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Highly Enantioselective Intermolecular Alkylation of Aldehydes with Alcohols by Cooperative Catalysis of Diarylprolinol Silyl Ether with Brønsted Acid

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The catalytic enantioselective intermolecular α-alkylation of aldehydes is one of the long-standing problems in asymmetric catalysis.[1] The conventional organometallic methods are plagued by the need of preformed metal enolates, stoichiometric amounts of chiral auxiliaries, as well as difficulty in controlling the reaction with many undesirable side reactions.[2] This elusive reaction was soon deemed as "the Holy Grail" reaction for asymmetric aminocatalysis.[1b] Although List and Vignola have reported a highly enantioselective organocatalytic intramolecular version of this reaction using an alkyl halide as the alkylating agent, the corresponding intermolecular version has been proven difficult.[3] On the other hand, in situ-generated stable carbocations[4] have been employed as alternative alkylating agents to accomplish this challenging goal as pioneered by the groups of Petrini, Melchiorre, and Cozzi.[5] It was not until recently that some breakthroughs were achieved, in which high enantioselectivities were observed by using Jacobsen's hydrogen-bond catalysis through anion binding[6] and MacMillan's SOMO catalysis or photoredox catalysis combination strategy.[7] Despite these significant advances, the highly enantioselective α-alkylation of aldehydes is rare and development of new systems, which work with a wide variety of substrates still remains a great challenge.[8] With our earlier successes in employing carbocationic intermediates to perform various organic transformations[9] as well as new organocatalyst design,[10] we envisioned that highly enantioselective alkylation of aldehydes could be realized through reaction of aldehydes with stabilized carbocations, generated in situ from an activated alcohol under Lewis acidic or Brønsted acidic conditions in the presence of a chiral secondary amine catalyst. The obvious advantage of this strategy is the generation of water as the single byproduct, thereby making it an efficient, economical, and environmentally valuable process (Scheme 1).

However, designing such a catalytic system is further complicated by the susceptibility of a Lewis basic amine catalyst towards an unproductive alkylation reaction and self-quenching reaction with the acid, deactivation of the acid through the reaction with the water byproduct, as well as potentially severe racemization of the product. Despite the report that diarylprolinol silyl ether[11] was inefficient for this type of reaction,[5,8a] we envisaged the use of cooperative catalysis by combining Lewis or Brønsted acid catalysis with organocatalysis to solve the reactivity problem.[12] Herein, we report the efficient cooperative catalytic systems, involving diarylprolinol silyl ether **I** with Brønsted acids to effect the highly enantioselective α-alkylation of aldehydes.

Initially, the model reaction between butyraldehyde and xanthydrol was carried out in the presence of different metal catalysts (20–50 mol%) to screen for a suitable catalytic system. Expectantly, the control reaction in dichloromethane using **I** without any acid did not give the desirable

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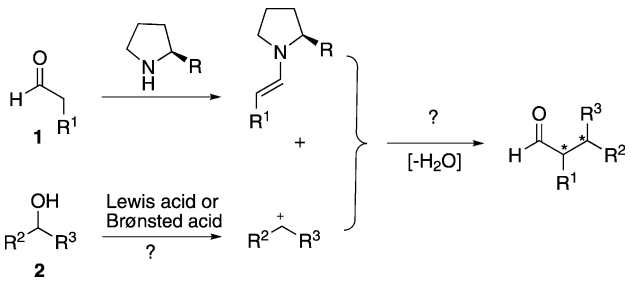
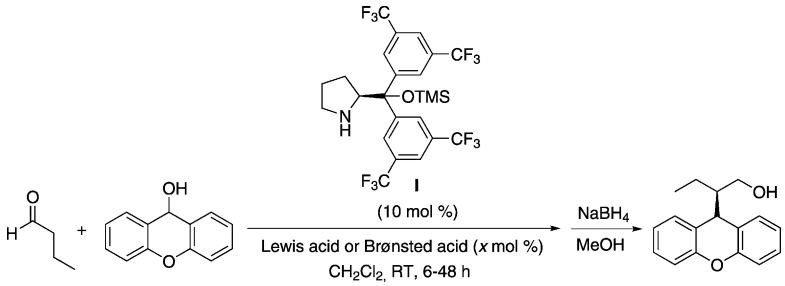


Scheme 1. Asymmetric alkylation of aldehydes with alcohols by cooperative catalysis.

Table 1. Screening of the acids.

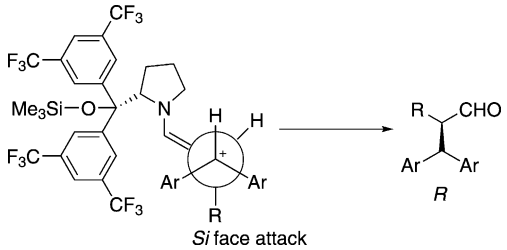


Entry[a]	Acids	x [mol %]	t [h]	Yield [%][b]	*ee* [%][c]
1	–	0	12	0	–
2	$InCl_3$	50	12	0	–
3	$FeCl_3$	50	12	0	–
4	$LaCl_3$	50	12	0	–
5	$In(OTf)_3$	50	12	0	–
6	$Zn(OTf)_2$	50	12	0	–
7	$La(OTf)_3$	50	12	0	–
8	CAN	50	12	24	33
9	$CuCl_2$	50	12	59	86
10	CSA	10	6	trace	–
11	$C_6H_5CO_2H$	10	48	trace	–
12	TFA	10	6	56	79
13	*p*-TSA	10	6	48	94
14	2-NO_2-$C_6H_4CO_2H$	10	24	72	93
15	3-NO_2-$C_6H_4CO_2H$	10	12	67	95
16	4-NO_2-$C_6H_4CO_2H$	10	8	80	90
17	4-CF_3-$C_6H_4CO_2H$	10	6	64	94
18	$(HO)_3C_6H_2CO_2H$[d]	10	6	92	95
19	$(HO)_3C_6H_2CO_2H$[e]	5	12	91	95
20	$(HO)_3C_6H_2CO_2H$[f]	2	15	83	96

[a] Reactions were conducted with butyraldehyde (0.4 mmol), xanthydrol (0.1 mmol), catalyst **I** (0.01 mmol), and acid in CH_2Cl_2 (0.5 mL) at room temperature. [b] Yield of isolated product. [c] *ee* was determined by chiral HPLC on a chiral stationary phase. [d] 2,3,4-Trihydroxybenzoic acid. [e] catalyst **I** (5 mol %) was used. [f] Catalyst **I** (2 mol %) was used. CAN = ceric ammonium nitrate.

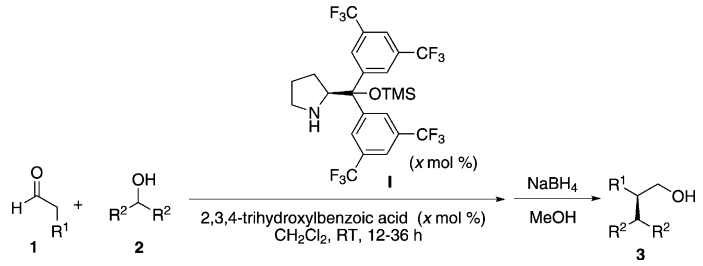
product (Table 1, entry 1). Subsequently, a wide variety of commonly used Lewis acids were added in addition to **I**. It was found that the commonly used Lewis acids such as indium salts, lanthanide complexes, and zinc complexes are all ineffective for this transformation (Table 1, entries 2–8). It is interesting to note that $CuCl_2$ catalyzed the reaction to afford the desired product in good enantioselectivity, albeit in moderate yield (Table 1, entry 9). Next, we turned our attention to examine if Brønsted acids can work well with organocatalyst **I.** During our screening of a different combination of Brønsted acids with **I**, it was found that good yields and high enantioselectivities (90 %–95 % *ee*) could be obtained for most of the electron-deficient benzoic acids (Table 1, entries 14–17). However, no reaction was observed with camphorsulfonic acid (CSA) and benzoic acid (Table 1, entries 10–11). Trifluoroacetic acid (TFA) and *p*-TSA can also afford satisfactory results (Table 1, entries 12–13). Among them, 2,3,4-trihydroxybenzoic acid was found to give the best results and the catalyst loading of organocatalyst **I** and acid could be decreased to as low as 2 mol % without compromising the reactivity and enantioselectivity (Table 1, entries 18–20). Therefore, our method provides the successful example of a pyrrolidine-based catalyst, capable of effecting the highly enantioselective asymmetric alkylation of aldehydes and overcomes the fallacy of the failure of pyrrolidine-based catalysts in this elusive reaction.[5,8a]

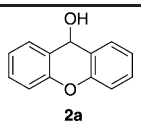
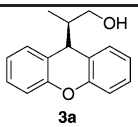
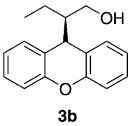
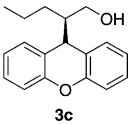
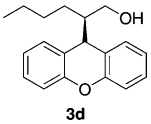
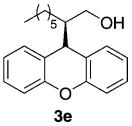
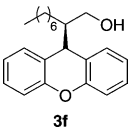
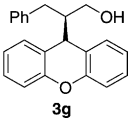
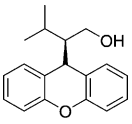
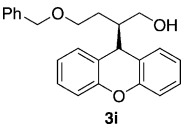
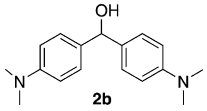
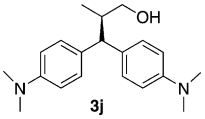
With the optimized conditions in hand, we proceeded to examine the substrate scope using **I**/2,3,4-trihydroxybenzoic acid (2–5 mol %) as the catalytic system in the reaction of xanthydrol with different aldehydes (Table 2, entries 1–9). Gratifyingly, in all cases, the desired products were obtained in good to high yields with excellent enantioselectivities (91–98 % *ee*), thus making this methodology highly valuable in view of the biochemical and pharmaceutical importance of xanthene derivatives.[13] With propionaldehyde, bis(4-(dimethylamino)phenyl)methanol **2b**[14] gave the desired product **3j** in 87 % yield and 91 % *ee* (Table 2, entry 10). Given the vital importance of ferrocene-based chiral ligands and catalysts in asymmetric catalysis[15] and the key role of the indole skeleton in natural products and pharmaceutical chemisty,[16] we proceeded to investigate the reactions of ferrocene- and indole-based substrates. The results are summarized in Table 3. To our surprise, the catalytic system **I**/2,3,4-trihydroxybenzoic acid did not work for ferrocene- and indole-based substrates. Fortunately, it was found that **I**/TfOH (TfOH = trifluouromethanesulfonic acid), on the other hand, was an effective catalytic system for these two important substrates. For ferrocene-based substrates, high yields and *ee* were observed (**3k** and **3l**). In sharp comparison, for Cozzi's system, 90 mol % of MacMillan's catalyst was necessary to drive the reaction to completion and the product was obtained in low yield and moderate *ee*.[5b] To our delight, for indole-based substrates, the **I**/TfOH system can also catalyze reaction of substrate **2d** (without 2-substitution) with aldehydes to provide **3m** and **3n** in good yields (70 % yield and 69 % yield, respectively), excellent enantioselectivities (97–99 % *ee*), and excellent diastereoselectivities (*anti*/*syn* = 93:7 for **3m**, *anti*/*syn* = 92:8 for **3n**). In strong contrast with Melchiorre's report on the asymmetric α-alkylation of aldehydes through vinylogous iminium ion intermediates generated by indole derivatives,[17] substrate **2d** gave the product in only 11 % *ee* and



Scheme 2. Transition-state model for asymmetric alkylation of aldehydes.

Table 2. Substrate scope.



Entry[a]	Substrates	Product	x [mol%]	t [h]	Yield [%][b]	ee [%][c]
1	 2a	 3a	2	36	50	91
2		 3b	2	15	83	96
3		 3c	2	12	84	96
4		 3d	2	12	85	97
5		 3e	2	12	92	96
6		 3f	2	12	82	96
7		 3g	2	12	80	98
8		 3h	5	24	85	98
9		 3i	5	12	76	96
10	 2b	 3j	5	12	87	91

[a] Unless otherwise noted, reactions were conducted with aldehyde **1** (1 mmol), alcohol **2** (0.25 mmol), catalyst **I** (0.005 mmol), 2,3,4-trihydroxybenzoic acid (0.005 mmol) in CH_2Cl_2 (1 mL) at room temperature. [b] Yield of isolated product. [c] *ee* was determined by chiral HPLC on a chiral stationary phase. The absolute configuration was determined by comparison of optical rotations and chiral HPLC retention times of the aldehyde product with those reported in the literature (Refs. [5] and [8]).

pyrrolidine-based chiral secondary amines did not work at all.[5a]

The stereoinduction could be rationalized by the following transition-state model (Scheme 2). The bulky silyl ether functional group efficiently shielded the *Re* face to force the in situ-generated carbocation attack from the *Si* face to afford the desired product with *R* configuration

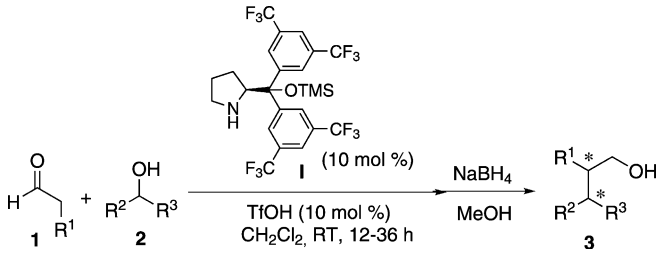
In summary, we have developed two cooperative systems, **I**/2,3,4-trihydroxybenzoic acid and **I**/TfOH, to circumvent the elusive asymmetric intermolecular α-alkylation of aldehydes. Both of these unprecedented systems could afford the desired enantioenriched functionalized aldehydes in high yields, excellent enantioselectivities, and good diastereoselectivities with broad substrate scope. Particularly, the ferrocene derivatives and indole derivatives could be synthesized in good yields and excellent enantioselectivities by use of our catalyst system **I**/TfOH; this makes these methods extremely useful in asymmetric synthesis and natural product chemistry.

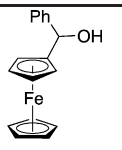
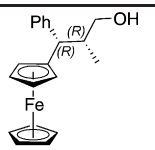
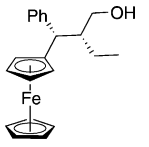
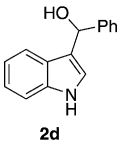
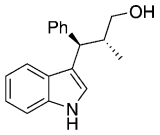
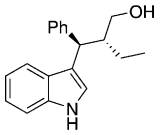
Experimental Section

General Procedure for the Asymmetric α-Alkylation of Aldehydes with Alcohols

To a solution of alcohol **2** (0.25 mmol) in 1 mL CH_2Cl_2 was added catalyst **I** (0.005 mmol) and 2,3,4-trihydroxybenzoic acid (0.005 mmol) prior to the addition of aldehyde (1 mmol). The resulting solution was stirred at room temperature for the indicated time. Upon the completion of reaction, as monitored by TLC, MeOH (1 mL) was added. $NaBH_4$ was then cautiously added to the yellow solution and stirred at room temperature for 0.5 h. The reaction was subsequently quenched with water (1 mL) and HCl (1 M) was added. The organic phase was separated and the aqueous solution was extracted with ethyl acetate (2 mL × 3). The combined organic

Table 3. Substrate scope.



Entry[a]	Substrates	Product	Yield [%][b]	d.r. [%][c]	*ee* [%][d] syn/anti
1	 **2c**	 **3k**	60	50:50	95 *syn* 92 *anti*
2		 **3l**	93	48:52	98 *syn* 94 *anti*
3	 **2d**	 **3m**	70	93:7	99 *anti* 97 *syn*
4		 **3n**	69	92:8	99 *anti* 99 *syn*

[a] Reactions were conducted with aldehyde **1** (1 mmol), alcohol **2** (0.25 mmol), catalyst **I** (0.025 mmol), and TfOH (0.025 mmol) in CH_2Cl_2 (1 mL) at room temperature. [b] Yield of isolated product. [c] Diastereomeric ratio (*anti*:*syn*) was determined by chiral HPLC on a chiral stationary phase. [d] *ee* was determined by chiral HPLC on a chiral stationary phase and absolute configuration was determined by comparison of chiral HPLC retention time of the aldehyde product with those reported in the literature (Ref. [5]). TfOH = trifluouromethanesulfonic acid.

phases were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the resulting yellow oil was purified by preparative chromatography or column chromatography (hexane/ethyl acetate = 4:1) to afford the desired product **3**. Both the enantiomeric excess and diastereomeric ratios were determined by chiral HPLC using AS-H, AD-H, or OD-H columns.

Acknowledgements

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Keywords: alkylation · brønsted acid · cooperative catalysis · enantioselectivty · organocatalysis

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