Thiazolium-derived *N*-heterocyclic carbene-catalyzed cross-coupling of aldehydes with unactivated imines†

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Cross-coupling of aromatic aldehydes or benzoins with unactivated imines catalyzed by an *N*-heterocyclic carbene (NHC) affords α-amino ketones smoothly.

Reversing the reactivity of aldehydes, also known as *Umpolung*,[1] by nucleophilic *N*-heterocyclic carbene (NHC) has become an area of intense interest recently, providing unconventional access to some important target molecules.[2,3] Being the most extensively studied in this *Umpolung* endeavour, aromatic aldehydes and α,β-unsaturated alkenes have been utilized as acyl anion receptor in the Benzion[4] and Stetter[5] reactions, respectively. Several receptors, such as ketones,[6] aziridines[7] and nitroalkenes[8] have recently been explored, increasing the versatility of this *Umpolung* approach. Further explorations on both acyl donors and receptors will be highly desirable for this NHC-catalyzed acyl anion addition reaction. Imines have rarely been used as the receptor for the acyl anion addition despite the fact that the resulting α-amino ketones are an important class of biologically relevant molecules.[9] Iminium salts, derived from formaldehyde and morpholine, and arylsulfonylamides, precursors for acylimines, are two classes of imine derivative receptors for thiazolium-catalyzed direct acyl transfer of aldehydes reported so far (Fig. 1).[10] In both cases, the products are proposed to be formed under kinetic control, where receptors must react faster with the Breslow intermediate[4a] than another molecule of aldehyde, but slower towards the NHC catalyst. In addition, activated imine analogues were used in both cases. Considering the importance of α-aminoketone derivatives, we envisaged that synthesis of α-aminoketones could be achieved under thermodynamic control, taking advantage of the reversibility of benzoin formation from benzaldehyde. A less reactive imine reacting with the Breslow intermediate at a higher temperature without significant interference with the thiazolium catalyst would lead to the formation of α-aminoketones. Herein we report, using such a strategy, thiazolium-catalyzed cross-coupling of aldehydes with unactivated imines, affording α-amino ketones for a wide range of substrates.

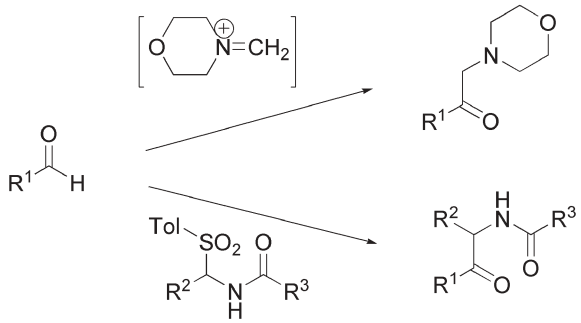
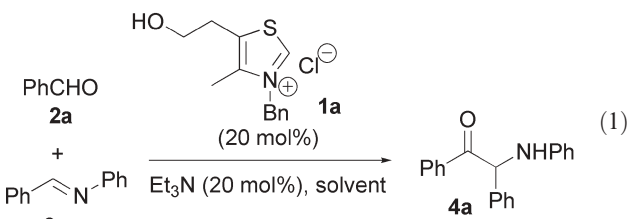
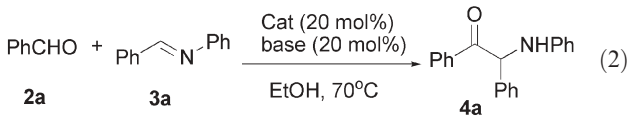


Fig. 1 Cross-coupling of aldehydes and imine derivatives by NHC.

Our studies began with an initial examination of thiazolium salt, **1a**, in the cross-coupling of benzaldehyde, **2a**, and *N*-benzylidenebenzenamine, **3a**, in the presence of triethylamine (eqn 1). The results are summarized in Table 1. The reaction was sluggish at room temperature, affording the desired product, **4a**, in 24% yield after the reaction was carried out in EtOH for 3 days (entry 1, Table 1). We are delighted to find that the reaction temperature plays a critical role in both reaction rate and yield. The yield was improved to 51% at 50 °C and 82% at 70 °C in two days (entries 2 and 3, Table 1). Further increasing the reaction temperature did not lead to a higher yield. Different solvents, such as tetrahydrofuran, acetonitrile, toluene, and *tert*-butanol, have been tested in this reaction, and ethanol was found to be optimal in terms of yield (entries 4–7, Table 1).



(1)



(2)

Table 1 Optimization of cross-coupling of benzaldehyde **2a** and imine **3a**

Entry[a]	Solvent	*T*/°C	Time/d	Yield (%)[b]
1	EtOH	25	3	24
2	EtOH	50	3	51
3	EtOH	70	2	82
4	THF	70	2	49
5	CH_3CN	70	2	57
6	Toluene	70	2	53
7	*tert*-Butanol	70	2	76

[a] Reaction conditions: **1a** (20 mol%), Et_3N (20 mol%), **2a** (1.2 equiv), **3a** (1.0 equiv), 1.0 mol L^{-1} of **3a**. [b] Isolated yields.

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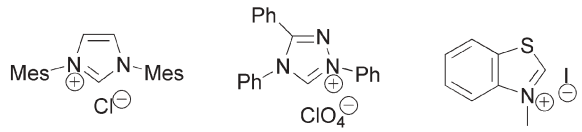
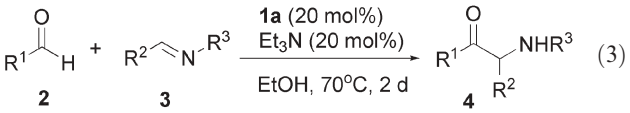


1b **1c** **1d**

Fig. 2 Structures of several NHC precursors.

Several readily accessible *N*-heterocyclic carbene precursors have been tested under the above optimized reaction conditions (Fig. 2 and eqn 2). As is summarized in Table 2, using imidazolium chloride, **1b**, the reaction did not give any observable desired product in the presence of either Et_3N or DBU (entry 2, Table 2). It should be noted that benzoin product was also not detectable during the reaction. When triazolium salt **1c** was used, only 10% of the desired product was isolated after 2 days (entry 3, Table 2). Surprisingly, catalyst derived from thiazolium iodide **1d** gave α-aminoketone in only 18% yield despite the structural similarity between **1a** and **1d** (entry 4, Table 2).

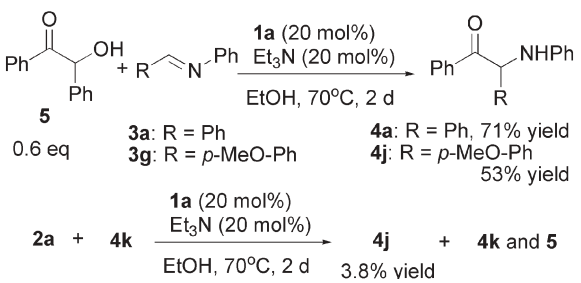
Next, we chose the optimized reaction conditions as follows: in the presence of 20 mol% of thiazolium salt, **1a**, and 20 mol% Et_3N, the reaction was run at 70 °C in EtOH for 2 days. A variety of substituted aromatic aldehydes and imines have been explored as substrates for this reaction, and the results are listed in Table 3 (eqn 3). The *pseudo*-homo-cross-coupling, defined as an aldehyde reacting with an imine derived from the same aldehyde ($R^1 = R^2$), went well in all cases. Imine derived from aniline bearing either an electron-withdrawing group, such as Cl, or electron-donating group, such as methyl, could react with benzaldehyde, affording the desired α-aminoketones in good yields (entries 2 and 3, Table 3). For the substituents of the aromatic aldehydes, good yields were obtained with electron-withdrawing groups, while moderate yields were given with electron-donating groups (entries 4–7, Table 3). It should be noted that this methodology is also suitable for hetero-cross-coupling, defined as an aldehyde reacting with an imine derived from a different aldehyde ($R^1 \neq R^2$). For substituted benzaldehydes and Schiff bases, moderate yields could be obtained (entries 8–10, Table 3). In addition, several hetero-aromatic aldehydes have also been examined in the cross-coupling reaction. To our surprise, the reaction between benzofuran-2-carboxaldehyde, **2g**, and imine, **3g**, went to completion in 3 h, affording α-aminoketone, **4k**, in 95% yield (entry 11, Table 3). Furfural, **2h**, and thiophene-2-carboxaldehyde, **2i**, could also react with imine **3g** to give their corresponding α-aminoketones in 74% and 67% yield, respectively (entries 12 and 13, Table 3). A cross-coupling reaction between benzofuran-2-carboxaldehyde, **2g**, and imine, **3h**, led to product **4n** in 64% yield (entry 14, Table 3). However, an attempt at cross-coupling isonicotinaldehyde, **2j**, and imine, **3e**, failed to give the desired product. Pivalyl, **2k**, also failed to afford cross-coupling product with imine **3e**.



2 **3** **4** (3)

In order to understand the reaction mechanism, 0.6 equiv benzoin, **5**, was utilized instead of 1.2 equiv benzaldehyde to react with the imine, **3a**, under the optimized reaction conditions (Scheme 1). Interestingly, the desired α-aminoketone, **4a**, was isolated in a comparable yield, 71%, after 2 days. Similarly, when the cross-coupling reaction between benzoin, **5**, and imine, **3g**, was carried out, the desired product, **4j**, was obtained in 53% yield, which is only slightly lower than that of the cross-coupling reaction between benzaldehyde and imine **3g** (67% yield, entry 10, Table 3). In addition, an experiment has been performed to discover if α-aminoketone formation could be reversed. Benzaldehyde, **2a**, and α-aminoketone, **4k**, were subjected to the standard reaction conditions. **4j** was obtained in 3.8% yield after 2 days, suggesting that the α-aminoketone formation is also reversible. It should be noted that **4j** was undetectable if the reaction was run at room temperature. These experiments indicated that reaction is likely, at least partially, under thermodynamic control.

Our results are noticeably different from previous findings by Murry *et al*. on the thiazolium-catalyzed cross-coupling reaction of aldehydes with acylimines.[10b] In their experiments, the corresponding benzoin products are not observed and also do not serve as



Scheme 1 Cross-coupling of benzoin and imines.

Table 2 Cross-coupling of benzaldehyde **2a** and imine **3a** using different catalysts

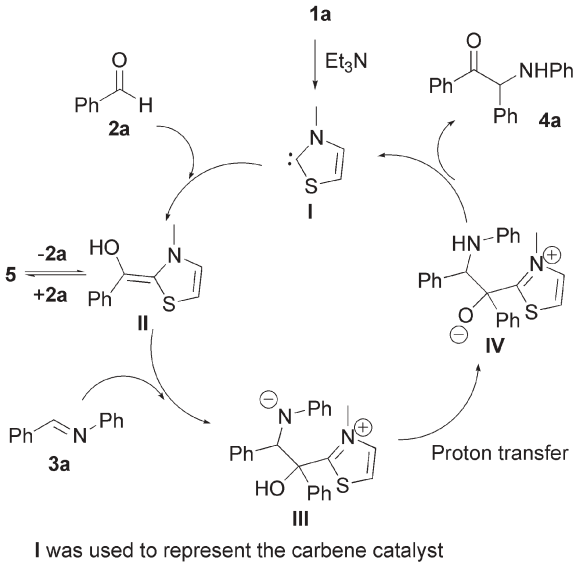
Entry[a]	Catalyst	Base	Yield (%)[b]
1	**1a**	Et_3N	82
2	**1b**	DBU or Et_3N	<5
3	**1c**	Et_3N	10
4	**1d**	Et_3N	18

[a] Reaction conditions: cat (20 mol%), base (20 mol%), **2a** (1.2 equiv), **3a** (1.0 equiv), 1.0 mol L^{-1} of **3a** in EtOH at 70 °C for 2d. [b] Isolated yields.

Table 3 The scope of substrates in cross-coupling reaction

Entry[a]	**2**, R^1	**3**, R^2	R^3	**4**, yield (%)[b]
1	**2a**, Ph	**3a**, Ph	Ph	**4a**, 82
2	**2a**, Ph	**3b**, Ph	*p*-Cl–Ph	**4b**, 80
3	**2a**, Ph	**3c**, Ph	*p*-Me–Ph	**4c**, 85
4	**2b**, *p*-Cl–Ph	**3d**, *p*-Cl–Ph	Ph	**4d**, 72
5	**2c**, *p*-Br–Ph	**3e**, *p*-Br–Ph	Ph	**4e**, 85
6	**2d**, *p*-Me–Ph	**3f**, *p*-Me–Ph	Ph	**4f**, 68
7	**2e**, *p*-MeO–Ph	**3g**, *p*-MeO–Ph	Ph	**4g**, 58
8	**2f**, *p*-Br–Ph	**3a**, Ph	Ph	**4h**, 72
9	**2f**, *p*-Br–Ph	**3g**, *p*-MeO–Ph	Ph	**4i**, 66
10	**2a**, Ph	**3g**, *p*-MeO–Ph	Ph	**4j**, 67
11[c]	**2g**, 2-benzofuran	**3g**, *p*-MeO–Ph	Ph	**4k**, 95
12[d]	**2h**, 2-furan	**3g**, *p*-MeO–Ph	Ph	**4l**, 74
13[d]	**2i**, 2-thiophene	**3g**, *p*-MeO–Ph	Ph	**4m**, 67
14[d]	**2g**, 2-benzofuran	**3h**, *o*-MeO–Ph	*o*-Cl–Ph	**4n**, 64
15	**2j**, 4-pyridyl	**3e**, *p*-Br–Ph	Ph	<5%
16	**2k**, *t*-Bu	**3e**, *p*-Br–Ph	Ph	<5%

[a] Reaction conditions: **1a** (20 mol%), Et_3N (20 mol%), **2** (1.2 equiv), **3** (1.0 equiv), 1.0 mol L^{-1} of **3** in EtOH at 70 °C for 2 d. [b] Isolated yields. [c] Reaction was run for 3 h. [d] Reaction was run for 12 h.



Scheme 2 A plausible catalytic cycle for the cross-coupling reaction.

substrates in the cross-coupling reactions. The latter could mean that the NHC catalyst may react with acylimines at a high temperature, which is necessary for reversing benzoin formation in the presence of the NHC catalyst. In our case, Schiff bases do not react with the NHC catalyst even at high temperature which warrants the existence of the NHC in the reaction mixture.

A plausible catalytic cycle was proposed, as illustrated in Scheme 2. Carbene **I** is generated by deprotonation of thiazolium salt **1a** in the presence of Et_3N. **I** then reacts with benzaldehyde to give the Breslow intermediate **II**, which could lead to benzoin, **5**, or intermediate **III** by reacting with benzaldehyde or imine **3a**, respectively. Upon proton transfer, intermediate **III** will give intermediate **IV**, which could further release the carbene catalyst **I** and product **4a** to finish the catalytic cycle.

In summary, we have found that the readily available thiazolium salt in the presence of triethylamine catalyzes cross-coupling of aromatic aldehydes with unactivated imines. This organocatalytic process affords α-aminoketones smoothly, using a cheap and commercially available catalyst and mild reaction conditions. A preliminary study shows that the reaction is probably under a thermodynamic control. This strategy provides a novel access to the acyl anion addition reaction involving a less reactive acyl receptor. Further development of new acyl anion receptors and related mechanistic investigations are currently under way.

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