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Enantioselective Direct Mannich Reactions of Cyclic β-Ketoesters Catalyzed by Chiral Phosphine via a Novel Dual-Reagent Catalysis

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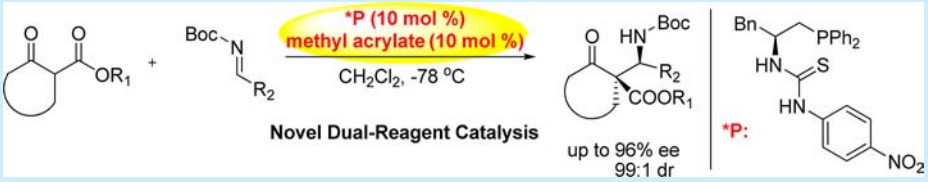
Supporting Information

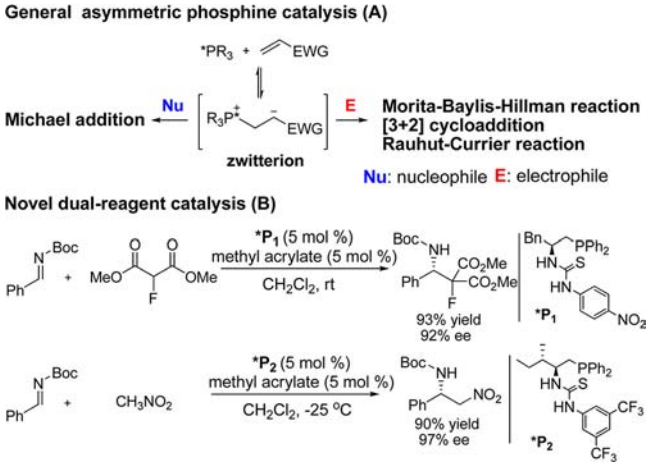


ABSTRACT: A combination of an amino acid derived chiral phosphine catalyst and methyl acrylate efficiently catalyzed the direct Mannich reaction of cyclic β-ketoesters and *N*-Boc-aldimines. The dual-reagent catalysis was presumed to function through the formation of a zwitterion, which catalyzed the reaction with excellent stereocontrol via a hydrogen-bonding assisted chiral ion-pair pathway.

Organophosphorus compounds are widely used in synthetic organic chemistry.[1] In the past 10 years, reports of chiral phosphines as nucleophilic catalysts have grown significantly.[2] In a general catalysis mode, the reaction of nucleophilic phosphines and electron-deficient alkenes can rapidly proceed to generate stable zwitterions, via Michael-type addition.[3] The zwitterions can then react with suitable electrophiles such as electron-deficient alkenes (the Rauhut−Currier reaction),[4] allenes (cycloaddition),[5] or aldehydes (the Morita−Baylis−Hillman reaction)[6] to afford various useful products (Scheme 1A). The electron-deficient alkenes that participate in the catalysis are finally transformed into the products, and thus such a catalysis mode is limited to reactions involving electron-deficient alkenes, allenes, or alkynes. Therefore, the investigation of other types of reactions by asymmetric phosphine catalysis is worthy of being further developed.[7]

Recently our group has developed chiral phosphine catalyzed Mannich-type reactions of dimethyl 2-fluoromalonates or nitroalkanes to *N*-Boc imines, via asymmetric dual-reagent catalysis through in situ generated zwitterions formed from the phosphine catalyst and methyl acrylate.[8] This novel catalytic strategy exhibited high efficiency and an excellent degree of enantiocontrol in creating products with one chiral center (Scheme 1B). As a continued study, we became very interested in testing both the enantio- and diastereocontrolling capacity of the dual-reagent catalysis in reactions that would generate products bearing multiple chiral centers. The direct asymmetric Mannich reaction of a β-ketoester with an *N*-Boc imine was selected for investigation, due to the high potential of the resultant chiral product for the syntheses of pharmaceutical and agrochemical molecules. Previously, the asymmetric Mannich reactions of β-ketoesters have been realized by using organocatalysis with cinchona alkaloid-derived bifunctional organocatalysts containing thiourea functionality[9] or metal catalysis.[10] In both cases, relatively long reaction times, ranging from 10 to 100 h, are often required under the corresponding optimal temperatures. Herein, we wish to report a highly efficient catalytic enantioselective Mannich reaction of β-ketoesters. By using the combination of amino acid based bifunctional chiral phosphine-thiourea catalysts and methyl acrylate as the catalyst,

Scheme 1. Asymmetric Reactions Catalyzed by Chiral Phosphine (A: General Asymmetric Phosphine Catalysis; B: Novel Dual-Reagent Catalysis)



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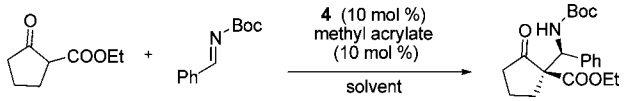
highly enantioenriched molecules containing adjacent quaternary and tertiary stereocenters could be obtained within 1 h.

In a model investigation, the reaction between ethyl 2-oxocyclopentanecarboxylate (**1a**) and *N*-Boc-benzaldimine (**2a**) was evaluated (Table 1). When the reaction was performed in toluene at room temperature in the presence of bifunctional chiral phosphine catalysts **4a**, **4b**, or **4c** derived from L-*tert*-butyl-leucine, the reaction did not proceed to full conversion even after an extended reaction time. Better results came with the catalyst **4a** bearing a thiourea, which afforded the desired product **3a** with 4.5:1 dr and 51% ee (Table 1, entries 1–3). So next, with the thiourea part in place, four additional chiral phosphine catalysts derived from phenylalanine and isoleucine were evaluated. It is notable that the chiral phosphine catalysts derived from phenylalanine improved both the enantio- and diastereoselectivity (Table 1, entries 4–7). Catalyst **4f** with the strongly electron-withdrawing nitro group at the para position of the phenyl group of the thiourea moiety turned out to be the best one. The reactions were finished in 5 min and gave the desired products in good yield and high diastereoselectivity. On the occasion that ethyl acrylate was used, instead of methyl acrylate, similar results were obtained (Table 1, entry 8).

Table 1. Screening of Chiral Catalysts for the Asymmetric Mannich Reaction of 1a and 2a[a]



1a 2a 3a

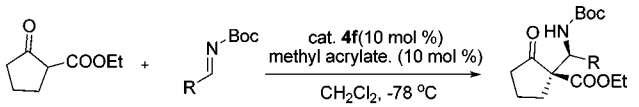
entry	cat.	solvent	temp/°C	t/min	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**4a**	toluene	rt	10	62	82:18	51
2	**4b**	toluene	rt	10	65	88:11	7
3	**4c**	toluene	rt	10	73	68:32	49
4	**4d**	toluene	rt	10	65	79:21	54
5	**4e**	toluene	rt	10	67	79:21	56
6	**4f**	toluene	rt	5	85	92:8	78
7	**4g**	toluene	rt	5	80	93:7	72
8[e]	**4f**	toluene	rt	5	83	91:9	76
9	**4f**	toluene	−20	10	91	94:6	83
10	**4f**	CH_2Cl_2	−20	10	92	94:6	88
11	**4f**	Et_2O	−20	10	91	94:6	78
12	**4f**	$CHCl_3$	−40	15	83	95:5	92
13	**4f**	CH_2Cl_2	−40	15	85	95:5	92
14	**4f**	CH_2Cl_2	−78	20	83	97:3	95
15[f]	**4f**	CH_2Cl_2	−78	30	83	98:2	96
16[g]	**4f**	CH_2Cl_2	−78	90	90	96:4	93

[a]Reactions were carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and acrylate (0.01 mmol) in the presence of chiral phosphine **4** in solvent (0.5 mL) at the specified temperature. [b]Isolated yields of **3a**. [c]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [d]The ee value was determined by chiral HPLC analysis. [e]Ethyl acrylate was used instead of methyl acrylate. [f]The reaction was carried out in CH_2Cl_2 (1 mL). [g]The reaction was carried out with 5 mol % of **4f** and 5 mol % of methyl acrylate in CH_2Cl_2 (1 mL). Boc = *tert*-butoxycarbonyl, Bn = benzyl.

Next, we investigated the effect of solvent and temperature on the Mannich reaction. At lower temperature (−20 °C), the reactions in toluene, DCM, and Et_2O gave the products in higher yields. Especially in DCM, an improved enantioselectivity was also observed (Table 1, entries 9–11). The temperature could be even lowered to −40 °C and −78 °C without losing the reaction efficiency. Excellent diastereoselectivity (97:3 dr) and enantioselectivity (95% ee) were obtained when the reaction was performed in DCM at −78 °C (Table 1, entries 12–14). Finally, the optimal conditions were demonstrated by running the reaction in 1.0 mL of DCM at −78 °C to provide 98:2 dr and 96% ee (Table 1, entry 15).

With the optimal conditions in hand, we then examined the generality of the Mannich reaction with a variety of *N*-Boc-protected aldimines. As shown in Table 2, all the reactions were complete within 50 min at −78 °C, and the desired products **3** were obtained in high yields and with high diastereoselectivities (87:13–99:1). High-to-excellent enantioselectivities of **3** were obtained irrespective of the electronic nature of the substituents or substitution type (Table 2, entries 1–8). In the cases of heterocyclic and aliphatic aldimine substrates, the reactions proceeded to give almost single diastereoisomers and high enantioselectivities except for the 2-thienyl aldimine, which afforded the product **3l** with only 66% ee (Table 2, entries 9–12).

Table 2. Scope of the Mannich Reaction Catalyzed by the Dual-Reagent Catalysis[a]



1a 2 3

entry	3	R	t/min	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**3b**	4-MeC_6H_4	30	88	97:3	94
2	**3c**	3-MeC_6H_4	40	85	97:3	95
3	**3d**	2-MeC_6H_4	40	80	89:11	80
4	**3e**	4-ClC_6H_4	30	87	91:9	82
5	**3f**	3-FC_6H_4	30	83	87:13	88
6	**3g**	2-$MeOC_6H_4$	40	65	96:4	81
7	**3h**	3-$MeOC_6H_4$	30	77	98:2	86
8	**3i**	4-$NO_2C_6H_4$	20	91	91:9	87
9	**3j**	2-furanyl	30	90	99:1	90
10	**3k**	1-naphthyl	30	85	99:1	88
11	**3l**	2-thienyl	30	80	94:6	66
12	**3m**	cyclohexyl	30	72	99:1	86

[a]Reactions were carried out with **1a** (0.1 mmol), **2** (0.15 mmol), and methyl acrylate (0.01 mmol) in the presence of chiral phosphine **4f** in CH_2Cl_2 (1 mL) at −78 °C. [b]Isolated yields of **3**. [c]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [d]The ee value was determined by chiral HPLC analysis.

The catalytic system was also suitable for the Mannich reaction of a variety of cyclic β-ketoester substrates (Scheme 2). Replacement of ethyl ester with methyl, propyl, or benzyl groups had no obvious effect on the selectivity. Aromatic 1-indanone derived β-ketoesters were also a suitable substrate, albeit with a low diastereoselectivity. A decreased ee value was observed when an α-cyano ketone was used. The six-membered cyclic β-ketoester also worked quite well to afford the product with 91% ee and 99:1 dr.

To demonstrate the utility of the products, compound **3a** (92% ee) was reduced with $NaBH_4$ in EtOH, followed by treatment with trifluoroacetic acid to afford the β-amino alcohol **7** in 82% yield over two steps. Further manipulation was conducted to protect the alcohol with a TBS to provide **8**, which was transformed into spiro-lactam product **9** in good

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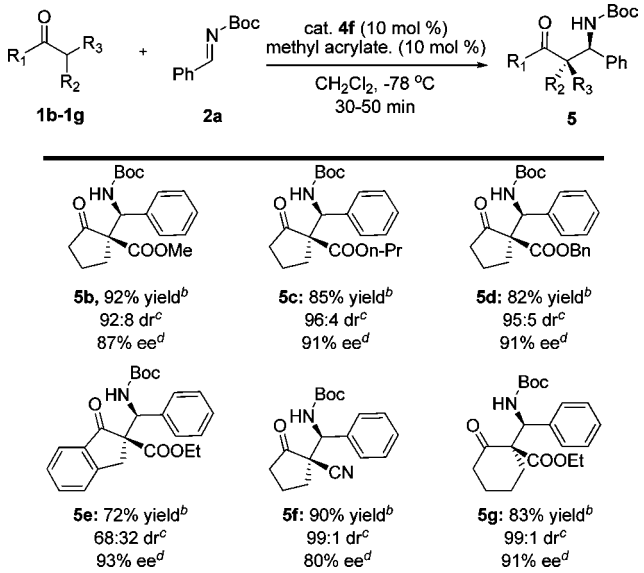
Scheme 2. Mannich Reaction of other β-Ketoesters or α-Cyano Ketone[a]



[a]Reactions were carried out with **1** (0.1 mmol), **2a** (0.15 mmol), and methyl acrylate (0.01 mmol) in the presence of chiral phosphine **4f** in CH_2Cl_2 (1 mL) at −78 °C. [b] Isolated yields of **5**. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [d] The ee value was determined by chiral HPLC analysis.

yield upon treatment with MeMgBr. Moreover, the β-amino alcohol **7** was also converted to the useful 1,3-oxazinan-2-one **10** with three consecutive chiral carbon centers in a highly diastereo- and enantioselective manner (Figure 1). The

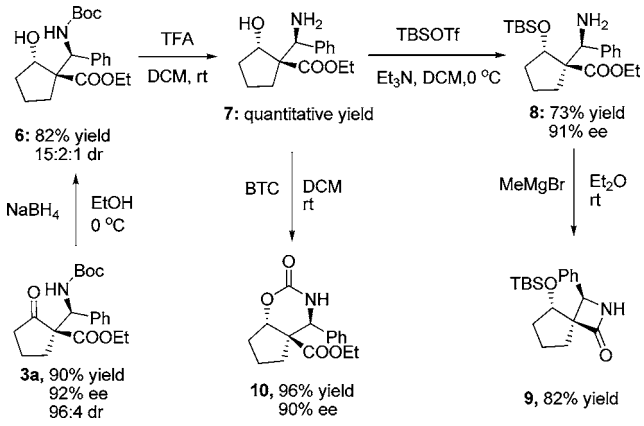


Figure 1. Representative transformations.

structure of the 1,3-oxazinan-2-one **10** was confirmed by X-ray crystallographic analysis (Figure 2A), from which the relative configuration of **3a** was deduced to be *trans*. The absolute configuration of **3a** was determined to be 1*R*, 2′*S* by comparing the chiral HPLC data and specific rotation with literature values.[9] The configurations of **3b**−**3m** and **5b**−**5g** were herein assigned by analogy.

Although the mechanism of this novel catalyst system is not completely clear, a possible transition state can be considered (Figure 2B). First the chiral phosphine adds to the methyl acrylate to form a phosphonium enolate, which activates **2a** as a Brønsted base. At the same time, the *N*-Boc-benzaldimine is activated by the thiourea moiety through hydrogen bonding,

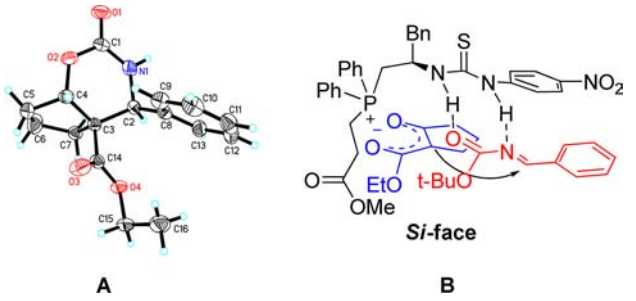


Figure 2. (A) X-ray crystal structure of 1,3-oxazinan-2-one **10**. (B) Possible transition state.

giving strict conformational control that results in an excellent recognition of the *Si*-face of the imine by the chiral ion pair. These interactions control the stereochemical outcome of the reaction.

In summary, we have developed a new asymmetric dual reagent catalyst system consisting of a bifunctional thiourea-phosphine derived from amino acids and methyl acrylate as the additive. This catalyst system can efficiently catalyze the direct Mannich-type reaction of β-ketoesters with *N*-Boc-aldimines at low temperature in a short time to afford the desired products in good yields and high diastereo- and enantioselectivities. The practicality of this method was also demonstrated by transforming one of the products into a novel β-amino alcohol and a spiro-lactam.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization, and X-ray crystallographic data (CIF) for **10** (CCDC 1040468). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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