DOI: 10.1002/adsc.201000071

Dual Amine- and Brønsted Acid-Catalyzed α-Allylic Alkylation of Aldehydes

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Received: January 28, 2010; Published online: June 8, 2010

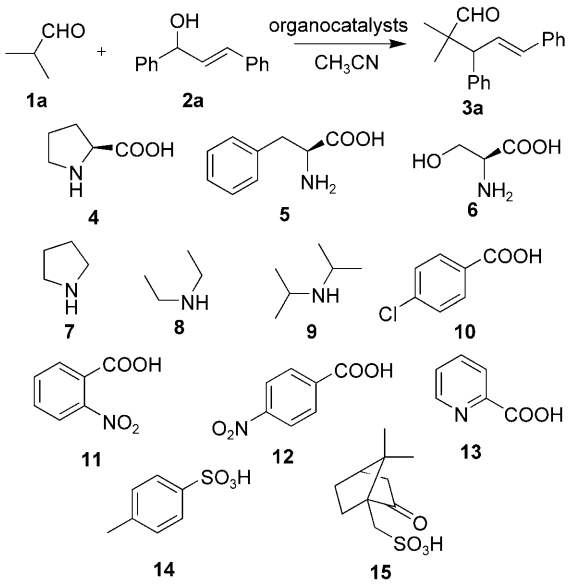
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000071.

Abstract: A very simple method was developed for the direct, palladium-free catalytic α-allylic alkylation of aldehydes. The direct organocatalytic intermolecular α-allylic alkylation reaction was mediated by a simple combination of Brønsted acid and enamine catalysis which furnished α-allylic alkylated aldehydes and cyclohexanone in high yields and chemoselectivities. The reaction conditions are mild and environmental friendly, the process is conducted under an atmosphere of air without the need for dried solvents, and water is the only side product of the allylic alkylation reaction.

Keywords: aldehydes; allylic alkylation; Brønsted acids; enamine catalysis; organocatalysis

Allylic alkylations are important C–C bond forming reactions in organic synthesis.[1] During the last 30 years, palladium-catalyzed allylic alkylation has become an attractive and mature synthetic method.[2,3] These processes inevitably produce a stoichiometric amount of alcohols or organic waste. The substitution of the halides and related compounds also produces salts waste and requires a stoichometric amount of a base.[4] In this respect, the use of allylic alcohols as substrates will be highly attractive since only water would be generated as an environmental benign by-product.[5] However, most of α-allylic alkylations of carbonyl compounds with allylic alcohols were limited to activated dicarbonyl compounds, such as β-keto esters or diketones. The alternative intermolecular direct ketone or aldehyde allylation is more difficult because there are competing side reactions such as aldol condensations, Cannizzaro or *O*-allylation reactions in the catalytic direct α-allylation of non-stabilized aldehyde and ketones.[6] Attempts to overcome this limitation have focused mainly on the development of the combinational use of palladium with amino organocatalysts. Since 2006, a direct catalytic intermolecular α-allylic alkylation of aldehydes and cyclic ketones has been successfully developed by the combination of enamine/Pd catalysis.[7] A related study employing Brønsted acids as co-catalysts in the palladium-catalyzed allylic allylation was reported by List and co-workers in 2007.[8] In metal-free organocatalysis, a direct catalytic intermolecular α-allylic alkylation of aldehydes is still a difficult challenge. To the best of our knowledge, there is only one example reported on organocatalyzed α-allylation of aldehydes,[9] in which allylic silane was used as substrate with SOMO activation. Although amino (enamine and iminium) catalysis[10] has been used as an efficient strategy for various transformations, include aldol, Michael, cycloaddition, Mannich, α-functionalization and domino reactions, allylic alcohols other than allylic acetates or allylic amines have not been investigated in the metal-free organocatalyzed α-allylic alkylation of aldehydes. Therefore, we herein report the first dual amine- and Brønsted acid-catalyzed α-allylic alkylation of aldehydes using allylic alcohols (Scheme 1).

The initial studies of the organocatalytic allylic alkylation focused on the screening of different amines and Brønsted acids as catalyst for the reaction of aldehyde **1a** and allylic alcohol **2a**. The results from these investigations are presented in Table 1. L-Proline and other primary amino acids were first evaluated but gave no conversion (entries 1–3). We then screened different Brønsted acids in the presence of



Scheme 1. Metal-free organocatalyzed α-allylic alkylation of isobutyraldehyde.

Table 1. Screening of different amines and Brønsted acids as catalysts for the α-allylic alkylation of isobutyraldehyde.

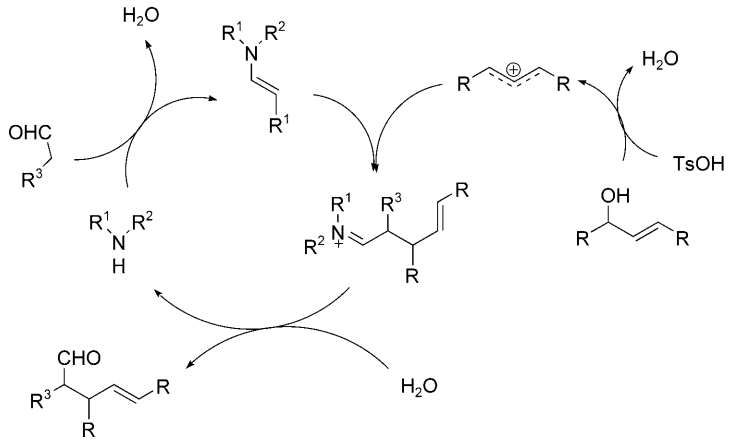
Entry	Amines	Brønsted acids	Time	Yield [%][a]
1	**4** (10 mol%)	–	48	0
2	**5** (10 mol%)	–	48	0
3	**6** (10 mol%)	–	48	0
4	**7** (10 mol%)	**10** (20 mol%)	24	0
5	**7** (10 mol%)	**11** (20 mol%)	24	0
6	**7** (10 mol%)	**12** (20 mol%)	24	0
7	**7** (10 mol%)	**13** (20 mol%)	24	0
8	**7** (10 mol%)	**14** (20 mol%)	24	32
9	**7** (10 mol%)	**15** (20 mol%)	24	31
10	**8** (10 mol%)	**14** (20 mol%)	24	95 (83)[b]
11	**9** (10 mol%)	**14** (20 mol%)	24	27
12	**4** (10 mol%)	**14** (15 mol%)	24	33
13	**5** (10 mol%)	**14** (15 mol%)	24	45
14	**6** (10 mol%)	**14** (15 mol%)	24	70
15	**8** (10 mol%)	**14** (10 mol%)	48	0

[a] NMR yield.
[b] Isolated yield in parenthesis.

pyrrolidine (entries 4–9), and surprisingly, *p*-toluenesulfonic acid (TsOH, **14**) or camphorsulfonic acid (CSA, **15**) proved to be an effective Brønsted acid cocatalyst in this reaction (entries 8 and 9). Obviously, in the absence of a Brønsted acid or base, isobutyraldehyde (**1a**) did not react with 1,3-diphenylprop-2-en-1-ol (**2a**) respectively. Therefore the presence of both a secondary amine and Brønsted acidic functions simultaneously are essential prerequisites for the α-allylic alkylation to proceed. After the next screening of different amines in this reaction, the combination of Et_2NH and TsOH turned out to be an excellent catalyst for the allylic alkylation of isobutyraldehyde with 1,3-diphenylprop-2-en-1-ol. The reaction was highly chemoselective, and we were able to isolate the corresponding alkylated aldehyde derivative easily in 83% of yield. In addition, we found that the combination of other acyclic or cyclic secondary amines with organic carboxylic acids or CSA used as catalysts for the direct allylic alkylation reactions between aldehyde and allylic alcohol resulted in lower conversion and chemoselectivity. However, the amount of TsOH was crucial for the process of allylic alkylation. The reason for an excess of TsOH in this reaction is easily provided: one equivalent of TsOH and Et_2NH are involved in the formation enamine intermediate, the excess of TsOH generated the allylic cation, thus there is a merging of two powerful catalytic cycles with activation *via* different mechanisms, which make the allylic alkylation proceed smoothly (Scheme 2).

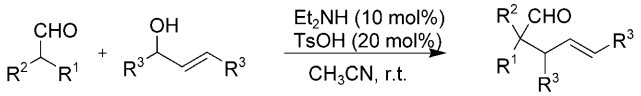
Encouraged by these initial results, we decide to investigate the dual amine- and Brønsted acid-catalyzed direct α-allylic alkylation reactions for a set of simple aldehydes and aromatic allylic alcohols. As shown in Table 2, the reactions proceeded smoothly to give the corresponding α-allylic alkylated aldehydes in moderate to excellent yields (54–91%). It should be noted that different aldehydes give a mixture of diastereomers under the optimal conditions. The diastereoselectivity is increased with smaller substituted group in aliphatic aldehyde: *i*-Pr < *n*-Pr < Et < Me (*dr* ranging from 1:1 to 15:1, Table 2, entries 1–5). In addition, the functional groups present on aromatic allylic alcohols have a strong impact on the diastereoselectivity (entries 11–13). It is remarkable that this methodology gives rise selectively to α-allylic alkylated aldehydes without formation of self-aldol adducts. However, non-phenyl ring substituted allylic alcohols shut down the allylic alkylation reaction and no conversion is observed (entry 16).

The reaction is not restricted to the use of aldehyde but can be transferred to the use of ketones under the same mild conditions. The α-allylation of cyclohexanone employing the same catalyst system with the combination of Brønsted acid and enamine catalysis furnished the corresponding α-allylic alkylated cyclohexanone derivative in excellent yield (90%) (Scheme 3). We also investigated a catalytic asymmetric version of the α-allylic alkylation. In preliminary studies, several cheap and available amino catalysts provide the α-allylic alkylated ketone in good yield but with poor enantioselectivity (up to 7% *ee*)[11]. Although our explorations in the asymmetric α-allylic alkylation of aldehydes or ketones were unsuccessful, further deep studies and screening of effective chiral amines are expected to result in improvements of the enantio- and diastereoselectivities in this allylic alkylation.



Scheme 2. Combined Brønsted acid and enamine catalysis.

Table 2. Metal-free organocatalyzed α-allylic alkylation of aldehydes.[a]

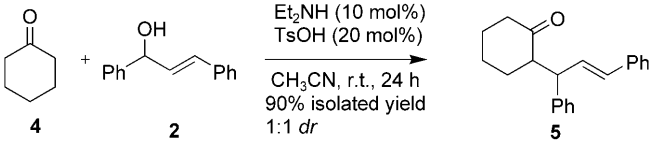


1 **2** **3**

Entry	R^1	R^2	R^3	Yield [%][b]	*dr*
1	CH_3	CH_3	Ph	**3a:** 83	–
2	H	CH_3	Ph	**3b:** 61	15:1
3	H	Et	Ph	**3c:** 85	10:1
4	H	*n*-Pr	Ph	**3d:** 91	2:1
5	H	*i*-Pr	Ph	**3e:** 85	–
6	-$(CH_2)_5$-		Ph	**3f:** 75	–
7	CH_3	CH_3	*o*-Br-C_6H_4	**3g:** 79	–
8	CH_3	CH_3	*o*-CH_3-C_6H_4	**3h:** 68	–
9	CH_3	CH_3	*p*-Cl-C_6H_4	**3i:** 66	–
10	CH_3	CH_3	*p*-F-C_6H_4	**3k:** 84	–
11	H	Et	*o*-CH_3-C_6H_4	**3l:** 63	2:1
12	H	Et	*p*-Br-C_6H_4	**3m:** 58	1:1
13	H	Et	*p*-F-C_6H_4	**3n:** 59	5:2
14	CH_3	CH_3	*p*-CH_3-C_6H_4	**3o:** 54	–
15	CH_3	CH_3	*m*-OCH_3-C_6H_4	**3p:** 75	–
16	CH_3	CH_3	H	NR	-

[a] See Experimental Section for the reaction conditions.
[b] Yield of the isolated product of the corresponding product after column chromatography on silica gel.

In summary, we have developed a very simple method for the direct, palladium-free organocatalytic α-allylic alkylation of aldehydes. The direct catalytic intermolecular α-allylic alkylation reaction is mediated by a simple combination of Brønsted acid and enamine catalysis which furnished α-allylic alkylated aldehydes and cyclohexanone in good yields and promising diastereoselectivities (up to 15:1 *dr*). Control experiments show the importance of the presence of an excess amount of Brønsted acid in the enamine-promoted α-allylic alkylation reaction of aldehydes. Unfortunately, employing several known enantiomerically pure chiral amino catalysts did not allow us to achieve a high level of enantioinduction during this alkylation. Thus, we expect that the combination of chiral Brønsted acid and asymmetric enamine catalysis can possibly be a step in the direction leading to the development of enantioselective reactions.



4 **2** **5**

Scheme 3. Dual amine- and Brønsted acid-catalyzed α-allylic alkylation of cyclohexanone.

Experimental Section

General Remarks

All reaction flask and solvent were dried according to standard methods prior to use. Flash column chromatography was performed over silica (100–200 mesh). NMR spectra were recorded on a 400 MHz spectrometer (Avance 400). ^{13}C NMR spectra were obtained with broadband proton decoupling. For spectra recorded in $CDCl_3$, unless otherwise noted, chemical shifts were recorded relative to the internal TMS (tetramethylsilane) reference signal. GC-MS was performed on a TRACE DSQ. IR spectra were recorded using an FT-IR apparatus (Nicolot 5700). Thin layer chromatography was performed using silica gel.

General Procedure for α-Allylic Alkylation of Aldehydes

Et_2NH (0.1 mmol) and TsOH (0.2 mmol) were added into a solution of aldehyde (2.0 mmol) and allylic alcohol (1.0 mmol) in CH_3CN (4 mL). After stirring at room temperature for 24 h, the mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), concentrated under

vacuum, and purified by column chromatography on silica gel (EtOAc-petroleum ether, 1:8) to gain the pure product.

All the products were confirmed by GC-MS, NMR, and IR, and characterization data for compounds **3** are listed in the Supporting Information.

3a (Table 2, entry 1): ^{1}H NMR ($CDCl_3$, 400 MHz), $\delta =$ 1.05 (s, 3H), 1.14 (s, 3H), 3.67 (d, $J = 8.8$ Hz), 6.51 (m, 2H), 7.21–7.36 (m, 10H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), $\delta = 19.66$, 20.60, 49.83, 55.39, 126.37, 126.98, 127.58, 127.93, 128.40, 128.55, 129.16, 133.07, 136.96, 139.90, 206.04; MS (EI): $m/z = 263.91$ ($C_{19}H_{20}O$); IR: $\nu = 3061$, 3028, 2989, 2930, 1724, 1495, 1453, 1107, 1020 cm^{-1}.

Acknowledgements

Partial financial support by the National Natural Science Foundation of China (No. 20973051) and Zhejiang Provincial Natural Science Foundation of China (Y4090139) is appreciated. XLW is greatly indebted to Prof. Shibasaki Masakatsu, Graduate School of Pharmaceutical Sciences, The University of Tokyo, and Prof. Chun-Gu Xia, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, for their help.

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512; c) (*R,R*)-1,2-diphenylethylenediamine (DPEN), Ts-DPEN, L-proline, L-serine, and L-tryptophan, L-threonine, quinine-derived primary amines, and other simple and commercial available secondary amino organocatalysts have been used in the asymmetric α-allylic alkylation of cyclohexanone, in which most of the amino catalysts gave no enantioselectivity and 7% *ee* was the best result for the L-tryptophan-catalyzed α-allylic alkylation of cyclohexanone in the presence of TsOH.

