Synlett B. Chen, X.-F. Wu Letter

Synthesis of Linear α,β-Unsaturated Amides from Isocyanates and Alkenylaluminum Reagents

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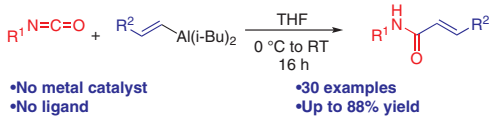

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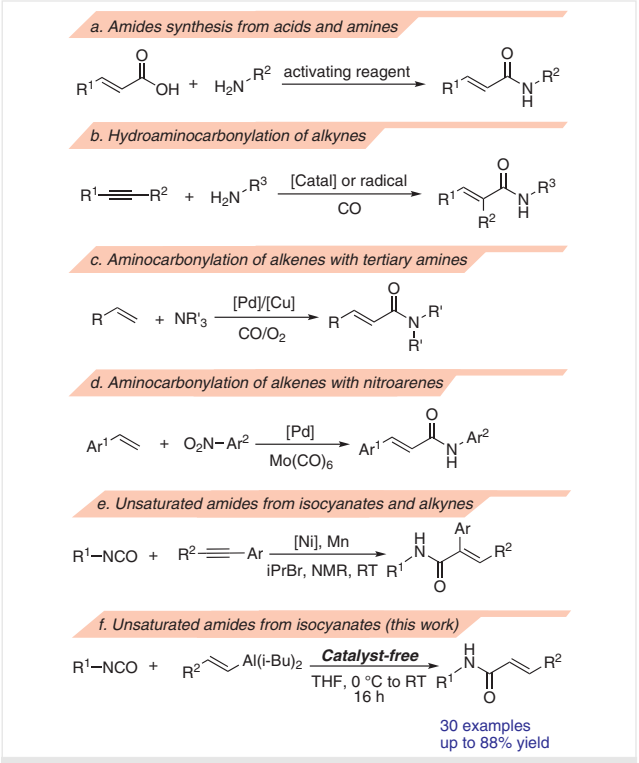
Abstract A new approach has been developed for the synthesis of linear α,β-unsaturated amides by the direct coupling of isocyanates with alkenylaluminum reagents. At room temperature, the desired α,β-unsaturated amides were isolated in good to excellent yields with good functional-group tolerance in the absence of any catalyst or additive.

Key words enamides, alkenylaluminum reagents, isocyanates, coupling reaction, catalyst-free

Linear α,β-unsaturated amides are important structural motifs in organic chemistry, functionalized materials, biologically active compounds, and pharmaceuticals.[1–4] Owing to the important applications of these compounds in synthetic chemistry and pharmaceuticals, the development of new and efficient synthetic pathways for their preparation has attracted continuous interest from organic chemists (Scheme 1).[5] Conventionally, α,β-unsaturated amides are prepared by nucleophilic substitution of the corresponding activated carboxylic acid derivatives with amines (Scheme 1a).[6] Alternatively, transition-metal-catalyzed carbonylations of alkenes or alkynes with amines or nitro compounds have also been developed (Schemes 1b–d).[7] However, these methods are limited by their use of carbon monoxide gas, which is highly toxic, odorless, and flammable, and requires high-pressure equipment. Additionally, isocyanates have also been explored as interesting amide precursors.[8] α,β-Unsaturated amides can be relatively easily prepared by lithiation of alkenyl halides and subsequent reaction with isocyanates. Nickel-catalyzed procedures for the synthesis of α,β-unsaturated amides from terminal alkenes and aliphatic isocyanates have also been reported.[9] More recently, Martin and co-workers developed a conceptually new hydroamidation of alkynes with isocyanates by using nickel hydrides generated in situ as catalysts (Scheme 1e). The method turns parasitic β-hydride elimination into a strategic advantage, rapidly affording desired acrylamides in good yields.[10] Inspired by these achievements, we become interested in developing a new synthetic protocol for the synthesis of linear α,β-unsaturated amides from isocyanates.



Scheme 1 Syntheses of linear α,β-unsaturated amides

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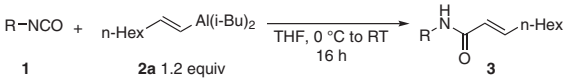
Here, we report a new method for the synthesis of linear α,β-unsaturated amides (Scheme 1f). Our initial investigations were carried out by using phenyl isocyanate and diisobutyl[(1*E*)-oct-1-en-1-yl]aluminum as model substrates. The later was readily prepared from oct-1-yne and diisobutylaluminum hydride (DIBAL-H). We dropped the alkenylaluminum solution into a solution of phenyl isocyanate in THF at 0 °C, and then let the solution slowly warm up to room temperature (25 °C) and continued to stir the mixture until the reaction was complete. The whole process took 16 hours. To our delight, the desired product (*E*)-*N*-phenylnon-2-enamide (**3aa**) was successfully obtained in 72% isolated yield (Table 1, entry 1).[11] Considering the easy manipulations and practical advantages of the reaction conditions, we were eager to examine the generality of this procedure. As a first step, we tested various substituted aryl isocyanates (entries 2–9). Both electron-donating and electron-withdrawing substituents on the aromatic ring were well tolerated, and the desired products **3aa–ia** were obtained in moderate to good yields. With regard to the influence of the position of the substituents on the yields of **3ba**, **3ca**, and **3da** (entries 2–4), we found that the *ortho*-group reduced the yield of the reaction because of its steric hindrance. According to the literature, nitro-substituted substrates are generally incompatible with alkenylaluminum reagents. To our delight however, 4-nitrophenyl isocyanate reacted smoothly to give a 56% yield of amide **3ia** (entry 9). Gratifyingly, aliphatic isocyanates were also well tolerated in this transformation and delivered the corresponding α,β-unsaturated amides **3ja** and **3ka** in yields of 81 and 68%, respectively (entries 10 and 11). However, the desired products were not detected when diisocyanate substrates were tested (see Supporting Information).

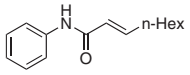
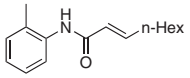
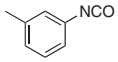
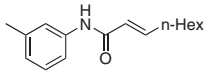
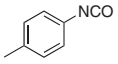
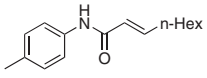
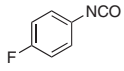
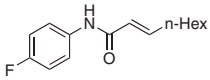
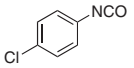
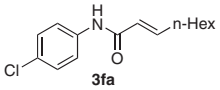
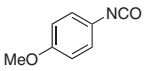
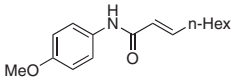
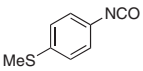
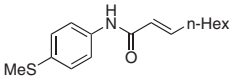
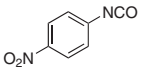
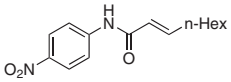
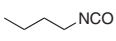
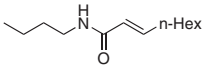
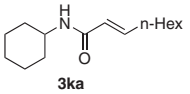
Subsequently, we tested various alkenylaluminum reagents under our reaction conditions (Table 2). Aliphatic alkenylaluminums, prepared from the corresponding alkynes, were successfully transformed into the desired products **3ab–ag** in moderate to good yields (Table 2, entries 1–6). Interestingly, a dienyl aluminum compound was also tolerated in this reaction and gave the target products **3ah** in 69% yield (entry 7). Moreover, aromatic alkenylaluminums were also tolerated, giving moderate yields of the corresponding products **3ai–am** (entries 8–12).

Next, we tested the reactions of 1-isocyanatobutane with various alkenylaluminum reagents under our standard conditions, and we obtained moderate to good yields of the target products **3jn–jj** (Table 3). It is also worth mentioning that the reaction of phenyl isothiocyanate with diisobutyl[(*E*)-oct-1-en-1-yl]aluminum was tested under our standard conditions, but none of the desired product was detected.

Table 1 Synthesis of α,β-Unsaturated Amides from Various Isocyanates[a]

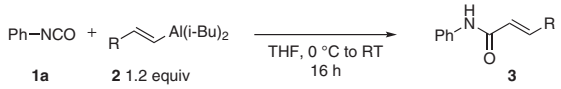


1 **2a** 1.2 equiv **3**

Entry	Isocyanate	Product	Yield[b] (%)
1		 **3aa**	72
2		 **3ba**	57
3		 **3ca**	77
4		 **3da**	73
5		 **3ea**	75
6		 **3fa**	70
7		 **3ga**	70
8		 **3ha**	78
9		 **3ia**	56
10		 **3ja**	81
11		 **3ka**	68

[a] Reaction scale: 0.50 mmol.
[b] Yield of the isolated product.

Table 2 Synthesis of α,β-Unsaturated Amides from Alkenylaluminum Reagents[a]



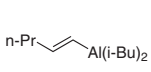
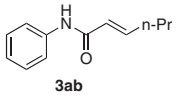
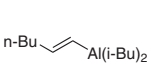
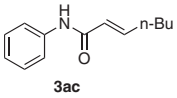
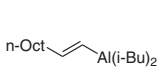
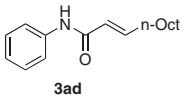
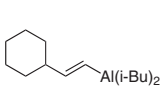
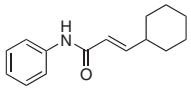
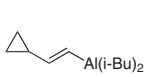
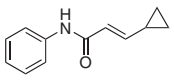
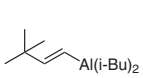
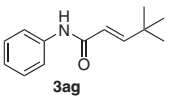
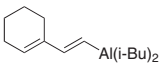
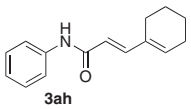
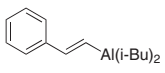
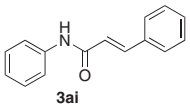
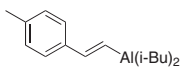
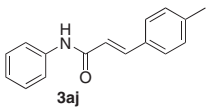
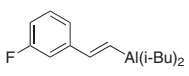
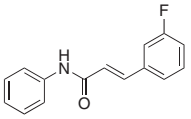
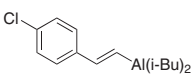
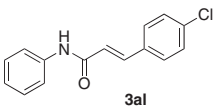
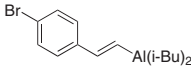
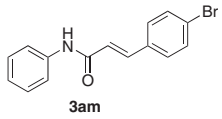
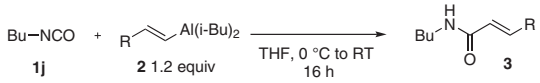
Entry	Alkenylaluminum	Product	Yield[b] (%)
1		 **3ab**	79
2		 **3ac**	82
3		 **3ad**	77
4		 **3ae**	75
5		 **3af**	65
6		 **3ag**	71
7		 **3ah**	69
8		 **3ai**	56
9		 **3aj**	53
10		 **3ak**	57
11		 **3al**	54

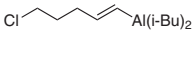
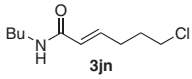
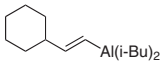
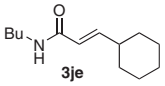
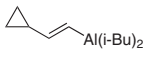
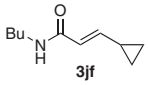
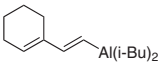
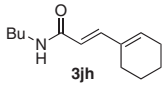
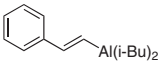
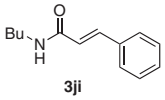
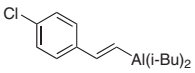
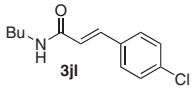
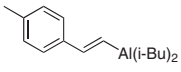
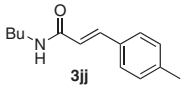
Table 2 (continued)

Entry	Alkenylaluminum	Product	Yield[b] (%)
12		 **3am**	56

[a] Reaction scale: 0.50 mmol.
[b] Yield of the isolated product.

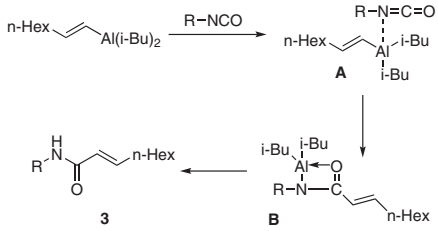
Table 3 Synthesis of α,β-Unsaturated Amides from 1-Isocyanatobutane[a]



Entry	Alkenylaluminum	Product	Yield[b] (%)
1		 **3jn**	61
2		 **3je**	83
3		 **3jf**	88
4		 **3jh**	82
5		 **3ji**	52
6		 **3jl**	51
7		 **3jj**	62

[a] Reaction scale: 0.50 mmol.
[b] Yield of the isolated product.

On the basis of our results and a report in the literature,[8] a plausible reaction pathway is proposed (Scheme 2). As aluminum is a strong Lewis acid, the isocyanate coordinates to the metal center through its nitrogen atom to forms complex **A**. Next, addition of the alkenylaluminum reagent to the isocyanate occurs to form intermediate **B**, which then delivers the target product **3**. The hydrogen in the amide product might come from the THF solvent or from the isobutyl group.



Scheme 2 Proposed reaction pathway

In summary, we have identified a convenient approach to the synthesis of linear α,β-unsaturated amides by the direct coupling of isocyanates with alkenylaluminum reagents at room temperature. The desired α,β-unsaturated amides were isolated in good to excellent yields with good functional-group tolerance. Considering the easy availability of the starting materials and the convenient reaction conditions, we believe this is a promising approach for the synthesis of linear α,β-unsaturated amides.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610753.

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(11) **Amides 3; General Procedure**
Under argon, a solution of the appropriate alkenylaluminum (0.6 mmol) in hexane (0.6 mL) was added dropwise to a fresh

solution of the appropriate isocyanate (0.5 mmol) in THF (1 mL) at 0 °C. The mixture was then warmed slowly to r.t. (25 °C) and stirred until the reaction was complete (16 h). After removal of solvent under reduced pressure, the pure product was obtained by column chromatography [silica gel, heptane–ethyl acetate (5:1)].

(2*E*)-*N*-Phenylnon-2-enamide (3aa)

Colorless oil; yield: 83 mg (72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64 (s, 1 H), 7.51 (d, *J* = 8.1 Hz, 2 H), 7.22 (t, *J* = 7.8 Hz, 2 H), 7.02 (t, *J* = 7.4 Hz, 1 H), 6.90 (dt, *J* = 15.1, 7.0 Hz, 1 H), 5.89 (dt, *J* = 15.3, 1.6 Hz, 1 H), 2.11 (qd, *J* = 7.1, 1.5 Hz, 2 H), 1.41–1.32 (m, 2 H), 1.21 (dddt, *J* = 14.6, 9.2, 6.6, 3.5 Hz, 6 H), 0.82 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.4, 146.6, 138.2, 129.1, 129.0, 124.2, 120.0, 32.2, 31.6, 28.9, 28.2, 22.6, 14.1. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{15}H_{22}NO$: 232.1701; found: 232.1702.