Organocatalysis

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Asymmetric Dual-Reagent Catalysis: Mannich-type Reactions Catalyzed by Ion Pair**

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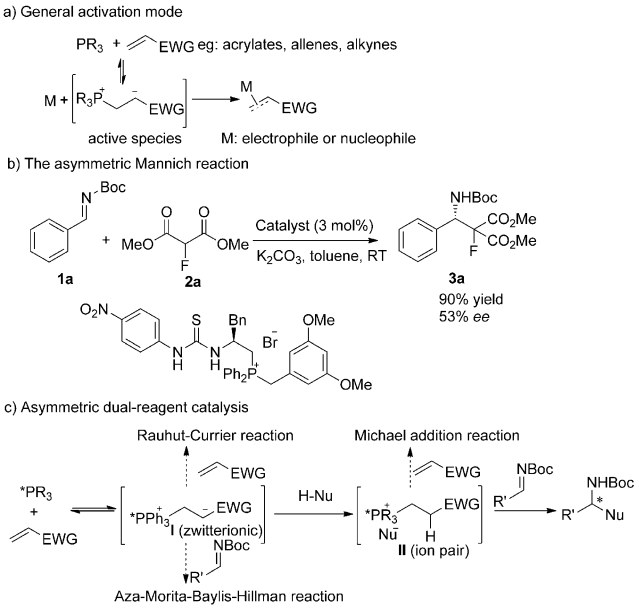
Abstract: *The combination of a new bifunctional phosphine and an acrylate generate a zwitterion in situ and it serves as an efficient catalyst for asymmetric reactions through a homogeneous ion-pairing mode. This new catalytic system has been successfully applied to Mannich-type reactions to give excellent results and it demonstrates a broad substrate scope. Such reactivity is not accessible with general organophosphine catalytic modes. Preliminary investigations into the mechanism are also presented.*

Over the past decades, chiral organophosphine catalysis[1] has demonstrated high catalytic efficiencies in a range of reactions such as the (aza)Morita–Baylis–Hillman reaction,[2] Rauhut–Currier reaction,[3] Michael (or γ) addition reaction,[4] and various annulations.[5] As a general concept, the catalysis and selectivity mediated by nucleophilic phosphine in these reactions have to be initiated by the addition of the phosphine to an electrophilic reactant to form a zwitterion, which then behaves as a key nucleophile or Brønsted base to participate in the catalytic cycle (Scheme 1 a). Limited by this routine activation mode, the chiral phosphine catalysis has only been applied to reactions with activated alkenes, allenes, or alkynes. As the reaction does not involve an electrophile that is capable of forming a zwitterion with the phosphine catalyst, a new activation mode has to be developed. In an earlier report, Tian and co-workers reported racemic dual-reagent-catalyzed Henry reactions in which electron-deficient alkenes served as only the precursor to the catalytic zwitterion intermediate, thus enabling the use of aldehydes as electrophiles in the reaction.[6] Such a dual-reagent strategy enables the use of other electrophilic reaction partners and can further expand the reaction scope of the organophosphine catalysis. However, to the best of our knowledge, an asymmetric version of this kind of dual-reagent organocatalysis remains unexplored.



Scheme 1. Different activation methods. a) General activation mode catalyzed by nucleophilic phosphines. b) The asymmetric Mannich reaction catalyzed by phase-transfer catalysis with chiral phosphonium salt. c) The novel activation mode of this work.

Our group has focused on the development of amino-acid-derived chiral organocatalysts and their applications in asymmetric catalysis to construct various molecular scaffolds useful in organic synthesis and medicinal chemistry.[7] Particularly, we have been interested in the synthesis of chiral fluorinated compounds because of their increasing popularity in various fields including pharmaceutical and agricultural chemistry. In this pursuit, we became interested in realizing an asymmetric Mannich-type reaction between dimethyl 2-fluoromalonate and N-Boc imines,[8] a reaction which would give potentially useful chiral fluorinated amino acid derivatives (Scheme 1 b). However, asymmetric phase-transfer catalysis (PTC) using a chiral phosphonium catalyst, previously developed by us for highly efficient aza-Henry reaction, provided a moderate enantioselectivity, probably because of the fast background reaction under the strongly basic conditions of PTC. In light of this, we assumed the asymmetric dual-reagent organocatalysis might provide mildly basic conditions for deprotonation of dimethyl 2-fluoromalonate for better enantiocontrol. Herein, we report on a catalyst combination consisting of a chiral phosphine catalyst, derived

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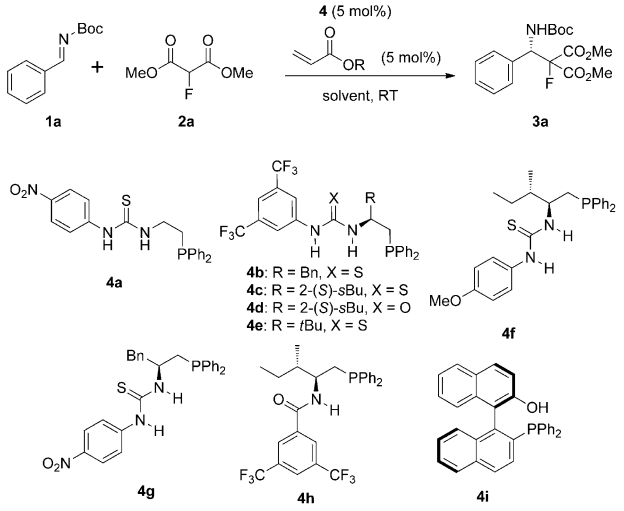
Table 1: Optimization of conditions and evaluation of chiral catalysts.[a]



Entry	Catalyst	R	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	Me	toluene	92	–
2	**4b**	Me	toluene	90	85
3	**4c**	Me	toluene	93	82
4	**4d**	Me	toluene	94	56
5	**4e**	Me	toluene	92	78
6	**4f**	Me	toluene	91	78
7	**4g**	Me	toluene	92	90
8	**4h**	Me	toluene	50	10
9	**4i**	Me	toluene	trace	nd
10	**4g**	Bn	toluene	86	84
11	**4g**	*t*Bu	toluene	82	86
12	**4g**	Me	$CHCl_3$	90	88
13	**4g**	Me	CH_2Cl_2	93	92
14	**4g**	Me	CH_3CN	68	70
15	**4g**	Me	Et_2O	95	89
16[d]	**4g**	Me	CH_2Cl_2	90	92

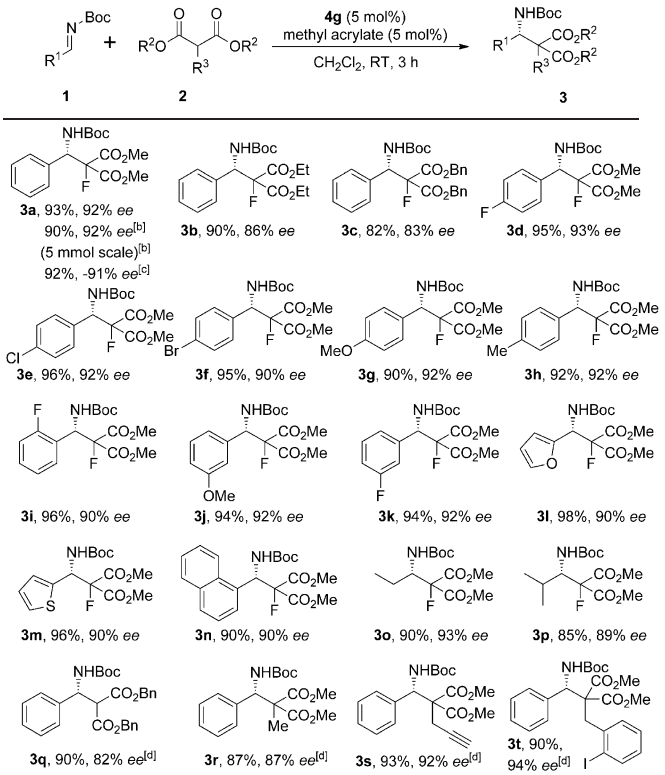
[a] Unless otherwise noted, the reactions were performed with **1a** (0.12 mmol), **2a** (0.1 mmol), and acrylates (5 mol%) in the presence of the chiral phosphines **4** (5 mol%) in solvent (1 mL) at room temperature for 3 h. [b] Yield of isolated **3a**. [c] The *ee* value was determined by HPLC analysis using a chiral stationary phase. [d] Reaction was performed at 0°C.

from L-phenylalanine and methyl acrylate, for this reaction, thus providing excellent yield and enantioselectivity while avoiding the sequestration of the key zwitterion through three possible competitive reactions such as the aza-Morita–Baylis–Hillman reaction, Rauhut–Currier reaction, and Michael addition reaction (Scheme 1c).

Initially, we performed the catalyst evaluation on the model reaction between the N-Boc imine **1a** and dimethyl 2-fluoromalonate (**2a**; Table 1). Although preliminary experiments using a combination of PPh_2Me (5 mol%) and methyl acrylate (5 mol%) as the catalyst only gave the product with 20% yield, the use of the new racemic bifunctional thiourea-phosphine **4a**, instead of PPh_2Me, under the same reaction conditions provided **3a** with 92% yield (entry 1), thus implying the importance of hydrogen-bonding interactions in this reaction. Encouraged by this result, a series of chiral bifunctional catalysts derived from α-amino acids were synthesized and evaluated in the reaction. Of the several catalysts screened, the chiral skeleton derived from L-phenylalanine seemed most favored in terms of enantioselectivity (entry 2). The thiourea moiety of these catalysts seemed crucial for both the reactivity and enantiocontrol, and when replaced by urea (**4d**) or an acyl group (**4h**) led to inferior results (entries 4 and 8). To our delight, the thiourea catalyst **4g**, bearing a cheaper 4-nitrophenyl group turned out to be the optimum one for this reaction. The acrylate component of the catalyst was also screened. The use of benzyl acrylate or *tert*-butyl acrylate failed to improve the either yield or enantioselectivity (entries 10and 11).[9] Further examination of the solvents and temperature showed that the reaction run in CH_2Cl_2 at room temperature was the best (entries 12–16). Notably, the (*R*)-binol-derived bifunctional catalyst **4i** was also investigated,[2c] however, no desired product was observed.

With the optimized reaction conditions in hand, the generality of the asymmetric dual-reagent catalysis in the Mannich-type reaction was then investigated (Table 2). Of the different 2-fluoromalonates, diethyl- or dibenzyl-substituted 2-fluoromalonates provided inferior results (**3b,c**). With **2a**, a series of substituted aromatic N-Boc imines, including

Table 2: Asymmetric Mannich reaction under the dual-reagent catalysis.[a]



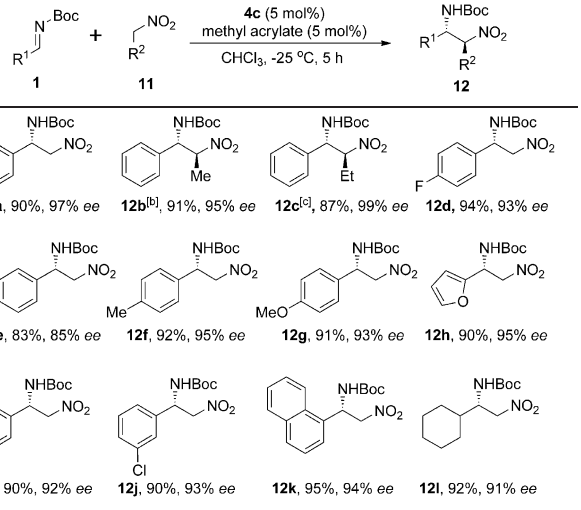
[a] Unless otherwise noted, the reactions were carried out with **1** (0.12 mmol), **2** (0.1 mmol), and methyl acrylate (5 mol%) in the presence of **4g** (5 mol%) in CH_2Cl_2 (1 mL) at RT for 3 h. Yields are those of isolated **3**. The *ee* values were determined by HPLC analysis using a chiral stationary phase. [b] The gram-scale experiment was carried out with 6 mmol **1a** and 5 mmol **2a** and **4g** (5 mol%) in CH_2Cl_2 at 0°C for 10 h. [c] The enantiomer of **4g** (5 mol%) was used. [d] Reaction at 0°C for 24 h.

one having a heteroaryl moiety, exhibited remarkably high reactivity (90–98% yield) and enantioselectivity (90–93% *ee*) regardless of the electronic nature and steric effects of the substituents on the aryl groups (**3a**, **3d–n**). Notably, a gram-scale reaction of **1a** and **2a** was also carried out to furnish 1.6 grams of the desired product **3a** in 90% yield upon isolation and 92% *ee* under similar reaction conditions. Also of note is that the enantiomer of **3a** could also be obtained in a similarly high yield and enantioselectivity by using the enantiomer of **4g** as the catalyst; *ent*-**4g** could be easily prepared from D-phenylalanine. In addition, challenging aliphatic imines also worked very well under the reaction conditions, thus furnishing the corresponding products (**3o**,**p**) in excellent enantioselectivities. Moreover, this catalytic system can also be extended to simple nonfluorinated malonates which have a higher pK_a value relative to that of **2a**, but a prolonged reaction time was required (**3q–t**).

To illustrate the utility of the reaction, some useful transformations of the products **3a**, **3s**, and **3t** were performed as shown in Figure 1. The one-step reduction of **3a** by $NaBH_4$ could be run on a gram scale to give the synthetically valuable chiral α-fluorine-β-amino alcohol **5** in high yield while maintaining the optical purity.[10] Further transformation of **5** by treatment with triphosgene gave the compound **6**. The absolute configuration of **3a** was determined to be *S* by X-ray crystallographic analysis of **6** (see Table S1 in the Supporting Information)[11] and the other products were determined by analogy. Alternatively, **5** could be easily protected with TsCl to give the synthetically useful monofluorinated compound **7** in high yield and *ee* value. As a key structural element in natural alkaloids and bioactive molecules, the tetrahydroquinoline **8** was easily synthesized by a cross-coupling reaction from **3t** with high yield and *ee* value. Importantly the azido glycoside **9** could also be modified by **3s** with a simple click reaction.

To further test the potential of the asymmetric dual-reagent catalyst system in the synthesis of chiral amino compounds, we then applied it to the aza-Henry reaction between N-Boc imines and nitroalkanes. The aza-Henry reaction is an important method for the preparation of chiral diamines in organic synthesis.[12] After screening several reaction parameters such as catalyst, solvent, and temperature, the optimum reaction conditions were established as 5 mol% of **4c** and methyl acylate in $CHCl_3$ at −25 °C for 5 hours (for details, see the Supporting Information). Table 3

Table 3: The scope of the asymmetric aza-Henry reactions.[a]



[a] The reactions were carried out with **1** (0.1 mmol), **11** (0.2 mmol), and methyl acrylate (5 mol%) in the presence of **4c** (5 mol%) in $CHCl_3$ (1 mL) at −25 °C for 5 h. Yields are those of isolated **12**. The *ee* values were determined by HPLC analysis. [b] d.r. = 10:1 as determined by ^{1}H NMR analysis. [c] d.r. = 15:1 as determined by ^{1}H NMR analysis.

summarizes the substrate scope study, which revealed that the reaction worked quite well with both nitroethane and nitropropane to furnish the corresponding products with excellent *ee* values and high diastereoselectivities. Similar to the reaction with dimethyl 2-fluoromalonate, in general, N-Boc imines with electronically and sterically different aromatic groups, including heteroaryl and aliphatic ones, were all well tolerated in this reaction to provide the corresponding products in excellent yields and enantioselectivities.

To get some insight into this asymmetric dual-reagent catalytic system, several control experiments were carried out (Figure 2 a–d). First, we performed ^{31}P NMR and mass spectroscopy analysis of **4g** and methyl acrylate in CH_2Cl_2 (see the Supporting Information), and observed formation of the zwitterion intermediate **A** as a new P NMR chemical shift was generated at $\delta = 27$ ppm. The presence of **A** was also confirmed by ESI-MS with a single peak (m/z for $(M+H)^+$: 586.2) and consistent with previous related studies.[4f,13] Moreover, when the nucleophile **2a** was mixed with the above solution of **4g** and methyl acrylate, a new single resonance appeared at $\delta = 26$ ppm thus suggesting the adduct of **4g** and methyl acrylate is converted into a new species, which we propose to be the ion-pair **B** (Figure 2 e).[14]

Subsequent efforts were directed at shedding some light on the stereochemical process of the reaction. When mon-

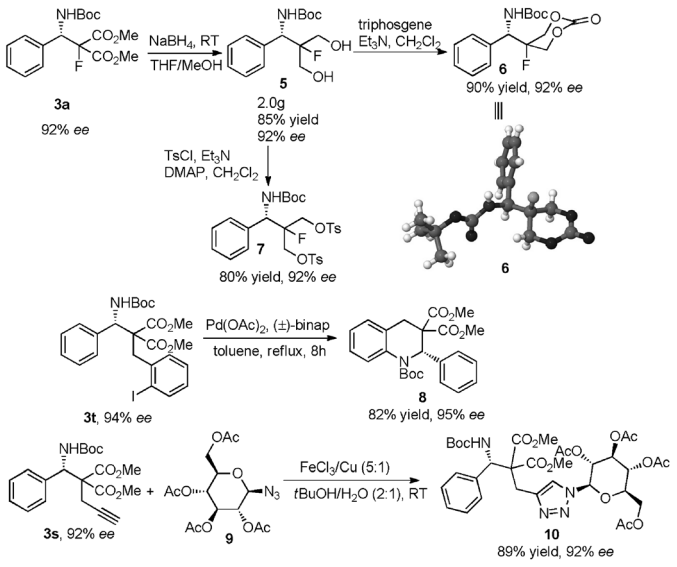


Figure 1. Representative transformations.

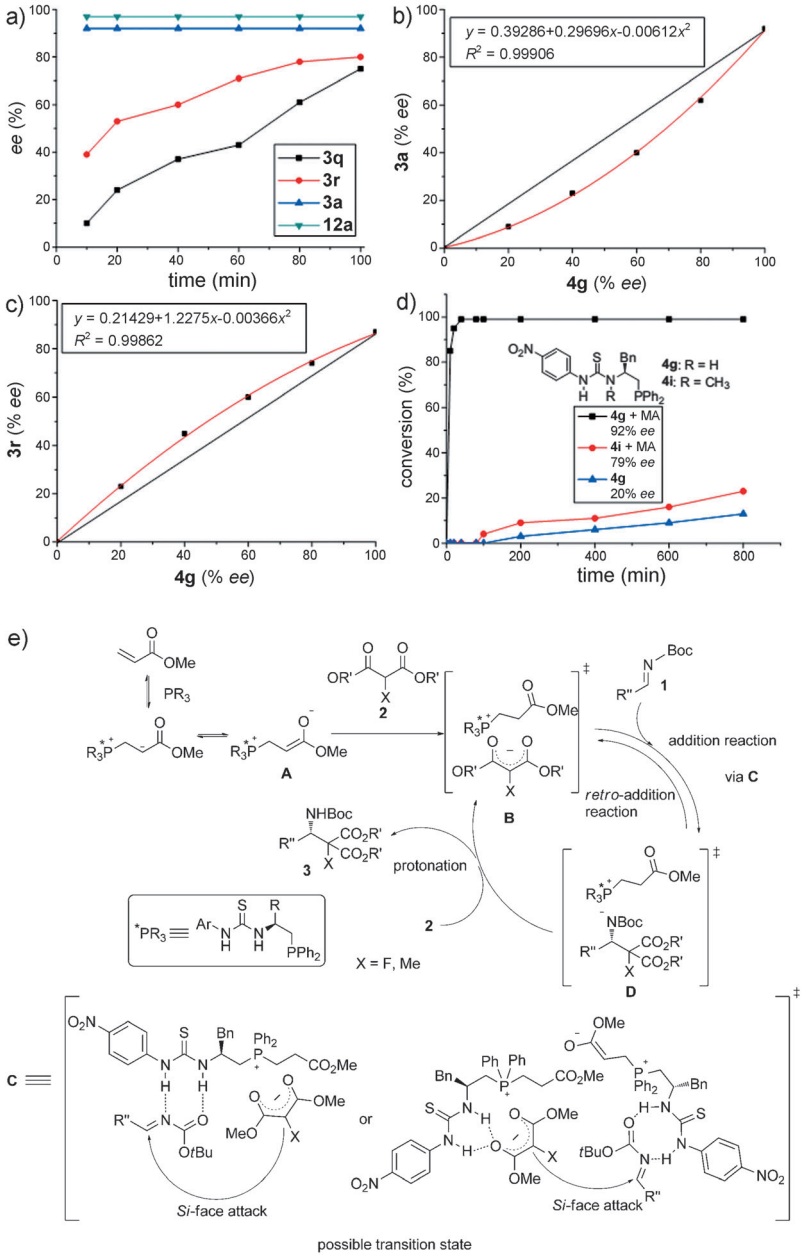


Figure 2. Mechanism study. a) Real-time monitoring of the *ee* values of the reactions by HPLC analysis using a chiral stationary phase. b,c) Nonlinear effects observed for **3a** and **3r**. d) Comparison of reaction rates and enantioselectivities of **3a** with the catalysts **4g** and **4i** as determined by ^{19}F NMR analysis of **3a**. The reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), and the catalyst (5 mol%) in CH_2Cl_2 at room temperature. e) Plausible reaction pathway. MA = methyl acrylate.

itoring the enantioselectivity of the reaction in real time by HPLC analysis using a chiral stationary phase (Figure 2a), we observed that the *ee* values of **3a** and **12a** showed no dependence on the reaction time while the *ee* values of **3q** and **3r** increased as the reaction proceeded. We assume that the addition to the imine is reversible, so the retro-Mannich reaction could racemize the newly generated stereogenic center if the final protonation step by removal of a proton from the corresponding reagents **2a**, **2q**, **2r**, or **11a** is not fast enough (rate-determining step). Moreover, because of the lower pK_a values of **2a** (or nitromethane **11a**), the proton transfer from **2a** (or **11a**) to the ion-pair **D** corresponding to **3a** (or **12a**) would be much faster than the proton transfer from either **2q** or **2r** to the anion **D** corresponding to **3q** or **3r**. The nonlinear effects of the corresponding reactions also showed some interesting differences (Figure 2b,c). The reaction of **2a** leading to **3a** had a negative nonlinear effect while the reaction of dimethyl 2-methylmalonate leading to **3r** showed a positive nonlinear effect, which suggests more than one molecule of the catalyst might be involved in the carbon–carbon bond-formation step. Moreover, control experiments indicated that both the hydrogen-bonding donor (thiourea moiety) and methyl acrylate are indispensable for achieving excellent yield and enantioselectivity (Figure 2d).

Based on the above experimental results and previous relevant studies, a possible mechanism for the reaction is outlined in Figure 2e. Firstly the chiral phosphine adds to the methyl acrylate to form the phosphonium enolate **A**, which, as a mild Brønsted base, is trapped by the malonate **2** to generate the ion-pair **B**, followed by the reaction with the imine **1** through the intermediates **C** and **D** and finally by proton exchange to produce the product **3** and regenerate the ion-pair **B**. At present we do not exactly know about the interaction between the catalyst and the substrates, a possible transition state **C** to control the stereoselectivity is proposed, and the further mechanistic studies will be explored.

In summary, we have developed a new asymmetric dual-reagent catalyst system composed of an amino-acid-derived bifunctional thiourea-phosphine and methyl acrylate. The catalyst combination demonstrates high catalytic efficiency in the nucleophilic additions of dimethyl 2-fluoromalonates or nitroalkanes to N-Boc imines, thus affording the desired products in excellent yields and enantioselectivity. Mechanistic studies shed some light on the relationships between catalyst/substrate structures and catalytic efficiency/enantiocontrol. These new findings have expanded the application of the asymmetric nucleophilic phosphine catalysis and hold great promise for application to other related reactions.

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