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Merging Organocatalysis with Transition Metal Catalysis: Highly Stereoselective α-Alkylation of Aldehydes

Jian Xiao*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China

xiaojian@dicp.ac.cn

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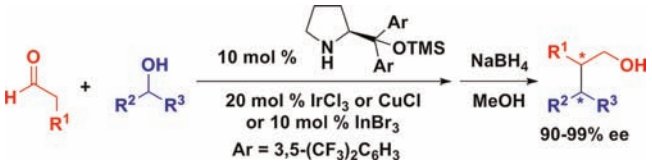
ABSTRACT



The unprecedented cooperative systems involving a diarylprolinol silyl ether with various Lewis acids have been found to effect the highly enantioselective intermolecular α-alkylation of aldehydes. A wide variety of aldehydes and alcohols can be transformed into the desired highly functionalized aldehydes in high yields, excellent enantioselectivities, and good diastereoselectivities at room temperature under mild conditions.

The past few decades have witnessed the revolutionary advancement of organocatalysis, which introduced large numbers of novel reactions to complement the existing transition metal catalysis and enzyme catalysis.[1] In this context, the concept of merging organocatalysis with transition metal catalysis has emerged as a promising strategy to uncover new reactivities and new reactions that are currently not viable.[2] However, most asymmetric examples in this new area involve cooperative catalysis of chiral BINOL-derived phosphoric acid with metal catalysis,[3] while the comparable combination of a Lewis acid with a chiral secondary amine is not common.[4,7−10] This is attributed to the ease of self-quenching of the Lewis acid by the secondary amine or water released during the catalytic cycle. However, the catalytic asymmetric intermolecular α-alkylation of aldehydes,[5] a long sought-after goal for transition metal catalysis,[6] has been tackled by several elegant cooperative systems comprising of chiral secondary amines with transition metals quite recently. The most impressive examples came from coupling of MacMillan's imidazolidinone catalysts with Ce(IV) salts

(1) For selected recents reviews, see: (a) Barbas, C. F., III *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (f) Westermann, B.; Ayaz, M.; Berkel, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. (g) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(2) (a) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. (b) Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999.

(3) For a review, see: (a) Rueping, M.; Koenigs, R. M.; Atodiresei, J. *Chem.—Eur. J.* **2010**, *16*, 9350. For selected examples, see: (b) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (c) Han, Z.-Y.; Xiao, H.; Chen, X.-H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (d) Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2008**, *130*, 14452. (e) Terada, M.; Toda, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6354. (f) Yang, T.; Ferrali, A.; Sladojevich, F.; Campbell, L.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 9140.

(4) (a) Zhao, G.-L.; Ullaḥ, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Córdova, A. *Chem.—Eur. J.* **2010**, *16*, 1585. (b) Jensen, K. L.; Franke, P. T.; Arroniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem.—Eur. J.* **2010**, *16*, 1750. (c) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923. (d) Sun, W.; Zhu, G.; Hong, L.; Wang, R. *Chem.—Eur. J.* **2011**, *17*, 13958.

(5) For reviews, see: (a) Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1360. (b) Alba, A.-N.; Viciano, M.; Rios, R. *ChemCatChem* **2009**, *1*, 437. (c) Tak-Tak, L.; Dhimane, H.; Dalko, P. I. *Angew. Chem., Int. Ed.* **2011**, *50*, 12146. For selected examples without a metal, see: (d) Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707. (e) Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313. (f) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem.—Asian J.* **2010**, *5*, 2047. (g) Gómez-Bengoa, E.; Landa, A.; Lizarraga, A.; Mielgo, A.; Oiarbide, M.; Palomo, C. *Chem. Sci.* **2011**, *2*, 353. (h) Xiang, S.; Zhang, B.; Zhang, L.; Cui, Y.; Jiao, N. *Chem. Commun.* **2011**, *47*, 5007. (i) Brown, A. R.; Kuo, W. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286. For asymmetric α-alkylation of ketones, see: (j) Zhang, L.; Cui, L.; Li, X.; Li, J.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2010**, *16*, 2045.

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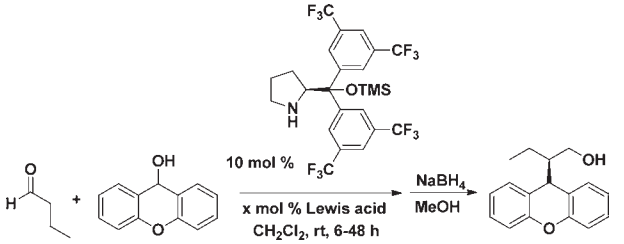
or Ru(II) salts, namely, SOMO catalysis[7] or photoredox catalysis,[8] which constitutes the landmark work for the combination of aminocatalysis with metal catalysis to address currently underdeveloped reactions. Thereafter, Nishibayashi developed a highly enantioselective propargylation of aldehydes with propargylic alcohols catalyzed by diarylprolinol silyl ether with a ruthenium complex.[9] A stereoselective α-alkylation of aldehydes with allylic alcohols or propargylic alcohols by use of the MacMillan catalyst with $InBr_3$ or $In(OTf)_3$ was achieved by Cozzi.[10] However, these examples suffered from the use of a single substrate, need for cryogenic conditions as well as high catalyst loading. Up to until now, no systematic study of the chiral secondary amine-transition metal catalytic system is presented. Thus, the development of a new highly efficient cooperative system involving a chiral secondary amine with a new transition metal for the highly enantioselective intermolecular α-alkylation of aldehydes is of great importance and poses a formidable challenge in organic synthesis. As part of our ongoing research program addressing new catalytic systems for asymmetric catalysis,[11] herein we report the unprecedented cooperative systems of diarylprolinol silyl ether[12] with CuCl, $IrCl_3$, or $InBr_3$ to effect the highly enantioselective intermolecular α-alkylation of aldehydes with alcohols at room temperature under very mild conditions with a wide substrate scope.

At the outset, the model reaction between butylaldehyde and xanthydrol was carried out with a range of Lewis acid catalysts (20−100 mol %) to uncover the best Lewis acid candidate. Among the various Lewis acid catalysts screened, most of them do not function in the cooperative system (see the Supporting Information), and only the successful examples are listed in Table 1. It was found that 1 equiv of $AuCl_3$ can afford good yield, while almost no product was observed with catalytic $AuCl_3$ (Table 1, entry 1). Interestingly, $CdCl_2 \cdot 2H_2O$ and $CuCl_2 \cdot 2H_2O$ can provide good results, implying that the carbocation intermediate was not quenched by the hydrate (Table 1, entries 2−3). Gratifyingly, we found that 20 mol % CuCl can afford 89% yield and 97% *ee*, but the analogous CuBr and CuI gave far inferior results (Table 1, entries 4−6). Eventually, it was found that 20 mol % $IrCl_3$ gave 77% yield and 94% *ee*, with both higher and lower catalyst loadings being less effective (Table 1, entries 7−9). This promising result represents the rare examples of $IrCl_3$ as a Lewis acid catalyst for organic transformations.[13] It is noteworthy that this new finding is consistent with the classification of Lewis acids on the basis of aldehyde and aldimine selectivity by Kobayashi, wherein the effective Lewis acids for this reaction such as $CuCl_2$ and CuCl are in Group B (weak and aldimine selective), while $CdCl_2$ and $IrCl_3$ are classified under Group C (inactive) in that domain.[14]

Table 1. Screening of the Lewis Acids[a]



entry	Lewis acid	*x* (mol %)	yield (%)[b]	*ee* (%)[c]
1	$AuCl_3$	100	79	77
2	$CdCl_2 \cdot 2H_2O$	50	44	86
3	$CuCl_2 \cdot 2H_2O$	50	51	93
4	**CuCl**	**20**	**89**	**97**
5	CuBr	20	53	53
6	CuI	20	38	73
7	$IrCl_3$	50	66	96
8	**$IrCl_3$**	**20**	**77**	**94**
9	$IrCl_3$	10	43	93

[a] Reactions were conducted with butyraldehyde (0.4 mmol), xanthydrol (0.1 mmol), catalyst **I** (0.01 mmol), and Lewis acids in 0.5 mL of CH_2Cl_2 at room temperature. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis on a chiral stationary phase.

(6) For representative examples, see: (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737. (b) Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. *Angew. Chem., Int. Ed.* **1981**, *20*, 207. (c) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (d) Helmchen, G.; Wierzchowski, R. *Angew. Chem., Int. Ed.* **1984**, *23*, 60. (e) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(7) (a) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582. (b) Jang, H.-Y.; Hong, J.-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (c) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (d) Sibi, M.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124.

(8) (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494. (c) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (d) Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332. (e) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. For a nonphotolytic approach, see: (f) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986.

(9) Ikeda, M.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *49*, 7289.

(10) (a) Capdevila, M. G.; Benfatti, F.; Zoli, L.; Stenta, M.; Cozzi, P. G. *Chem.—Eur. J.* **2010**, *16*, 11237. (b) Sinisi, R.; Vita, M. V.; Gualandi, A.; Emer, E.; Cozzi, P. G. *Chem.—Eur. J.* **2011**, *17*, 7404.

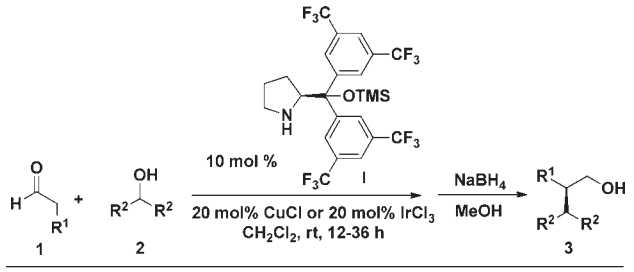
(11) (a) Liang, T.; Xiao, J.; Xiong, Z.; Li, X. *J. Org. Chem.* **2012**, DOI: 10.1021/jo2025114. (b) Xiao, J.; Zhao, K.; Loh, T. P. *Chem. Comm.* **2012**, *48*, 3548. (c) Xiao, J.; Zhao, K.; Loh, T. P. *Chem. Asian J.* **2011**, *6*, 2890. (d) Xiao, J.; Lu, Y. P.; Liu, Y. L.; Wong, P. S.; Loh, T. P. *Org. Lett.* **2011**, *13*, 876. (e) Xiao, J.; Xu, F. X.; Lu, Y. P.; Liu, Y. L.; Loh, T. P. *Synthesis* **2011**, 1292. (f) Xiao, J.; Xu, F. X.; Lu, Y. P.; Loh, T. P. *Org. Lett.* **2010**, *12*, 1220. (g) Xiao, J.; Wong, Z. Z.; Lu, Y. P.; Loh, T. P. *Adv. Synth. Catal.* **2010**, *352*, 1107. (h) Xiao, J.; Liu, Y. L.; Loh, T. P. *Synlett* **2010**, 2029. (i) Xiao, J.; Loh, T. P. *Org. Lett.* **2009**, *11*, 2876.

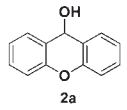
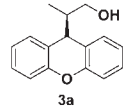
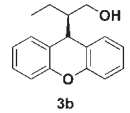
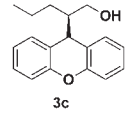
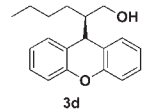
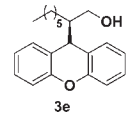
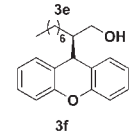
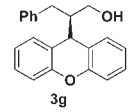
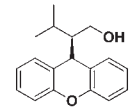
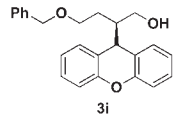
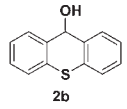
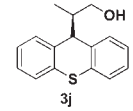
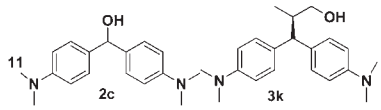
(12) (a) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (b) Mielgo, A.; Palomo, C. *Chem.—Asian J.* **2008**, *3*, 922. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(13) (a) Karamé, I.; Tommasino, M. L.; Lemaire, M. *Tetrahedron Lett.* **2003**, *44*, 7687. (b) Ding, F.; William, R.; Gorityala, B. K.; Ma, J.; Wang, S.; Liu, X. W. *Tetrahedron Lett.* **2010**, *51*, 3146.

(14) (a) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem.—Eur. J.* **2000**, *6*, 3491. For an example on the different behavior of various metallic chlorides, see: (b) Alcaide, B.; Almendros, P.; Campo, T. M. *Chem.—Eur. J.* **2008**, *14*, 7756.

Table 2. Substrate Scope[a]



entry[a]	substrates	product	$IrCl_3$ yield (%)[b]	$IrCl_3$ ee (%)[c]	CuCl yield (%)[b]	CuCl ee (%)[c]
1	 2a	 3a	94	90	95	91
2		 3b	77	97	89	97
3		 3c	75	96	92	96
4		 3d	83	95	93	96
5		 3e	82	95	92	97
6		 3f	96	95	93	95
7		 3g	63	94	91	99
8		 3h	94	98	77	97
9		 3i	70	92	84	94
10	 2b	 3j	66	94	65	94
11	 2c	3k	77	92	84	92

[a] Unless noted, reactions were conducted with aldehyde (0.4 mmol), alcohol (0.1 mmol), catalyst **I** (0.01 mmol), $IrCl_3$ or CuCl (0.02 mmol) in 0.5 mL of CH_2Cl_2 at room temperature. [b] Isolated yields. [c] The *ee* was determined by HPLC analysis on a chiral stationary phase.

With the optimized conditions in hand, the two cooperative catalytic systems, **I**/CuCl and **I**/$IrCl_3$, were employed to investigate the generality of aldehydes and activated alcohols (Table 2). Various aldehydes can be tolerated in this reaction. Both linear and bulky aldehdyes, as well as aldehydes bearing an oxygen atom, reacted with xanthydrol to produce chiral xanthene derivatives in high yields (63−96%) and excellent enantioselectivities (90−99% *ee*) (Table 1, enties 1−9), rendering this methodology highly valuable, considering the biochemical and pharmaceutical significance of xanthene derivatives.[15] Other activated alcohols, such as 9*H*-thioxanthen-9-ol (Table 1, entry 10) and bis(4-(dimethylamino)-phenyl)methanol (Table 1, entry 11) also work very well to afford the corresponding products in high yields and high levels of stereochemical control. For all these substrates, $IrCl_3$ and CuCl exhibited similar properties, affording similar yields and similar enantioselectivities.

The vital importance of ferrocene-based chiral ligands and catalysts in asymmetric catalysis[16] encouraged us to investigate the reaction of ferrocenyl(phenyl)methanol (**2d**) with aldehydes. It was found that **I**/CuCl and **I**/$IrCl_3$ fail to work for ferrocene-based activated alcohols. Eventually, we found that **I**/$InBr_3$ is an effective cooperative system for this new important class of compounds (see the Supporing Information). For instance, reaction of propionaldehyde and butyraldehyde with **2d** furnished **3l** and **3m** in higher than 90% *ee* for both diastereoisomers (Table 3, entries 1−2). Comparable results were also obtained with **3l** by use of **I**/$Zn(OTf)_2$ system. Catalyst **I** (10 mol %) with 10 mol % $Zn(OTf)_2$ can give **3l** in 88% yield with excellent enantioselectivities (94% *ee* for *anti*, 92% *ee* for *syn*) and similar diastereoselectivity (*anti*:*syn* = 47:53).

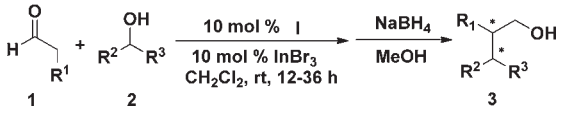
Indole skeleton is a unique structure motif ubiquitously present in a large number of biologically active natural products and pharmaceuticals.[17] Therefore, to develop new efficient methods for the synthesis of optically pure indole derivatives is of great importance for asymmetric synthesis.[18,19] Reaction of indole-based activated alcohols with aldehydes provides a facile access to a large variety of optically active carbonyl-functionalized indole derivatives, although such type of reaction is extremely rare.[5e,11b−c,19] Hence, we attempted to extend the scope to indole-based substrates. It was found that the cooperative system **I**/$InBr_3$ is an effective catalytic system for indolyl alcohols. For instance, phenyl(2-phenyl-1*H*-indol-3-yl)methanol

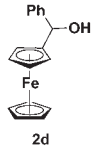
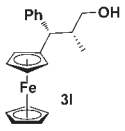
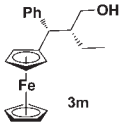
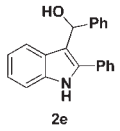
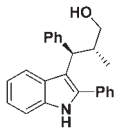
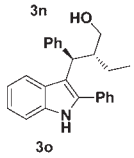
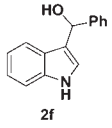
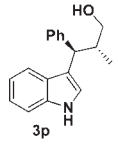
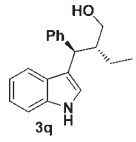
(15) (a) Poupelin, J. P.; Saint-Rut, G.; Foussard-Blanpin, O.; Narcisse, G.; Uchida-Ernouf, G.; Lacroix, R. *Eur. J. Med. Chem.* **1978**, *13*, 67. (b) Naya, A.; Sagara, Y.; Ohwaki, K.; Saeki, T.; Ichikawa, D.; Iwasawa, Y.; Noguchi, K.; Ohtake, N. *J. Med. Chem.* **2001**, *44*, 1429. (c) Ornstein, P. L.; Arnold, M. B.; Bleisch, T. J.; Wright, R. A.; Wheeler, W. J.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1919. (d) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P.-Y.; Ferguson, D. M. *J. Med. Chem.* **2006**, *49*, 2127.

(16) (a) Togni, A. *Angew. Chem., Int. Ed.* **1996**, *35*, 1475. (b) Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674. (c) Dai, L.-X.; Tu, T.; You, S.-L.; Deng, W.-P.; Hou, X.-L. *Acc. Chem. Res.* **2003**, *36*, 659. (d) Colacot, T. J. *Chem. Rev.* **2003**, *103*, 3101. (e) Miyake, Y.; Nishibayashi, Y.; Uemura, S. *Synlett* **2008**, 1747.

(17) For reviews, see: (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

Table 3. Substrate Scope[a]



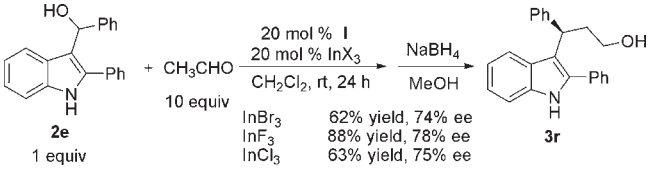
entry[a]	substrates	product	yield (%)[b]	dr (%)[c]	*ee* (%)[d]
1	 2d	 3l	99	48:52	94 *syn* 93 *anti*
2		 3m	93	48:52	98 *syn* 94 *anti*
3	 2e	 3n	70	73:27	97 *anti* 94 *syn*
4		 3o	76	63:37	96 *anti* 90 *syn*
5[e]	 2f	 3p	45	75:25	98 *anti* 98 *syn*
6		 3q	36	98:2	99 *anti* 99 syn

[a] Unless noted, reactions were conducted with aldehyde (0.4 mmol), activated alcohol (0.1 mmol), catalyst **I** (0.01 mmol), $InBr_3$ (0.01 mmol) in 0.5 mL of CH_2Cl_2 at room temperature. [b] Isolated yield. [c] The dr (*anti*:*syn*) was determined by chiral HPLC on a chiral stationary phase. [d] The *ee* (%) was determined by chiral HPLC on a chiral stationary phase, and absolute configuration was determined by comparison of chiral HPLC retention time with those reported in the literature. See the Supporting Information

(**2e**) reacted with both propionaldehyde and butyraldehyde to afford good yields and high enantioselectivities (90−97% *ee*) with good diastereoselectivities (Table 3, entries 3−4). Intriguingly, the problematic substrate (1*H*-indol-3-yl)(phenyl)methanol (**2f**), without 2-substitution, which afforded low yields and low enantioselectivities (11% *ee*) in previous report,[5d] provided excellent enantioselectivities (98% *ee* for **3p**, 99% *ee* for **3q**) and good to excellent diastereoselectivities (75/25−98/2), albeit in moderate yields.

Acetaldehyde, an active and unique aldehyde candidate in enamine catalysis,[20] can smoothly react with **2e** to furnish the product **3r** in good yields and good enantioselectivities in the presence of 20 mol % **I**/InX_3 (X = F, Cl, Br), of which InF_3 gave the best results (88% yield, 78% *ee*) (Scheme 1).

Scheme 1. Reaction of Acetaldehyde with **2e**



In summary, the unprecedented cooperative chiral secondary amine−Lewis acid systems of **I**/CuCl, **I**/$IrCl_3$, and **I**/$InBr_3$ have been discovered to catalyze the highly enantioselective intermolecular α-alkylation of aldehydes. A large variety of aldehydes and alcohols can be transformed to the desired highly functionalized aldehydes in high yields, excellent enantioselectivities and good diastereoselectivities. In particular, even the problematic and intriguing (1*H*-indol-3-yl)(phenyl)methanol and acetaldehyde can also be well-tolerated. Furthermore, the mild conditions and simple operation make this methodology very practical. Lastly, the systematic study of the synergistic catalysis[21] of a chiral secondary amine with Lewis acids paved the way for future new applications. Given the versatility of Lewis acids in electrophilic activation, we believe that these cooperative systems will trigger many new asymmetric reactions.[22]

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Supporting Information Available. Additional experimental procedures and spectrascopic data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

(18) For reviews, see: (a) Palmieri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259. (b) Loh, C. C. J.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 46. (c) Bartoli, G.; Bencivennia, G.; Dalpozzob, R. *Chem. Soc. Rev.* **2010**, *39*, 4449. (d) Zeng, M.; You, S. L. *Synlett* **2010**, *9*, 1289. For selected examples, see: (e) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4620. (f) Liang, T.; Zhang, Z.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 9734. (g) Wang, D. S.; Tang, J.; Zhou, Y. G.; Chen, M. W.; Yu, C. B.; Duan, Y.; Jiang, G. F. *Chem. Sci.* **2011**, *2*, 803. (h) Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 5558.

(19) (a) Han, B.; Xiao, Y.-C.; Yao, Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 10189. (b) Xu, B.; Guo, Z. L.; Jin, W. Y.; Wang, Z. P.; Peng, Y. G.; Guo, Q. X. *Angew. Chem., Int. Ed.* **2012**, *51*, 1059.

(20) For a review on organocatalytic reactions with acetaldehyde, see:Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4632.

(21) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633.

(22) These catalytic systems cannot work well for allylic and propargylic alcohols.

The authors declare no competing financial interest.