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Amides as surrogates of aldehydes for C–C bond formation: amide-based direct Knoevenagel-type condensation reaction and related reactions

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Aldehydes are perhaps the most versatile compounds that enable many C–C bond forming reactions, which are not amenable for other subclasses of carbonyl compounds. We report the first use of amides as surrogates of aldehydes for C–C bond formation, namely, the direct Knoevenagel-type condensation based on amides. The one-pot method consists of controlled reduction of an amide with LDBIPA [$LiAlH(iBu)_2(OiPr)$], Lewis acid-mediated release of a reactive iminium ion intermediate, nucleophilic addition, and *in situ* elimination of amine. The reaction shows good functional group tolerance. We also demonstrated that the Schwartz reagent could be used as an alternative of LDBIPA. The employment of nitromethane and a silyl enol ether as the nucleophiles opens an avenue for the unprecedented amide-based nitro-aldol condensation reaction and aldol condensation reaction, respectively.

amides, Knoevenagel condensation, C–C bond formation, one-pot reaction, amide transformation

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The carbonyl group is one of the most versatile functional groups in organic chemistry. However, there exists remarkable difference on reactivity among different classes of carbonyl compounds. In this regard, thanks to the high electrophilicity of their carbonyl groups, aldehydes and ketones display rich chemistry, whereas amides is a class of the least reactive carbonyl compounds. Actually, it is well-known that the aldol reaction, Mukaiyama reaction, Wittig reaction, and Knoevenagel reaction etc. are feasible only for aldehydes and ketones. In particular, only aldehydes and some unhindered ketones are feasible substrates for the Knoevenagel reaction (Scheme 1(a)) [1]. Although the Knoevenagel reaction is a classical reaction, this reaction is still being widely used in organic synthesis due to the versatility of the multi-functional α,β-unsaturated compounds that formed [2]. Moreover, in an essay appeared in 2010, List [3] revealed that the Knoevenagel reaction is the roots of aminocatalysis.

On the other hand, common amides are ubiquitous in Nature [4]. The inherent high stability of amides rend them ideal starting materials and versatile intermediates in organic synthesis and medicinal chemistry [5], and thus the subsequent transformation becomes imperative and challenging. This can account for the fact that multistep methods have long been employed for the transformations of amides [5g–5i]. The direct transformation of amides has attracted considerable attention in recent years [6], and breakthroughs have been achieved on several aspects [6–8]. However, to the best of our knowledge, the use of amides as surrogates of aldehydes for one-pot C–C bond formation is unprecedented.

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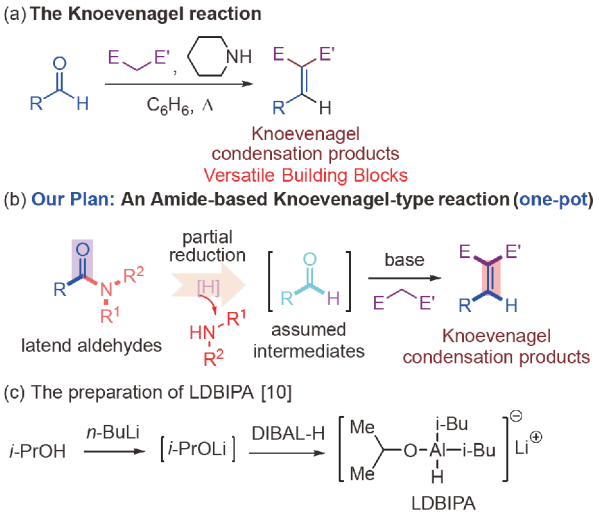


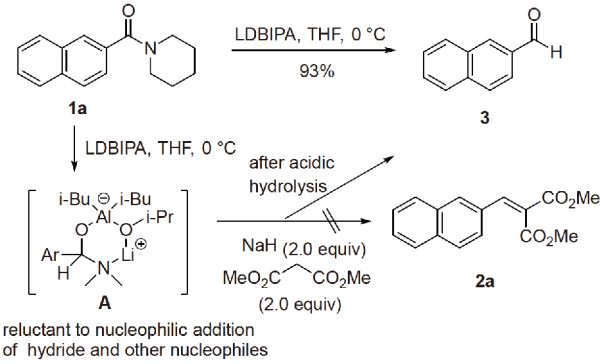
Scheme 1 (a) Classical Knoevenagel condensation reaction. (b) Our plan. (c) Preparation of LDBIPA. LDBIPA=lithium diisobutyl-isopropoxyaluminum hydride.

Whereas challenging, if this can be achieved, the scope of both the aforementioned classical C–C bond-forming reactions such as the Knoevenagel condensation reaction, and the chemistry of amides would be extended. Herein, we report a tertiary amide-based Knoevenagel condensation reaction leading to α,β-unsaturated compounds (Scheme 1(b)).

To realize our plan, we have to face with multiple challenges. First, we needed a reliable method for the partial reduction of quite stable tertiary amides. Second, we had to overcome the problem of chemoselectivity, namely, to generate an aldehyde (C–N bond cleavage) instead of an iminium intermediate (C–O bond cleavage) from an amide, although the latter is more popular (*vide infra*). Third, it was important to ensure that the subsequent tandem condensation of the aldehyde intermediate occurs chemoselectively with the carbanion generated *in situ* from active methylene compounds, instead of with the amine generated along with aldehyde (from amide). A survey of literature showed that the Schwartz reagent [9] and lithium diisobutyl-isopropoxyaluminum hydride [$LiAlH(iBu)_2(OiPr)$, LDBIPA) (Scheme 1(c)) [10] might suit our need. Taking advantages of the Schwartz reagent, Ganem and Georg have developed highly chemoselective and reliable methods for the partial reduction of amides to give imines [11] and aldehydes [12], respectively. Ganem *et al*. [13], Zhao *et al*. [14], and Chida and Sato *et al*. [8d,8e] have demonstrated independently that Schwartz's reagent can be used for the one-pot, chemoselective reductive functionalization of amides via an iminium intermediates (C–O bond cleavage) [13]. As regarding LDBIPA, An and co-workers [10] reported that the partial reduction of tertiary amides to aldehydes could be achieved in excellent yields (GC). In view of the easy preparation of LDBIPA from less expensive DIBALH, this reagent was selected for our purpose.

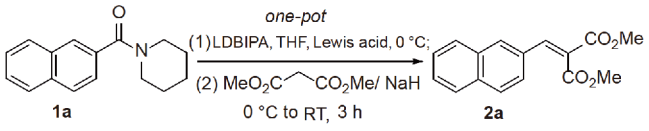
At the outset of our investigation, the chemoselective reduction of 2-naphthamide **1a** with LDBIPA was checked. Indeed, exposure of a THF solution of amide **1a** to LDBIPA, yielded, after acidic work-up with 1 M HCl, 2-naphthaldehyde (**3**) in excellent yield (93%, Scheme 2). Next, a one-pot tandem partial reduction-Knoevenagel condensation reaction was attempted. To our disappointment, after successive treatment of amide **1a** with LDBIPA, and with enolate generated from sodio dimethyl malonate and sodium hydride, the desired condensation product **2a** was not observed, instead 2-naphthaldehyde (**3**) was obtained again (Scheme 2 and Table 1, entry 1). These results implicated that the presumed chelating intermediate **A** [11], generated from the partial reduction of amide with LDBIPA, was stable enough which prevented further reduction or addition of another nucleophile.

It was envisaged that by employing a Lewis acid, it would be possible to release a reactive species from **A** allowing thus



Scheme 2 Unsuccessful attempt for the tandem reduction–Knoevenagel condensation reaction.

Table 1 Reaction conditions screening[a)]

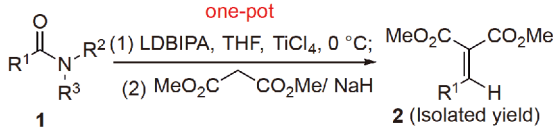


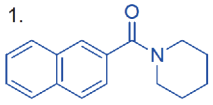
Entry	Lewis acid (equiv)	Nu. (equiv)	Isolated yield
1	–	3.0	0
2	$ZnCl_2$ (1.5)	3.0	0
3	$BF_3•Et_2O$ (1.5)	3.0	0
4	TMSOTf (1.5)	3.0	trace
5	$Ti(OiPr)_4$ (1.5)	3.0	0
6	$AlCl_3$ (1.5)	3.0	0
7	$SnCl_4$ (1.5)	3.0	68
8	$TiCl_4$ (1.5)	3.0	90
9	$TiCl_4$ (1.2)	3.0	86
10	$TiCl_4$ (0.6)	3.0	43
11	$TiCl_4$ (1.5)	2.0	89

a) Reaction conditions: amide **1a** (1.0 mmol), LDBIPA (1.2 mmol), THF (0.2 M), 0 °C, 1 h; Lewis acid, 10 min; sodium enolate, freshly prepared from dimethyl malonate and NaH for 30 min at 0 °C.

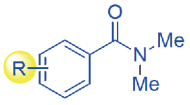
an *in situ* nucleophilic addition. For this purpose, several Lewis acids including $ZnCl_2$, BF_3•OEt_2, TMSOTf, Ti(O*i*Pr)$_4$, $AlCl_3$, $SnCl_4$, and $TiCl_4$ were surveyed. As can be seen from Table 1, whilst most of them are ineffective in promoting the tandem reduction–Knoevenagel condensation reaction (Table 1, entries 2–6), employment of 1.5 equiv. of $SnCl_4$ or $TiCl_4$ produced the desired product **2a** in 68% (entry 7) and 90% yield (entry 8), respectively. Thus, $TiCl_4$ was Lewis acid and a brief optimization was next undertaken. Use of a lower amount of $TiCl_4$ led to a decrease in yield (entries 9 and 10). To our delight, lowering the equivalents of nucleophile from 3.0 equiv. to 2.0 equiv., the yield was almost unaffected (entry 11 vs. entry 8). Thus, the optimized reaction conditions were defined as: amide (1.0 equiv.), LDBIPA (1.2 equiv.), $TiCl_4$ (1.5 equiv.), NaH (2.0 equiv.)/Nu (2.0 equiv.). Under these conditions, **2a** was obtained in 88% yield (Table 2, entry 1). It is worth mentioning that, during this investigation, no alcohol, namely, the over-reduction side product was observed.

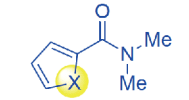
Table 2 Scope of the reaction with respect to the amide used[a)]

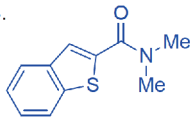


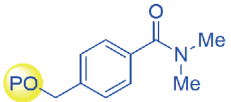
1. 
1a; **2a** (88%)

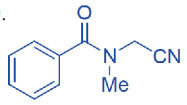
2. **1b**. (R = Me); **2a** (90%)
3. **1c**. (R = iPr); **2a** (0%)

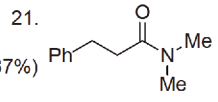

4. **1d**, R = H; **2b** (87%)
5. **1e**, R = *p*-Me; **2c** (86%)
6. **1f**, R = *m*-Me; **2d** (87%b)
7. **1g**, R = *o*-Me; **2e** (85%)
8. **1h**, R = 3,4,5-(MeO)$_3$; **2f** (89%)
9. **1i**, R = 2,4,6-Me$_3$; **2g** (0%)
10. **1j**, R = *p*-Br, **2h** (80%)
11. **1k**, R = *p*-O_2N, **2i** (68%)


12. **1l**, X = O, **2j** (84%)
13. **1m**, X = S, **2k** (86%)

14. 
1n; **2l** (88%)


15. **1o**, P = TBS; **2m** (82%)
16. **1p**, P = THP; **2n** (81%b)
17. **1q**, P = MOM; **2o** (82%)
18. **1r**, P = Allyl; **2p** (89%)
19. **1s**, P = Methyl propargyl; **2q** (87%)

20. 
1t; **2b** (88%)

21. 
1u; **2r** (0%)

a) Reaction condition: amide (1.0 mmol), LDBIPA (1.2 mmol), THF (0.2 M), 0 °C, 1 h; $TiCl_4$ (1.5 mmol), 10 min; sodium enolate (2.0 mmol), freshly prepared from dimethyl malonate and NaH (2.0 mmol) for 30 min at 0 °C.

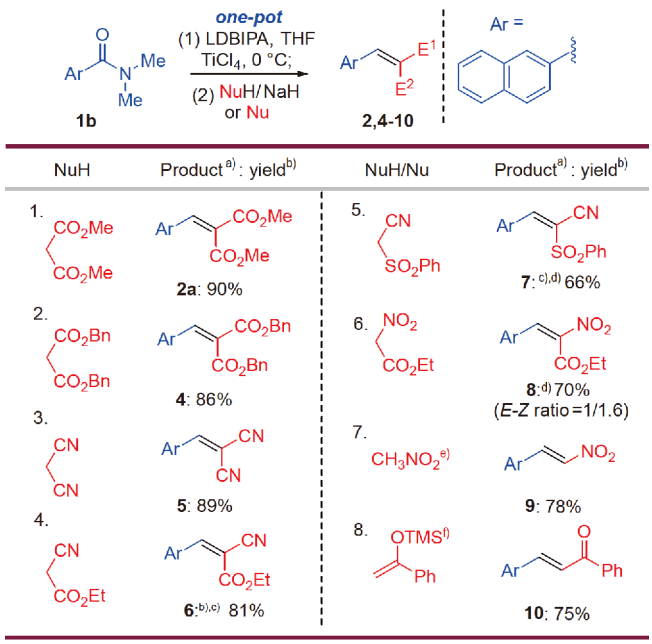
With the optimized reaction conditions in hand, scope of the one-pot reductive Knoevenagel-type condensation reaction was investigated. We first examined scope of amide substrate, and the results are displayed in Table 2. *N*,*N*-Dimethyl analogue (**1b**) of **1a** reacted smoothly to give **2a** in 90% yield (entry 2), whereas sterically hindered *N*,*N*-diisopropyl analogue (**1c**) failed to react (entry 3). The reactions of benzamide and derivatives bearing electron-donating groups including methyl at either *para*- *meta*-, or *ortho*-position, and 3,4,5-trimethoxybenzamide (**1d**–**1h**) reacted smoothly to yield the corresponding products **2b**–**2f** in excellent yields (85%–89%, entries 4–8). However, the sterically hindered 2,4,6-trimethylbenzamide (**1i**) failed to react (entry 9). *p*-Bromobenzamide (**1j**) reacted to afford **2h** in 80% yield (entry 10), implicating that the reaction also tolerated benzamide bearing an electron-withdrawing group. Indeed, even *p*-nitrobenzamide (**1k**) reacted to afford the desired product **2i** in 68% yield (entry 11) reflecting good functional group tolerance and chemoselectivity of the reaction. The reactions of electron-rich heteroaromatic amides *N*,*N*-dimethylfuran-2-carboxamide (**1l**), *N*,*N*-dimethylthiophene-2-carboxamide (**1m**), and *N*,*N*-dimethylbenzo[*b*]thiophene-2-carboxamide (**1n**) are also viable substrates, which reacted to give the desired products **2j**, **2k**, and **2l** in 84%–88% yields (entries 12–14).

The functional group tolerance was further surveyed. As shown in entries 15–19, the reaction tolerated several sensitive functional groups such as *t*-butyldimethylsilyl (TBS) (**1o**, a silyl ether), tetrahydropyranyl (THP) (**1p**, an acetal), methoxymethyl (MOM) (**1q**, an acetal), allyl (**1r**) and propargylic ether (**1s**), and the expected products were obtained in 81%–89% yields. Besides *para*-nitrobenzamide (**1k**) that bearing a reducible nitro group, the reaction of **1t** also proceeded chemoselectively at the amide group to produce **2b** in an excellent yield of 88% (entry 20). It is worth noting that **1t** contains both a reducible cyano group and an α-amidonitrile moiety, which is cleavable in the presence of a Lewis acid. It is remarkable that both sensitive functional groups remained intact under the reducing and Lewis acid-mediated reaction conditions. To our disappointment, attempted reaction of aliphatic amide **1u** was unsuccessful, and the corresponding aldehyde was observed.

We next turned our attention to investigate nucleophile scope. As can be seen from Table 3. The reactions of dibenzyl malonate, malononitrile, and ethyl 2-cyanoacetate gave the corresponding products **4**, **5**, and **6** in good to excellent yields (86%, 89% and 81%, Table 3, entries 2–4). 2-(Phenylsulfonyl)acetonitrile and ethyl 2-nitroacetate reacted without incident to afford the corresponding products **7** and **8** albeit in moderate yields (66% and 70%, entries 5 and 6).

To further extend the scope of the reaction, the reductive condensation of *N*,*N*-dimethyl-2-naphthamidethe (**1b**) with

Table 3 Scope of the reaction with respect to the nucleophile used



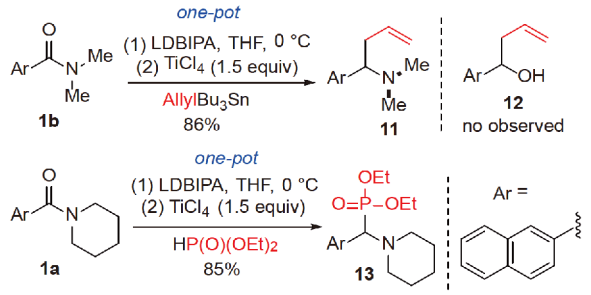
a) Ar= naphthalen-2-yl; b) isolated yield; c) single diastereomer; d) stereochemistry no determined; e) *t*-BuOK used as the base; f) no base used.

nitromethane was attempted. Unfortunately, following the general procedure, the desired product was not observed. Pleasantly, when potassium *tert*-butoxide was used to replace NaH as a base, the reaction proceeded smoothly to afford (*E*)-nitroalkene **9** in 78% yield (entry 7). The reason for the failure in using NaH as a base in this reaction is unclear at this stage, however, the base-dependence of the nitroalkane-based reactions have been documented previously [15]. This reaction can be viewed as an amide-based nitro-aldol condensation, which is also unprecedented. Next, the use of silyl enol ether as a nucleophile was examined. Pleasantly, when silyl enol ether derived from acetophenone was employed, its reductive condensation with *N*,*N*-dimethyl-2-naphthamidethe (**1b**) produced the expected α,β-unsaturated enone **10** in 75% yield (entry 8). This also constitutes the first example using an amide as a surrogate of an aldehyde for an amide-based direct reductive aldol condensation reaction.

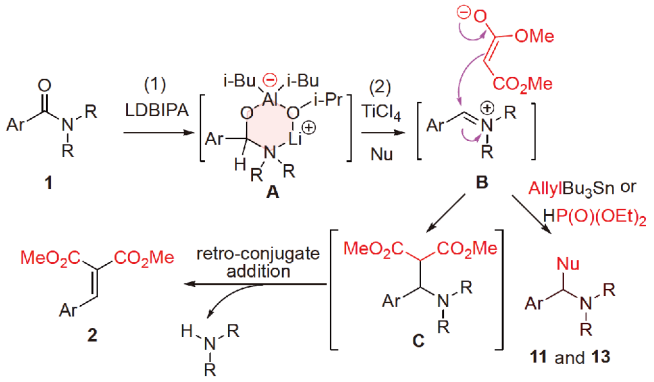
The reductive allylation of 2-naphthamide derivative **1b** was also attempted. Much to our surprise, instead of the expected alcohol **12**, homoallylic amine **11** was obtained in 86% yield. Moreover, successive treatment of **1a** with LDBIPA and diethyl phosphonate produced α-amino phosphonate **13** in 85% yield.

The results showed in Scheme 3 are very interesting, which not only constitute valuable chemo-divergent transformations of tertiary amides, but are also informative for an understanding of the mechanism of the amide-based direct Knoevenagel condensation reaction. Indeed, the observed reductive functionalization products **11** and **13** allowed precluding the possibility of intermediacy of an aldehyde. Thus, a plausible mechanism is displayed in Scheme 4. The reduction of an amide with LDBIPA generates a stable chelating intermediate **A**, which collapses to release the corresponding iminium intermediate **B** upon treating with a Lewis acid such as $TiCl_4$. A nucleophilic addition then occurs to yield β-amino diester **C**, which eliminates the amine to yield the Knoevenagel condensation product **2**.

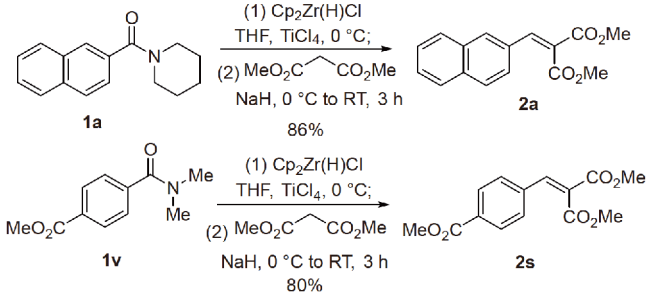
Encouraged by the success in employing LDBIPA as a chemoselective reducing agent for the tandem reaction, the use of the Schwartz reagent was examined. To our delight, successive treatment of naphthalen-2-yl(piperidin-1-yl) methanone **1a** with Schwartz reagent and dimethyl sodio malonate produced **2a** in 86% yield (Scheme 5), comparable with that with LDBIPA (90%). Moreover, the reductive



Scheme 3 Control experiments (color online).



Scheme 4 Plausible mechanisms of the tandem reduction-Knoevenagel condensation reactions of tertiary amides (color online).



Scheme 5 Employing the Schwartz reagent for the amide-based Knoevenagel-type one-pot condensation reaction.

Knoevenagel condensation reaction of amido ester **1v** occurred chemoselectively at the amide group to give compound **2s** in 80% yield.

In summary, we have realized, for the first time, the use of amides as surrogates of aldehydes for C–C bond formation. Although this concept has mainly demonstrated for the Knoevenagel condensation reaction, and the mechanism is different from what we have designed, successful examples also cover the amide-based reductive nitro-aldol condensation reaction and aldol condensation reaction. Moreover, the successful replacement of LDBIPA by the Schwartz reagent implicates that other amide reducing methods, including the catalytic ones, would find application in this methodology. This will on one hand, extend the scope of the aldehyde-based C–C bond forming reactions, and on the other hand, further validate amides as a class of stable and reliable building blocks in both natural product synthesis and medicinal chemistry. Work on these directions are ongoing in our laboratory, and the results will be reported in due course.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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