* (rel intensity) 55 (28), 56 (15), 82 (19), 110 (100), 153 (60); HRMS (EI) *m*/*z* calcd for $C_9H_{15}NO$ (M^+) 153.1154, found 153.1153.

*4.4.20. trans-N-Hex-1-enyl-3-phenyl-acrylamide (**3t**).* Synthesized by method B. Isolated as colorless crystals (86 mg, 75%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 25:75:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J*=10.5 Hz, 1H, NH), 7.69 (d, *J*=16.0 Hz, 1H), 7.44–7.47 (m, 2H), 7.26–7.33 (m, 3H), 6.93 (dd, *J*=14.0, 1.5 Hz, 1H), 6.55 (d, *J*=16.0 Hz, 1H), 5.33 (dt, *J*=14.5, 7.0 Hz, 1H), 2.00–2.07 (m, 2H), 1.32 (m, 4H), 0.86 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 142.1, 135.0, 130.0, 129.0, 128.1, 123.0, 120.5, 114.9, 32.2, 29.8, 22.4, 14.1; MS (EI) *m*/*z* (rel intensity) 103 (55), 131 (100), 132 (8), 230 (8), 252 (16); HRMS (EI) *m*/*z* calcd for $C_{15}H_{20}NO$ (M^++1) 230.1541, found 230.1539.

*4.4.21. Thiophene-2-carboxylic acid trans-hex-1-enylamide (**3u**).* Synthesized by method B. Isolated as colorless crystals (80 mg, 66%): mp=134–135 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 33:66:1); ; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.40 (d, *J*=6.5 Hz, NH), 7.78 (dd, *J*=4.0, 1.0 Hz, 1H), 7.71 (dd, *J*=5.0, 1.0 Hz, 1H), 7.13 (dd, *J*=5.0, 4.0 Hz, 1H), 6.88 (ddt, *J*=14.5, 10.0, 1.5 Hz), 5.39 (dt, *J*=7.5, 14.5 Hz, 1H), 2.08–2.03 (m, 2H), 1.38–1.30 (m, 4H), 0.89 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.5, 139.6, 130.9, 128.0, 127.7, 123.1, 113.0, 32.1, 29.5, 21.9, 13.3; MS (EI) *m*/*z* (rel intensity) 83 (5), 111 (100), 128 (12), 166 (14), 209 (17); HRMS (EI) *m*/*z* calcd for $C_{11}H_{15}NOS$ (M^+) 209.0874, found 209.0879.

*4.4.22. trans-4-Benzyl-3-hex-1-enyl-oxazolidin-2-one (**3w**).* Synthesized by method B. Isolated as a yellow oil (92 mg, 71%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 20:80:1); IR (thin film) ν 3427, 2927, 1769, 1672, 1417, 1234, 1088, 1029, 949, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.35 (m, 3H), 7.16 (d, *J*=7.0 Hz, 2H), 6.56 (d, *J*=14.5 Hz, 1H), 5.08 (dt, *J*=14.5, 7.0 Hz, 1H), 4.12–4.29 (m, 3H), 3.19 (dd, *J*=14.0, 3.0 Hz, 1H), 2.76 (dd, *J*=14.0, 8.5 Hz, 1H), 2.09–2.15 (m, 2H), 1.31–1.44 (m, 4H), 0.92 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 135.7, 129.5, 129.2, 127.5, 122.8, 112.5, 66.5, 55.2, 36.3, 32.5, 30.0, 22.3, 14.1; MS (EI) *m*/*z* (rel intensity) 117 (16), 190 (21), 216 (9), 260 (100), 282 (28); HRMS (EI) *m*/*z* calcd for $C_{16}H_{22}NO_2$ (M^++1) 260.1645, found 260.1646.

*4.4.23. 2,2-Diethoxy-trans-N-styryl-acetamide (**5b**).* Synthesized by method B. Isolated as yellow crystals (80 mg, 65%): mp=64–65 °C;

crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 50:50:1); ^1H NMR (400 MHz, acetone-d_6) δ 9.30 (d, J=9.5 Hz, NH), 7.49 (dd, J=10.5, 14.5 Hz, 1H), 7.37–7.34 (m, 2H), 7.31–7.26 (m, 2H), 7.19–7.14 (m, 1H), 7.47 (d, J=14.5 Hz, 1H), 3.73–3.60 (m, 4H), 1.21 (t, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, acetone-d_6) δ 165.7, 137.0, 128.9, 126.6, 125.6, 122.6, 113.9, 98.9, 62.5, 14.8; MS (EI) m/z (rel intensity) 75 (45), 91 (40), 103 (100), 118 (40), 249 (23); HRMS (EI) m/z calcd for $C_{14}H_{19}NO_3$ (M^+) 249.1365, found 249.1353.

*4.4.24. trans-N-(3-Methoxy-propenyl)-benzamide (**5f**).* Synthesized by method B. Isolated as a colorless oil (86 mg, 60%); crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 50:50:1); IR (KBr pellet) ν 3334, 2935, 2340, 1724, 1567, 1301, 1207, 1098, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, J=10.5 Hz, 1H, NH), 7.80 (dd, J=7.0, 1.0 Hz, 2H), 7.51 (tt, J=7.5, 1.0 Hz, 1H), 7.42 (t, J=7.5 Hz, 2H), 7.20 (dd, J=14.0, 10.5 Hz, 1H), 5.43 (dt, J=7.0, 14.0 Hz, 1H), 3.95 (dd, J=7.0, 1.0 Hz, 2H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 133.6, 132.3, 128.9, 127.4, 127.2, 109.2, 71.4, 57.6; MS (EI) m/z (rel intensity) 105 (100), 106 (6), 160 (22), 178 (2), 214 (4); HRMS (EI) m/z calcd for $C_{11}H_{13}NO_2Na$ (M^++Na) 214.0838, found 214.0840.

*4.4.25. 2-Chloro-trans-N-(3-methoxy-propenyl)-acetamide (**5g**).* Synthesized by method B. Isolated as colorless crystals (80 mg, 98%): mp=47–48 °C; crude product was purified by silica gel column chromatography (eluting with EtOAc/hexanes/Et_3N 33:66:1); ^1H NMR (400 MHz, acetone-d_6) δ 9.31 (s, NH), 6.91 (ddt, J=14.5, 10.5, 1.0 Hz, 1H), 5.46 (dt, J=14.5, 6.5 Hz, 1H), 4.13 (s, 2H), 3.88 (dd, J=6.5, 1.5 Hz, 2H), 3.21 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 163.8, 125.6, 109.7, 70.5, 56.5, 42.2; MS (EI) m/z (rel intensity) 49 (15), 77 (25), 82 (100), 96 (20), 163 (8); HRMS (EI) m/z calcd for $C_6H_{10}NO_2Cl$ (M^+) 163.0400, found 163.0407.

*4.4.26. Potassium cis-styryl trifluoroborate (**2c**).* To a solution of *cis*-styryliodide **6**[53] (10:1 cis/trans) (1.09 g, 4.7 mmol) in Et_2O (10 ml) at −78 °C was slowly added ^{t}BuLi (6.06 mL, 1.7 M in pentane, 10.3 mmol). The reaction mixture was stirred for 2 h at −78 °C and triisopropylborate (1.09 ml, 4.7 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 1 h at room temperature. It was then cooled to −20 °C and an aqueous solution of KHF_2 (2.20 g, 28.2 mmol) was slowly added. The reaction mixture was allowed to warm up to room temperature and stirred for an additional 2 h at room temperature. The solvents were evaporated in vacuo. To the crude product was added acetone (50 mL) and the mixture was filtered. The solution was concentrated, and the crude product was redissolved in a minimum amount of acetone and the product was precipitated with Et_2O. The mixture was filtered to afford the title compound as a white solid (512 mg, 52%). The spectral data were identical to those reported in the literature.[63]

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Supplementary data

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