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The versatile roles of ammonium salt catalysts in enantioselective reduction and alkylation of α,β-unsaturated aldehydes: iminium catalysis, enamine catalysis and acid catalysis†

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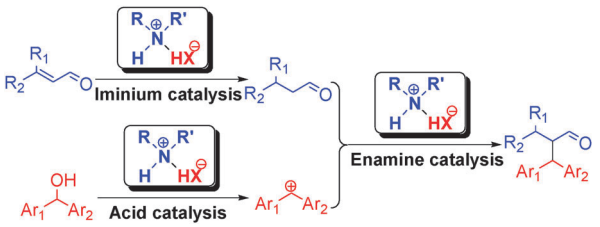
A novel strategy for highly efficient utilization of chiral ammonium salt catalysts has been described in this paper. Three kinds of catalytic functions including iminium catalysis, enamine catalysis, and acid catalysis of chiral ammonium salt catalysts, have been achieved in the enantioselective reduction and alkylation reaction of α,β-unsaturated aldehydes with alcohols.

To make synthetic chemistry more green, atom-economic, and sustainable is undoubtedly the goal of organic synthesis. Although numerous strategies have been disclosed, such as the cascade reactions and the new transformation processes to improve the atom efficiency,[1] alternatively, the discovering versatility of one catalyst as multifunctional catalyst has still been an extremely attractive but challenging task. With the booming of organocatalysis, ammonium salts have been widely utilized in asymmetric iminium catalysis[2] or enamine catalysis.[3] Recently, ammonium salts were also disclosed as acid catalysts by Fu,[4] Johnston,[5] Ishihara,[6] Cozzi[7] and others.[8] On the basis of these generalist ammonium salts, ingenious designs merging iminium catalysis and enamine catalysis of one ammonium salt in one reaction have been simultaneously realized by the research groups of List,[9] MacMillan,[10] and Jørgensen[11] in 2005. Since then, various kinds of reactions highly employing double functions of ammonium salts as iminium catalysis and enamine catalysis have been developed.[12] However, to the best of our knowledge, highly efficient utilization of one ammonium salt as three kinds of catalysts in one transformation has not been achieved. Herein, we describe an enantioselective reduction[13] and alkylation reaction of α,β-unsaturated aldehydes with alcohols, in which the ammonium salt catalyst performed as three kinds of catalytic functions, namely iminium catalysis, enamine catalysis and acid catalysis (Scheme 1).

The organocatalytic asymmetric intramolecular α-alkylation of aldehydes has been significantly developed.[14] In contrast, the intermolecular α-alkylation of aldehydes is still a challenging task.[15] MacMillan and coworkers realized the enantioselective α-alkylation of aldehydes with alkyl bromides by merging enamine catalysis and photocatalysis.[15a,b] The enantioselective α-alkylation of aldehydes with a stabilized carbon cation[7,16] has been recently developed by Petrini and Melchiorre *et al.*,[16a] and Cozzi.[7] Despite these advances, the organocatalytic asymmetric intermolecular α-alkylation of aldehydes in cascade reaction has not been achieved yet.



Scheme 1 Multifunctional catalysis of ammonium salts.

We recently developed a coupling reaction of terminal alkynes with benzylic alcohols as the precursor of carbon cations.[17] The continued effort on the coupling of carbon cations encouraged us try the cascade intermolecular α-alkylation of aldehydes with a carbon cation *in situ*. We initially investigated enantioselective reduction and alkylation reaction of *trans*-cinnamaldehyde **1a**, with ethyl Hantzsch ester **2** and bis(4-dimethylamino-phenyl)-methanol **3a** in the presence of different catalysts using toluene as solvent. Gratifyingly, the catalyst **B** (Fig. 1) gave a better result of 74% yield with 79% ee value (entry 2, Table 1). Different solvents were then screened. The result indicated that the reactions in toluene exhibited the best efficiency (entries 2 and 5–8, Table 1). When the temperature was reduced to −5 °C, the yield decreased

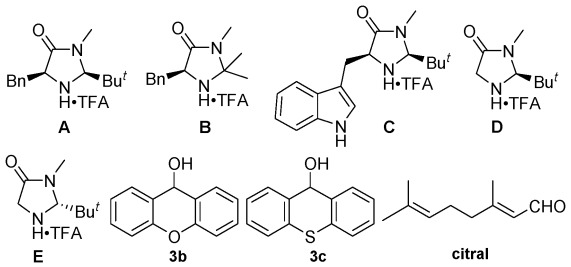


Fig. 1 The structure of catalysts, benzylic alcohols and citral.

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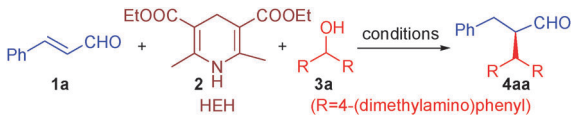
Table 1 The reaction of *trans*-cinnamaldehyde **1a**, ethyl Hantzsch ester **2** and bis(4-dimethylamino-phenyl)methanol **3a** under different conditions[a]



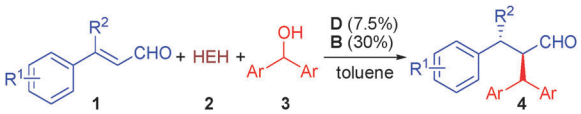
Entry	Catalyst (mmol%)	Solvent	T/°C	Time (h)	Yield (%)	ee (%)
1	**A** (20)	toluene	20	84	76	41
2	**B** (20)	toluene	20	84	74	79
3	**C** (20)	toluene	20	84	75	2
4	**D** (20)	toluene	20	84	59	66
5	**B** (20)	CH_2Cl_2	20	84	88	54
6	**B** (20)	$CHCl_3$	20	84	57	68
7	**B** (20)	Et_2O	20	84	32	65
8	**B** (20)	THF	20	84	27	32
9[b]	**B** (20)	toluene	−5	120	8	89
10[b]	**A** (7.5) + **B** (30)	toluene	−5	120	83	86
11[b]	**D (7.5) + B (30)**	**toluene**	**−5**	**120**	**95**	**87**
12[b]	**E** (30) + **B** (30)	toluene	−5	120	99	37
13[b]	**D** (30)	toluene	−5	120	96	73

[a] All reactions were carried out in the scale of **1** (0.3 mmol), **2** (0.24 mmol), **3** (0.2 mmol), catalyst, in 2 mL solvent at appointed temperature. **3a** was added after 12 h. Enantiomeric excess was determined by chiral HPLC analysis. The yields were isolated yields. [b] **3a** was added after 24 h.

regretfully to 8%, in spite of a high ee value of 89% (entry 9). It was noteworthy that the combination of catalysts **D** and **B** gave the best result of 95% yield with 87% ee (entry 11, Table 1). Compared with the results of entries 9 and 11, it seemed that the catalyst combination (7.5 mmol% of **D** and 30 mmol% of **B**) underwent the cyclic-specific catalysis.[10] However, the results employing **B** or **D** as the solo catalyst, respectively, (entries 9 and 13) indicate that both of **B** and **D** can enable the reduction and the alkylation steps. Furthermore, catalyst combination (30 mmol% of **E** and 30 mmol% of **B**) of opposite absolute configuration promote the reaction yield (99%) but result in low enantioselectivity (37% ee, entry 12). On the basis of the results of entries 9–13, it indicates that although catalyst **D** dominated the reduction step, whereas catalyst **B** is more active than catalyst **D** in the alkylation step; the cyclic-specific catalysis is not so strong in the alkylation step.

The scope of the tandem enantioselective reduction and alkylation reaction was expanded to a variety of enals **1** and benzylic alcohols **3** (Table 2). Cinnamaldehyde derivatives **1** with both electron-donating groups and electron-withdrawing groups smoothly underwent this kind of transformation generating **3** in excellent yields (86–95%) with moderate to excellent ee values (81–90%) (entries 1–4, Table 2). Moreover, β,β-disubstituted enals were tolerated in this tandem reduction and alkylation transformation (entries 7–14, Table 2). Variation in the electronic nature of the aldehyde component has little influence on the enantioselectivity (entries 7–11). Notably, the substrates with β-halophenyl substituent such as **1g** and **1h**, were converted into the desired **4ga** and **4ha** with very excellent enantioselectivities, respectively, (96% and >99% ee, entries 9–11). With the decrease of the reaction temperature, the diastereoselectivity increases (*cf*. entries 10 and 11). In addition, not only the aromatic, but also aliphatic β-substituted enals can be converted to the corresponding aldehydes **4**. The reaction of citral **1i** produced **4ia** in

Table 2 The tandem reduction and alkylation of different enals **1**, ethyl Hantzsch ester **2** and different benzylic alcohols **3**[a]



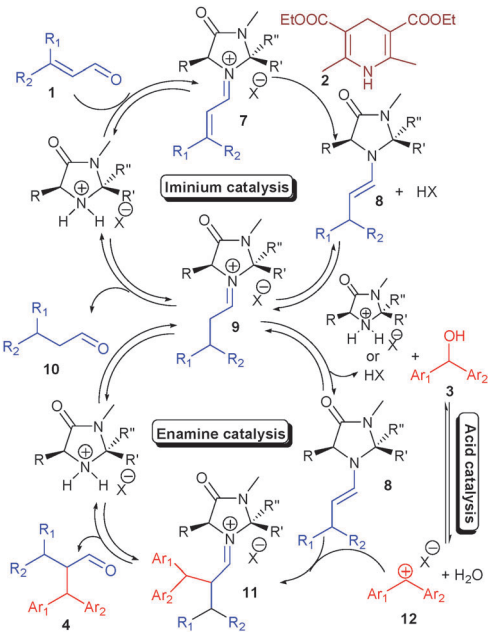
Entry	**1** (R^1,R^2)	**3** (Ar)	T/°C	**4**	Yield (%)	ee (%)	dr
1[b]	H,H (*E*)	**1a** **3a**	−5	**4aa**	95	87	—
2[b]	*p*-Me,H (*E*)	**1b** **3a**	−5	**4ba**	93	81	—
3[b]	*p*-Cl,H (*E*)	**1c** **3a**	−5	**4ca**	87	80	—
4[b]	*o*-F,H (*E*)	**1a** **3a**	−5	**4da**	95	90	—
5[c]	H,H (*E*)	**1a** **3b**	−10	**4ab**	96	70	—
6[c]	H,H (*E*)	**1a** **3c**	−10	**4ac**	86	67	—
7[d]	H,Me (*E*/*Z* = 3/1)	**1e** **3a**	−5 to +20	**4ea**	82	93	7 : 1
8[d]	*p*-OMe,Me (*E*)	**1f** **3a**	−5 to +20	**4fa**	74	94	6 : 1
9[d]	*p*-F,Me (*E*)	**1g** **3a**	−5 to +20	**4ga**	61	96	7 : 1
10[d]	*p*-Br,Me (*E*)	**1h** **3a**	−5 to +20	**4ha**	60	>99	6 : 1
11[d]	*p*-Br,Me (*E*)	**1h** **3a**	−5 to +5	**4ha**	40	>99	15 : 1
12[d]	citral (*E* + *Z*)	**1i** **3a**	−5 to +20	**4ia**	59	85	2 : 1
13[d,e]	H,Me (*E*/*Z* = 3/1)	**1e** **3b**	−5 to +26	**4eb**	58	90	>25 : 1
14[d,e]	H,Me (*E*/*Z* = 3/1)	**1e** **3c**	−5 to +26	**4ec**	39	86	>25 : 1

[a] All the reactions were carried out on the scale of **1** (0.3 mmol), **2** (0.24 mmol), **3** (0.2 mmol), catalyst **D** (7.5 mmol%), catalyst **B** (30 mmol%), in 2 mL toluene at the appointed temperature for 5 days. Enantiomeric excess (major isomer) was determined by chiral HPLC analysis. The yields were isolated yields. The dr values were determined by ^{1}H-NMR or by chiral HPLC analysis on the crude reaction mixture. The ratios indicated were *anti*/*syn*. [b] **3a** was added after 24 h. [c] **3b** or **3c** was added after 1.5 days. The reactions were carried out in $MeNO_2$. [d] The reaction was carried out at −5 °C for 36 h firstly, then the temperature was increased to +20 °C for the subsequent 4 days. [e] The reaction was stirred at −5 °C for 1.5 days firstly, then the temperature was increased to +26 °C for the subsequent 4 days. The reactions were carried out in $MeNO_2$.

59% yield with 85% of ee (dr: 2 : 1, entry 12, Table 2). Two other benzylic alcohols **3b** and **3c** could also execute this kind of transformation (entries 5–6 and 13–14). It is noteworthy that the diastereoselectivities were very high in the reactions of **1e** with **3b** and **3c**, respectively (>25 : 1, entries 13–14).

The relative and absolute configuration of compound **4aa** was determined to be *R* by comparison of the elution order of the products from a chiral phase HPLC column to those reported in the literature.[7] The relative and absolute configuration of compound **4eb** was determined to be 2*R*, 3*R* by anomalous dispersion X-ray crystallography of the corresponding tosylated alcohol **6**, obtained by reducing simple aldehyde **4eb** to alcohol **5** (see ESI†).[16a]

The probable catalytic cycles for this transformation were illustrated in Scheme 2. Three catalytic cycles including iminium catalysis, enamine catalysis, and acid catalysis are involved. Initially, α,β-unsaturated aldehydes **1** are exposed to ammonium salt catalysts to generate activated iminium species **7**, which are attacked by hydrido-nucleophile ethyl Hantzsch ester **2** to generate the saturated aldehydes **10** which subsequently undergo the second cycle. The ammonium salt catalysts or the free acid (HX) promote the generation of the carbocation **12** from alcohols[7,17,18] in the acid catalytic cycle. Subsequently, the activated enamine species **8** react



Scheme 2 Proposed catalytic cycle for this transformation.

with carbocation **12** to form the iminium intermediates **11**. Finally, the products **4** are produced by the hydrolysis of **11** with the formation of the ammonium salt catalysts to complete the catalytic cycle.

In summary, we developed a cascade enantioselective conjugate reduction and alkylation reaction of α,β-unsaturated aldehydes with alcohols. In this transformation, the chiral ammonium salt catalysts have been highly efficiently employed playing three of kinds of catalytic functions including iminium catalysis, enamine catalysis, and acid catalysis. The further research is ongoing in our laboratory.

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Notes and references

1 (*a*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; (*b*) B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695; (*c*) J.-J. Cao, F. Zhou and J. Zhou, *Angew. Chem., Int. Ed.*, 2010, **49**, 4976; (*d*) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; (*e*) J. Dupont, R. F. de Souza and P. A. Z. Suarez, *Chem. Rev.*, 2002, **102**, 3667; (*f*) V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615; (*g*) *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005; (*h*) *Metal Catalyzed Cascade Reactions*, ed. T. J. J. Müller, Springer-Verlag, Berlin Heidelberg, 2006; (*i*) *Handbook of Green Chemistry-Green Catalysis*, ed. P. T. Anastas and R. H. Crabtree, Wiley-VCH, Weinheim, 2009.

2 (*a*) A. Erkkilä, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416; (*b*) M. Reiter, S. Torssell, S. Lee and D. W. C. MacMillan, *Chem. Sci.*, 2010, **1**, 37.

3 S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471.

4 (*a*) B. L. Hodous and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 10006; (*b*) S. L. Wiskur and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 6176; (*c*) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542.

5 B. M. Nugent, R. A. Yoder and J. N. Johnston, *J. Am. Chem. Soc.*, 2004, **126**, 3418.

6 (*a*) K. Ishihara, S. Nakagawa and A. Sakakura, *J. Am. Chem. Soc.*, 2005, **127**, 4168; (*b*) M. Hatano, T. Maki, K. Moriyama, M. Arinobe and K. Ishihara, *J. Am. Chem. Soc.*, 2008, **130**, 16858.

7 P. G. Cozzi, F. Benfatti and L. Zoli, *Angew. Chem., Int. Ed.*, 2009, **48**, 1313.

8 (*a*) K. Wakasugi, T. Misaki, K. Yamada and Y. Tanabe, *Tetrahedron Lett.*, 2000, **41**, 5249; (*b*) T. Akiyama, J. Itoh and K. Fuchibea, *Adv. Synth. Catal.*, 2006, **348**, 999; (*c*) J. Huang and E. J. Corey, *Org. Lett.*, 2004, **6**, 5027; (*d*) D. Enders, A. A. Narine, F. Toulgoat and T. Bisschops, *Angew. Chem., Int. Ed.*, 2008, **47**, 5661.

9 J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036.

10 Y. Huang, A. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051.

11 M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710.

12 (*a*) X. Zhang, S. Zhang and W. Wang, *Angew. Chem. Int. Ed.*, 2010, **49**, 1481; (*b*) J. Wang, H. Li, H. Xie, L. Zu, X. Shen and W. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 9050; (*c*) W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354; (*d*) B. List, *Chem. Commun.*, 2006, 819; (*e*) C. Liu, X. Zhang, Rui. Wang and W. Wang, *Org. Lett.*, 2010, **12**, 4948; (*f*) X. Companyo, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyanoa and R. Rios, *Chem. Commun.*, 2010, **46**, 6953; (*g*) L.-S. Zu, H. Li, H.-X. Xie, J. Wang, W. Jiang, Y. Tang and W. Wang, *Angew. Chem., Int. Ed.*, 2007, **46**, 3732; (*h*) D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861; (*i*) J. L. Vicario, S. Reboredo, D. Badoa and L. Carrillo, *Angew. Chem., Int. Ed.*, 2007, **46**, 5168; (*j*) C. Grondal, M. Jeanty, D. Enders and M. R. M. Hüttl, *Nat. Chem.*, 2010, **2**, 167; (*k*) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (*l*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*m*) B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 4349; (*n*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422.

13 (*a*) S.-L. You, *Chem.–Asian J.*, 2007, **2**, 820; (*b*) S. G. Ouellet, A. M. Walji and D. W. C. Macmillan, *Acc. Chem. Res.*, 2007, **40**, 1327; (*c*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *Angew. Chem., Int. Ed.*, 2004, **43**, 6660; (*d*) M. Rueping and T. Theissmann, *Chem. Sci.*, 2010, **1**, 473.

14 (*a*) N. Vignola and B. List, *J. Am. Chem. Soc.*, 2004, **126**, 450; (*b*) A. Fu, B. List and W. Thiel, *J. Org. Chem.*, 2006, **71**, 320; (*c*) J. Lv, J. Zhang, Z. Lin and Y. Wang, *Chem.–Eur. J.*, 2009, **15**, 972; (*d*) I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sunden, P. Dziedzic and A. Cordova, *Chem.–Eur. J.*, 2008, **14**, 7867; (*e*) R. Rios, H. Sunden, J. Vesely, G.-L. Zhao, P. Dziedzic and A. Cordova, *Adv. Synth. Catal.*, 2007, **349**, 1028; (*f*) H. Xie, L. Zu, H. Li, J. Wang and W. Wang, *J. Am. Chem. Soc.*, 2007, **129**, 10886; (*g*) D. Enders, C. Wang and J. W. Bats, *Angew. Chem., Int. Ed.*, 2008, **47**, 7539.

15 (*a*) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (*b*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (*c*) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton and D. W. C. MacMillan, *Science*, 2007, **316**, 582; (*d*) J. C. Conrad, J. Kong, B. N. Laforteza and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 11640; (*e*) J. E. Wilson, A. D. Casarez and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 11332; (*f*) A. R. Brown, W.-H. Kuo and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2010, **132**, 9286; (*g*) I. Ibrahem and A. Córdova, *Angew. Chem., Int. Ed.*, 2006, **45**, 1952; (*h*) E. Gómez-Bengoa, A. Landa, A. Lizarraga, A. Mielgo, M. Oiarbide and C. Palomo, *Chem. Sci.*, 2011, **2**, 353.

16 (*a*) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2008, **47**, 8087. For two examples of γ-alkylation of aldehydes: (*b*) G. Bergonzini, S. Vera and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2010, **49**, 9685; (*c*) J. Stiller, E. Marqués-López, R. P. Herrera, R. Fröhlich, C. Strohmann and M. Christmann, *Org. Lett.*, 2010, **13**, 70.

17 S.-K. Xiang, L.-H. Zhang and N. Jiao, *Chem. Commun.*, 2009, 6487.

18 (*a*) L. Zhang, L. Cui, X. Li, J. Li, S. Luo and J.-P. Cheng, *Chem.–Eur. J.*, 2010, **16**, 2045; (*b*) L.-W. Xu, G. Gao, F.-L. Gu, H. Sheng, L. Li, G.-Q. Lai and J.-X. Jiang, *Adv. Synth. Catal.*, 2010, **352**, 1441; (*c*) M. G. Capdevila, F. Benfatti, L. Zoli, M. Stenta and P. G. Cozzi, *Chem.–Eur. J.*, 2010, **16**, 11237; (*d*) Q.-X. Guo, Y.-G. Peng, J.-W. Zhang, L. Song, Z. Feng and L.-Z. Gong, *Org. Lett.*, 2009, **11**, 4620.