Metal-Free C–H Alkyliminylation and Acylation of Alkenes with Secondary Amides

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Carbon–carbon bond formation by metal-free cross-coupling of two reactants with low reactivity represents a challenge in organic synthesis. Secondary amides and alkenes are two classes of bench-stable compounds. The low electrophilicity of the former and low nucleophilicity of the latter make the direct coupling of these two partners challenging yet highly desirable. We report herein an unprecedented intermolecular reaction of secondary amides with alkenes to afford $\alpha,\beta$-unsaturated ketimines or enones, which are versatile intermediates for organic synthesis and are prevalent in bioactive compounds and functional materials. Our strategy relies on the chemoselective activation of the secondary amide with trifluoromethanesulfonic anhydride (Tf$_2$O)/2-fluoropyridine to generate a highly reactive nitrilium intermediate, which reacts efficiently with alkenes. This metal-free synthesis is characterized by its mild reaction conditions, excellent functional group tolerance and chemoselectivity, allowing the preparation of multi-functionalized compounds without using protecting groups.
Results and Discussion

Reaction design. To realize the direct cross-coupling of an alkene with a secondary amide, it is necessary to activate one of the reaction partners. Inspired by the B–N reaction, we opted for the in situ activation of the amide group. Considering the low efficiency of the classical amide activators such as P₂O₅ and POCl₃, highly electrophilic trifluoromethanesulfonic (triflic) anhydride (Tf₂O) was selected for our purpose. Tf₂O in combination with a base such as 2,6-di-tert-butyl-4-methylpyridine (DTBMP), Hünig base, 2-chloropyridine, 2-fluoropyridine, 2-iodopyridine, 2,4,6-collidine, and 3-cyanopyridine had been employed for the activation of amides in various C–C bond-forming reactions. A secondary amide A, once treated with Tf₂O, would generate a highly reactive nitriilium intermediate A (Fig. 2). The latter could then be captured by an alkene to give...
Optimization of reaction conditions. To avoid possible side reactions such as 1,5-hydride migration reaction\(^3^6\), the amides 1 bearing a \(N\)-2,6-dimethylphenyl group were designed as substrates for the investigation (Fig. 3). At the outset of our studies, base-free amide activation protocol was attempted. To our delight, successive treatment of a solution of secondary amide 1a (1.0 equiv) in \(CH_2Cl_2\) (0.25 M) with \(\text{Tf}_2\text{O}\) (1.1 equiv) at 0 °C for 10 min and then styrene (3.0 equiv) at room temperature for 2 h produced the desired \(\alpha,\beta\)-unsaturated ketimine 2a in 51% yield as a mixture of \(E/Z\) isomers in a ratio of 5.5:1 (entry 1). The stereochemistry of major geometric isomer was determined as \(E\) by NOESY technique (cf. Supplementary Figure 53). Note that \(\text{Tf}_2\text{O}\) failed to promote the B–N cyclization reaction in the absence of a base unless highly electron-rich substrates were used\(^4^4\). Encouraged by this result, the effects of base were surveyed. Among the bases screened, 2-F-pyridine was found to be the best (entries 3–9). Under these conditions, the amount of styrene could be reduced to 1.2 equiv without affecting the reaction efficiency (entries 10 and 11). The optimal conditions were thus defined as successive treatment of a solution of secondary amide 1a (1.0 equiv) and 2-fluoropyridine (1.2 equiv) in \(CH_2Cl_2\) (0.25 M) with \(\text{Tf}_2\text{O}\) (1.1 equiv) at 0 °C for 10 min, and then with styrene (1.2 equiv) at room temperature or 40 °C for 2 h. The reaction mixture was concentrated without work-up and subjected to flash chromatographic purification to give \(\alpha,\beta\)-unsaturated ketimine 2a.

Substrate scope of the direct C–H alkyliminylation. With optimized conditions in hand, the coupling reactions of a series of \(N\)-(2,6-dimethylphenyl)benzamides 1 with a number of alkenes were investigated (Fig. 4). Styrene bearing electron-donating groups (Me, OMe) and electron-withdrawing halogens (Br, Cl, F) reacted smoothly to give the corresponding enimines in excellent yields (2b–2f, 88–99% yields), demonstrating superior reactivity compared with reported methods. \(\alpha\)-Methylnitrostyrene and \(\alpha\)-phenylisostearene were also competent substrates (2g, 2h). Gratifyingly, the reaction was also compatible with the use of di- and trisubstituted aliphatic alkenes and 1,3-dienes (2i–2l). The reaction of 2-methyl-2-buten produced non-conjugated \(\beta,\gamma\)-unsaturated ketimine 2k. Further investigation revealed that the reaction was rather insensitive to the electronic properties of the benzamide derivatives and tolerated electron-donating groups such as methyl group (2m) and methoxy group (2n), as well as the highly electron-withdrawing nitro group (2p, 2q).

The current reaction is characterized by its broad tolerance of sensitive functional groups including bromo (2o), nitro (2p, 2q), ester (2r, 2w), ketone (2s, 2z), aldehyde (2t), cyano (2u), azido (2x), tertiary amide (2v, 2y), sulfonamide (2aa), phenol (2ab) and silyl ether groups (2ac), many of which are not compatible with organometallic reagents. The highly functionalized products were all obtained in good to excellent yields, demonstrating great potential for the \(\text{Tf}_2\text{O}\)-promoted method in the synthesis of complex structures. Interestingly, \(\text{p-vinylstyrene}\)
could react selectively at one end giving 2ad in 87% yield, or at both alkenes leading to 2ae in 85% yield. Finally, the reaction could be scaled up to 20 mmol-scale without yield loss as demonstrated by the reaction of 1a with styrene (2a, yield: 95%, 5.91 g, Fig. 4).

Figure 4. Metal-free direct coupling of N-2,6-dimethylbenzamides with alkenes to give α,β-unsaturated ketimines 2. aReaction conditions: Amide (1.0 equiv), 2-F-Pyr. (1.2 equiv), CH₂Cl₂ (0.25 M), then 0 °C, Tf₂O (1.1 equiv), 10 min. Alkene (1.2 equiv), 2 h. bIsolated yield. cReaction ran at room temperature (rt). dReaction ran at 40 °C. eThe E/Z ratio of imines was determined by ¹H NMR. fThe structure was determined by X-Ray analysis (cf. Supplementary Figure 54). g2.5 equiv of amide 1f and 1.0 equiv of 1,4-divinylbenzene were used.

Ts = 4-toluenesulfonyl, TBS = tert-butyldimethylsilyl.
Substrates scope of the direct C–H acylation. We then turned our attention to the synthesis of enones by in situ hydrolysis of the ketimine products. After the Tf₂O/2-fluoropyridine-mediated dehydracoupling, the reaction mixture was concentrated and heated to reflux in a mixture of ethanol and 3 M HCl (1:1, v/v) to afford the desired enones (Fig. 5). Functionalized chalcones were synthesized in good to excellent yields by employing styrenyl alkenes and benzamide derivatives as substrates. Aliphatic and α,β-unsaturated amides were also excellent substrates (3i–3k, 3m). N-Alkyl amides are valuable directing group for both classical lithiation-functionalization and modern C–H functionalization reactions. As a result, the transformation of the functionalized amide products obtained in these reactions into other classes of compounds are imperative. To demonstrate the value of our method in this context, the N-methyl amides 1t, 1u, and 1v, which were previously obtained through transition-metal-catalyzed C–H activation, were converted into the corresponding enones in 60–73% yields.

Synthetic applications. To demonstrate the synthetic potential of the enone synthesis, the coupling reaction of styrene with (S)-N-methyl-tetrahydro-5-oxo-2-furaneamide (1w), readily available in 99% ee from L-glutamic acid, was undertaken (Fig. 6a). To our delight, the desired enone (S)-3q was obtained in 70% yield without racemization (cf. Supplementary Figure 55). Multi-functionalized lactone-enones like 3q are versatile building blocks for the synthesis of bioactive natural products. The synthetic utility was further demonstrated by the synthesis of okanin (4) (Fig. 6b), a natural product that has been found in various folk medications used in China and Korea for treating inflammation, malaria, hypertension, diabetes, snake bite and smallpox. The amide 1x, prepared in one step from commercially available 2,3,4-trimethoxybenzoic acid by amidation using Ye’s coupling reagent (cf. Supplementary Figure 60), reacted smoothly with 3,4-dimethoxystyrene to afford enone 3r in 86% yield. Exhaustive demethylation using BBr₃ furnished okanin (4) in 84% yield.

Mechanistic investigation. To provide some experimental proofs for the presumed intermediacy of a highly electrophilic nitrilium ion, a series of NMR experiments were carried out. Secondary amide was chosen for the mechanistic studies and base-free amide activation with Tf₂O was first investigated (Fig. 7a). After addition of Tf₂O into a solution of amide 1p, the formation of iminium salt (as a 3.4:1 mixture of two geometric isomers) and nitrilium ion in a ratio of 37:63 (1H NMR, Fig. 8a) was observed. The presence of Nitrilium ion was manifested by the characteristic triplet resonance and the coupling constant of a nitrilium which appeared at δC=123.4 (t, J13C-14N=45.6 Hz), as well as the nitrilium N-α aromatic carbon at δC=121.9.
besides, the formation of TfOH was also observed by 1H and 13C NMR spectra. The same reaction by bench chemistry produced the enimine 2af in 51% yield along with the recovered

**Figure 6.** Mildness of the method and Synthetic applications. (a) Racemization-free synthesis of a versatile chiral building block 3q. (b) Short synthesis of okanin (4).

**Figure 7.** Proposed mechanisms for the direct C–H functionalization of alkenes with secondary amides. (a) Reaction in the absence of a base. (b) Tf2O/2-fluoropyridine-mediated reaction.

(\(J_{13C-14N} = 13.5 \text{ Hz}^2\)) (13C NMR, Fig. 8b). Besides, the formation of TfOH was also observed by 1H and 13C NMR spectra. The same reaction by bench chemistry produced the enimine 2af in 51% yield along with the recovered
starting 1p in 31% yield (Fig. 7a). Hence, the results obtained from the NMR experiments (Cp:Ap = 37:63) and those from the bench reaction (2af:1p = 38:62) suggested that nitrilium ion Ap was probably the only competent intermediate that reacted with styrene to produce enimine 2af. The less reactive iminium salt Cp was inert to styrene addition and hydrolyzed upon work-up to regenerate the starting material 1p. These results also implicated that addition of a base would facilitate the conversion of iminium salt Cp to nitrilium ion Ap, and thus improve the yield of enimine 2af. Experimentally, the addition of 1.2 equiv of 2-fluoropyridine boosted the yield of 2af to 97%. In addition, treating a mixture of amide 1p and 2-fluoropyridine in CD2Cl2 with Tf2O at 0 °C resulted in quantitative formation of nitrilium ion intermediate Ap (Fig. 7b) along with 2-fluoropyridinium salt D within 10 min (cf. Supplementary Figure 57 for NMR spectrum). These results confirmed that 2-fluoropyridine promoted the transformation of the iminium salt Cp to nitrilium ion intermediate Ap (Fig. 7b). Moreover, the in situ IR monitoring showed the formation of iminium salt Cp (1663 cm⁻¹) and nitrilium ion Ap (2310 cm⁻¹) upon

Figure 8. In situ NMR monitoring of the base-free direct C–H functionalization of styrene with secondary amide 1p. (a) ¹H NMR spectrum. (b) ¹³C NMR spectrum.
treatment of amide 1p with Tf₂O. The former was converted completely into the latter by action of 2-fluoropyridine. A strong absorption of 2-F-pyridinium trifluoromethanesulfonate\(^3\) (1635 cm\(^{-1}\)) was observed, while no absorption corresponding to pyridinium ion Ep was observed (cf. Supplementary Figure S8 for in situ IR spectra).

**Conclusion**

In summary, we have developed a general method for the metal-free intermolecular C–H functionalization of alkenes with secondary amides. This method provides a direct and high-yielding access to \(\alpha,\beta\)-unsaturated ketimines and enones from two classes of readily available and stable starting materials. The one-pot reaction exhibits excellent functional group tolerance for both alkenes and amides allowing convenient and efficient synthesis of a variety of functionalized \(\alpha,\beta\)-unsaturated ketimines and enones. The present method could find wide applications in organic synthesis especially considering the remarkable chemoselectivity.

**Methods**

**General procedure for the direct C–H alkyliminylation and acylation of alkenes with secondary amides to give \(\alpha,\beta\)-unsaturated ketimines (enamines) 2 and \(\alpha,\beta\)-unsaturated ketones 3 (enones).**

Into a dry 10-mL round-bottom flask equipped with a magnetic stirring bar were added successively a secondary amide (0.5 mmol, 1.0 equiv), 2 mL of anhydrous CH₂Cl₂ and 2-fluoropyridine (0.6 mmol, 1.2 equiv) under an argon atmosphere. After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf₂O) (0.55 mmol, 1.1 equiv) was added dropwise via a syringe and the reaction was stirred for 10 min. To the resulting mixture, an alkene (0.6 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm-up to room temperature (or 40 °C) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel to afford the desired \(\alpha,\beta\)-unsaturated ketimine 2.

Alternatively, to the resulting residue were added 5 mL of EtOH and 5 mL of an aqueous solution of HCl (3.0 M). The resulting mixture was heated to reflux until completion of the reaction as monitored by TLC analysis (2–12 h). After being cooled to room temperature, 10 mL of CH₂Cl₂ was added, and the mixture extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel to afford the desired \(\alpha,\beta\)-unsaturated ketone 3.

**Data availability.** The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC), under deposition number CCDC 1438540 (for 2w). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author Contributions
P.-Q.H. conceived, initiated and directed the project, and wrote the manuscript. Y.-H.H. contributed to the conception of the project, carried out the experimental work, and analyzed the data. H.G. contributed, in part, to the experimental work and data analysis. J.-L.Y. contributed to the in situ NMR analysis and analysis of single crystal X-ray data. All authors commented on the manuscript.

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