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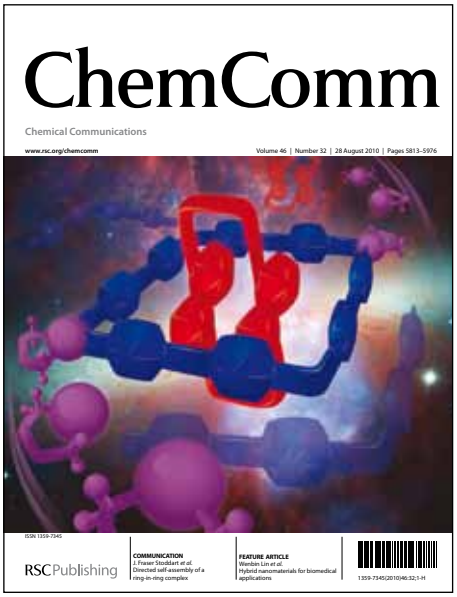


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# NHC-Catalyzed C-O or C-N Bond Formation: Efficient Approaches to α,β-Unsaturated Esters and Amides

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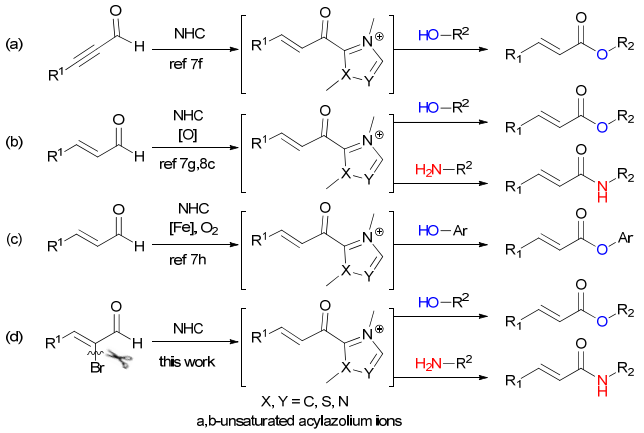
**Simple and efficient NHC-catalyzed transformations of bromoenal or α,β-dibromoenal into α,β-unsaturated esters or amides with high stereoselectivity through C-O or C-N bond formation have been demonstrated. The NHC-catalyzed processes occur under mild conditions. The ready availability of the starting materials, avoidance of external oxidants and the usefulness of the products all make the strategy quite attractive.**

Carboxylic acid esters and amides represent an important class of compounds found in numerous bioactive products as well as in medicines and materials.[1] In addition, carboxylic acid esters and amides are versatile building blocks in organic synthesis and of significant importance for industrial application.[2,3] In general, synthetic methods for esters and amides bond formation utilize acids and alcohols or amines as coupling partners and rely on the stoichiometric preparation of an activated carboxylate followed by nucleophilic substitution.[1a-b,4] However, some disadvantages of conventional method are obvious, including the formation of copious byproducts, extensive protection of other functional group and harsh reaction condition. Therefore, the development of catalytic process for ester and amide bond formation under mild reaction conditions is highly desirable and challenging.

In recent years, a number of catalytic methods for ester and amide bond formation have been successfully established.[5,6] Among them, *N*-heterocyclic carbene (NHC)-catalyzed redox esterification and amidation of aldehydes with alcohol and amine have become a powerful strategy for ester and amide bond formation.[7,8] However, in these NHC-catalyzed reactions, synthetic methods for α,β-unsaturated esters and amides bond formation are rare.[7f-h,8c] In 2006, Zeitler reported a NHC-catalyzed redox esterification of alkynyl aldehydes by internal redox process (a, Scheme 1).[7f] However, the yield was moderate and alkynyl aldehydes as the substrate were not readily available. More recently, a significant direct esterification or amidation of α,β-unsaturated aldehydes were realized by Studer, Grimme, and coworkers in the presence of an external oxidant (b, Scheme 1).[7g,8c] Despite its breakthrough in ester and amide bond formation, the use of equivalent oxidant may reduce this process sustainability.




**Scheme 1**. NHC-Catalyzed Approaches to α,β-Unsaturated Esters and Amides

Moreover, by the use of NHC/Fe cooperative catalysis, Gois and co-workers realized an aerobic oxidative esterification of aldehydes (c, Scheme 1).[7h] However, the process was shown to be effective only with phenols as nucleophiles. Hence, a simple, efficient and practical protocol for NHC-catalyzed ester and amide bond formation is still highly desired. α,β-unsaturated acylazolium ions III (Scheme 1) is a key intermediate for ester and amide bond formation in above transformations. Inspired by this intermediate, we envisioned that α,β-unsaturated acylazolium ions III could be readily generated from bromoenal and NHC through $a^3$-$d^3$ umpolung and subsequent debromination, which should react with alcohols or amines without any external oxidants.[9] Herein, we describe a novel NHC-catalyzed C-Br bond cleavage and C-O or C-N bond formation for the synthesis of α,β-unsaturated esters and amides under mild conditions (d, Scheme 1).

The study was initiated by investigating the reaction of commercially available α-bromocinnamaldehyde **1a** with benzyl alcohol **2a** in the presence of NHCs. The results showed that imidazolium salt **A** is an effective organocatalyst for this transformation which gave the desired product **3aa** in 78% yield with high stereoselectivity (only *E*-isomer was obtained) (see entry 1, Table S1). The various solvents were surveyed and revealed dioxane to be the best choice (see entry 13, Table S1). Finally, base screening showed that $Cs_2CO_3$

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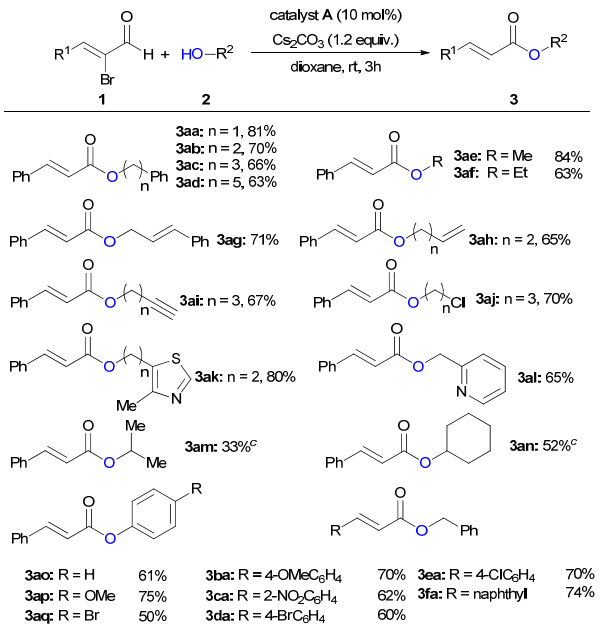
**Table 1.** The reaction scope for NHC-catalyzed ester bond formation[a, b]




[a] Reacion condition: see entry 13, Table S1. [b] Isolated yields. [e] 3.0 equiv of **2** was used.

was preferable (see entry 13, Table S1).

With the optimized conditions in hand, the scope of this reaction with different alcohols was then investigated (Table 1). A wide range of aliphatic alcohols smoothly underwent this transformation generating the desired products **3aa-3ad** in moderate to good yield (63-81%, Table 1). Moreover, reactions worked well with some simple alcohols such as methanol and ethanol to give **3ae** and **3af** in 84% and 63% yield, respectively. Alcohols containing olefin, alkyne, halogen and heterocycle were compatible with good yields (**3ag-3al**, 65-80%; Table 1). It is noteworthy that α-bromocinnamaldehyde **1a** with the sterically more hindered isopropanol and cyclohexanol also gave the desired product **3am** and **3an** in 33% and 52%, respectively (Table 1). This method proved to be effective for phenol containing an electron-rich or electron-deficient group, leading to moderate to good yield (**3ao-3aq**, 50-75%; Table 1).

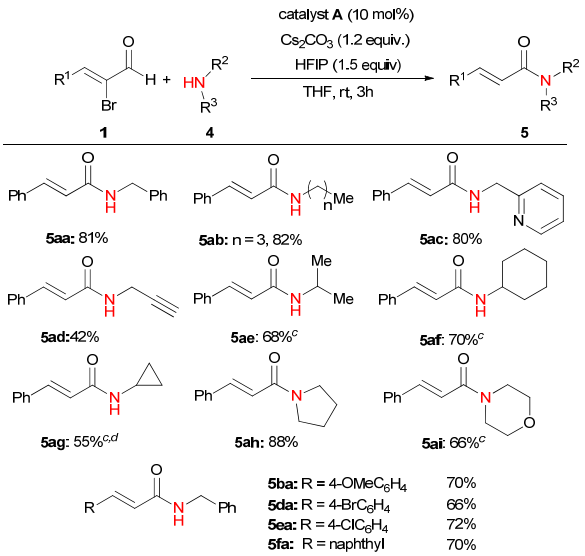
We then examined the scope of various bromoenal (Table 1). Bromoenals containing electron-rich or electron-deficient phenyl groups were tolerated in this reaction, affording the desired products **3ba-3ea** with good yields (60-70%; Table 1). Moreover, naphthyl-derived bromoenalenal also underwent this transformation well generating the desired products **3fa** in 74% yield (Table 1).

Encouraged by the aforementioned ester bond formation, we extended the reaction to amide bond formation by using amines as the nucleophiles. Disappointingly, the reaction of α-bromocinnamaldehyde **1a** with benzylamine **4a** in the presence of catalyst **A** and $Cs_2CO_3$ in THF at room temperature did not afford the desired product **5aa** (see entry 1, Table S2). The intermediate acylazolium ions Ⅲ did not react fast enough with benzylamine **4a**, leading to the formation of imine. Thus, we then tested a number of additives in this reaction. Interestingly, the desired product **5aa** was obtained in 13% yield by employing imidazole as the additives (see entry 2, Table S2). Benzimidazole and pentafluorophenol (PFPOH) as the additives suppressed the formation of amide **5aa** (see entries 3 and 7, Table S2). The reactions in the presence of DMAP, HOBt and HOAt did not produce the desired product **5aa** (see entry 4-6, Table S2). Gratifyingly, when hexafluoroisopropanol (HFIP) was used as the additives in this reaction, the yield of **5aa** was improved to 50% (see entry 8, Table S2). The catalytic amounts of HFIP provided low efficiency (see entry 9, Table S2). A range of NHCs were then screened. The results showed that catalyst **A** is an effective organocatalyst for this transformation (see Table S3). Solvent and base screening were subsequently performed and showed that THF and $Cs_2CO_3$ were preferable. Finally, the yield increased to 81% by raising the loading of **4a** to 2.0 equiv (see entry 16, Table S2). When 3.0 equiv **4a** was employed, the same result was observed (see entry 17, Table S2). We also tested the possibility of the addition of benzylamine at the beginning of this reaction. However, the reaction exhibited lower efficiency (see entry 18, Table S2).

The scope of this reaction with different amines was then investigated (Table 2). Amines containing alkyl, heterocycle and alkyne proceeded efficiently and afforded the desired products **5ab-5ad** in moderate to good yields (42-82%; Table 2). For the sterically more hindered amine, the amidations were slower (**5ae-5ag**, 55-70%; Table 2). Moreover, pyrrolidine and morpholine were suitable substrates, affording **5ah** and **5ai** in 88% and 66% yield, respectively (Table 2). Various bromoenal was then examined (table 2). Bromoenals containing electron-rich or electron-deficient phenyl groups were suitable partners in this reaction, affording **5ba-5ea** in good yields (66-72%; Table 2).

Intriguingly, when α,β-dibromoaldehyde **6** was employed in place of the α-bromocinnamaldehyde **1a** in the reaction, the final product **3a** and **5a** were efficiently generated in 78% and 76% yield, respectively (Eq. 1 and Eq. 2; also see SI).

**Table 2.** The reaction scope for NHC-catalyzed amide bond formation[a,b]




[a] Reacion condition: see entry 16, Table S2. [b] Isolated yields. [c] Amidation for 6 h. [d] Amidation at 50 ℃.

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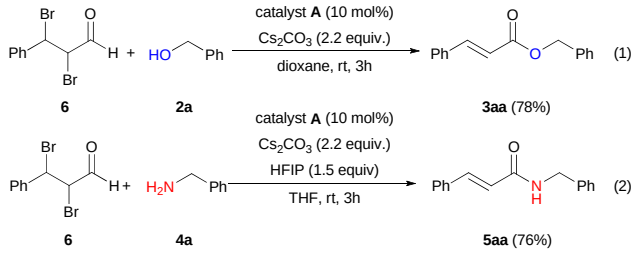
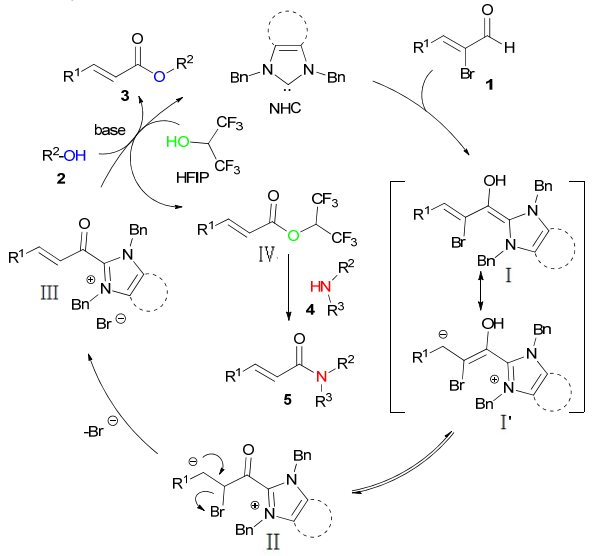



A plausible mechanism for this reaction is illustrated in Scheme 2. The addition of the NHC to bromoenals **1** affords the Breslow intermediates Ⅰ after addition and rearrangement, which are the tautomer of the intermediates Ⅱ. The leaving of the bromide generates the α,β-Unsaturated acylazolium ions III as the key intermediates. Subsequent nucleophilic attack by the alcohols **2** affords the esters **3** with the regeneration of the NHC catalysts (Scheme 2). In the amidation process, the activated esters Ⅳ are produced by attack of HFIP with the formation of NHC to complete the catalytic cycle. Subsequent substitution reaction with the amines **4** affords the amides **5**.

In summary, we have demonstrated a simple and efficient NHC-catalyzed transformation of bromoenal into α,β-unsaturated esters or amides with high stereoselectivity through C-Br bond cleavage and C-O or C-N bond formation. The NHC-catalyzed processes occur under mild conditions. More, the ready availability of the starting materials, avoidance of external oxidants and the usefulness of the products all make this strategy quite attractive. Further studies on the scope, and the synthetic applications are ongoing in our laboratory.




**Scheme 2**. Proposed Catalytic Cycles for NHC-catalyzed ester and amide bond formation

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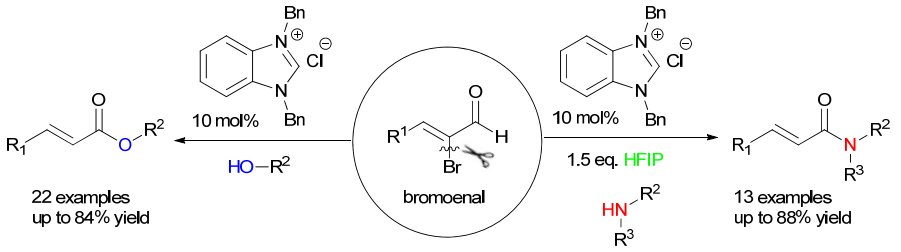


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