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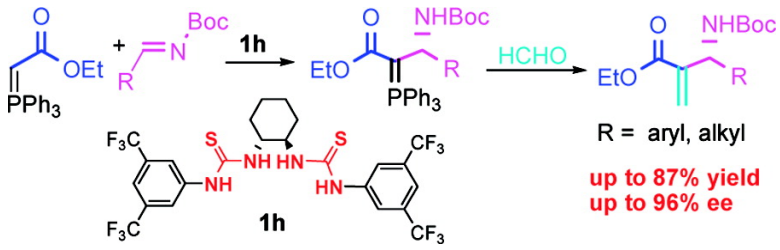

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Organocatalytic Enantioselective Mannich-Type Reaction of Phosphorus Ylides: Synthesis of Chiral *N*-Boc-β-Amino-α-methylene Carboxylic Esters

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β-Amino carbonyl compounds containing an α-alkylidene group are highly densely functionalized materials which are widely applied in the synthesis of medicinal reagents and natural products.[1] They are usually prepared through the classic aza-Morita−Baylis−Hillman (MBH) reaction of activated imines and electron-deficient alkenes catalyzed by tertiary amines or phosphines.[2] Enormous efforts have been devoted to this valuable process including its asymmetric variant in the past decades, nevertheless, the aza-MBH reaction remains to be restricted in substrate scope and enantiocontrol.[3] In addition, the nucleophilic catalysts typically utilized in aza-MBH reactions may induce product racemization.[4] Here we would like to report the development of a novel but facile strategy to the enantioselective synthesis of *N*-Boc-β-amino-α-methylene carboxylic esters.[5]

Stabilized phosphorus ylides (P-ylides) have previously been shown to be good nucleophiles. Aside from the traditional Wittig reaction with carbonyl compounds, P-ylides also found uses in alkylation reactions.[6] Nevertheless, their potential application as versatile synthons in asymmetric synthesis has not been addressed yet.[7] We envisaged that P-ylides could act as competent nucleophilic species to attack appropriately activated imines, and the functionalized P-ylides with a chiral center would be generated after proton transfer. Following the reaction with formaldehyde should provide the desired β-amino-α-methylene carbonyl products (Scheme 1).

In light of the above consideration, the reaction of P-ylide **2a** and *N*-Boc imine **3a** was initially investigated in toluene at room temperature *without any catalyst*. Gratifyingly, the expected P-ylide **4a** (R = Et) could be isolated as a relatively stable compound, and aza-MBH product **5a** (R = Et) was cleanly obtained after reaction with formalin (Table 1, entry 1).[8] Then we were inspired to explore the possible asymmetric Mannich-type reaction of **2a** and **3a** catalyzed by chiral Brønsted acids at 0 °C (see Figure 1).[9] While low ee values were obtained with catalysis by various phosphoric acids[10] after conversion to **5a** (entries 2−4),[11] thiourea **1d** also gave poor chiral induction (entry 5).[12,13] Moderate ees were received when new thioureas **1e**−**g** were applied (entries 6−8). To our delight, much better enantioselectivity was attained by employing the easily available bisthiourea **1h** (entry 9).[14] As a result, *the concerted hydrogen bonding interaction of **2a** and **3a** with two thiourea functional groups might be responsible for the higher enantiocontrol in the Mannich-type reaction step*.[15] Ylides **2b** and **2c**, differing at the ester functionality, led to lower enantioselectivity (entries 10 and 11). Later the reaction was conducted at lower temperature to improve the enantioselectivity, and in general more reliable results could be obtained when **4a** was previously isolated before quenching with HCHO.[16] Superior results were observed in *m*-xylene (entry 12 vs 13). Bisthiourea **1i** and **1j** provided identical enantioselectivities compared to **1h** (entries 14 and 15). In addition, the stabilized P-ylides containing a ketone carbonyl exhibited much lower reactivity with *N*-Boc imines under the current catalytic system. Attempts to synthesize β-substituted derivatives[3g,5] with aldehydes other than HCHO failed owing to the steric hindrance of the chiral P-ylide **4a** and its instability to refluxing THF.[6c] Such problems remain to be further explored.[17]

Consequently, the tandem Mannich-type/Wittig reaction for the synthesis of diverse chiral *N*-Boc-β-amino-α-methylene carboxylic esters was investigated with **2a** and a variety of *N*-Boc aldimines catalyzed by 10 mol % of bisthiourea **1h**. As demonstrated in Table 2, the reaction sequence showed substantial generality resulting in broad substrate scope. Excellent enantioselectivities with good

Scheme 1. A Novel Approach to Chiral β-Amino-α-methylene Carbonyl Compounds

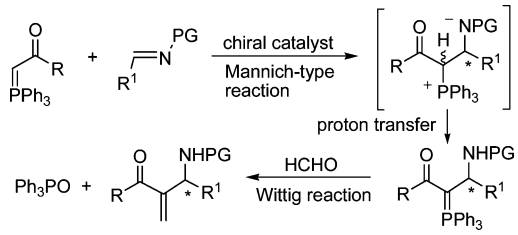
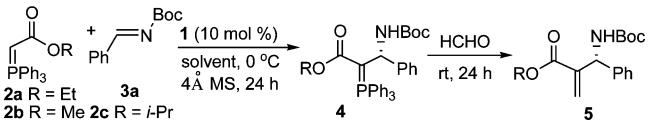


Table 1. Screening Studies of Organocatalytic Mannich-type Reaction and Subsequent Synthesis of *N*-Boc-β-amino-α-methylene Carboxylic Esters[a]



entry	catalyst	2	solvent	yield[b] (%)	ee[c] (%)
1[d]	-	**2a**	toluene	**5a**−53	-
2	**1a**	**2a**	toluene	**5a**−62	31
3	**1b**	**2a**	toluene	**5a**−75	45
4	**1c**	**2a**	toluene	**5a**−60	12
5	**1d**	**2a**	toluene	**5a**−84	15
6	**1e**	**2a**	toluene	**5a**−80	63
7	**1f**	**2a**	toluene	**5a**−69	73
8	**1g**	**2a**	toluene	**5a**−62	57
9	**1h**	**2a**	toluene	**5a**−62	80
10	**1h**	**2b**	toluene	**5b**−77	77[e]
11	**1h**	**2c**	toluene	**5c**−51	52
12[f]	**1h**	**2a**	toluene	**5a**−89	83
13[f]	**1h**	**2a**	*m*-xylene	**5a**−87	89
14[f]	**1i**	**2a**	*m*-xylene	**5a**−71	89
15[f]	**1j**	**2a**	*m*-xylene	**5a**−87	89

[a] Unless noted otherwise, reactions were performed with 0.1 mmol of **2**, 0.15 mmol of **3a**, 10 mol % of **1**, 40 mg 4 Å MS in 0.5 mL solvent at 0 °C for 24 h. Then excess HCHO was added and stirred at room temp for another 24 h. [b] Isolated yield for two steps. [c] Determined by chiral HPLC analysis. [d] At room temp for 48 h. [e] The absolute configuration was determined by converting **5b** to a known compound.[3c] [f] At −20 °C for 60 h, and then **4a** was isolated before treating with formalin in THF for 24 h.

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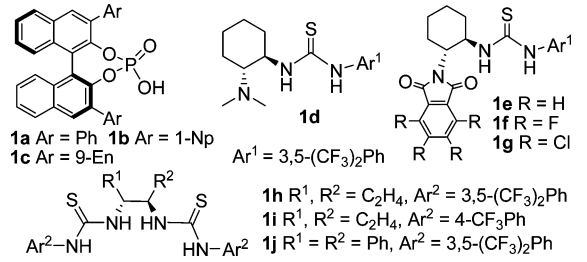
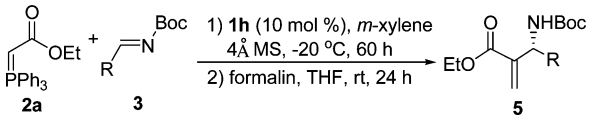


Figure 1. The structures of chiral Brønsted acid catalysts.

Table 2. Asymmetric Synthesis of *N*-Boc-β-amino-α-methylene Carboxylic Esters via Tandem Mannich-Type/Wittig Reaction[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1	Ph	**5a**	87	89
2	*p*−F−Ph	**5d**	67	87
3	*p*−Cl−Ph	**5e**	65	90
4	*m*−Cl−Ph	**5f**	53	83
5	*o*−Cl−Ph	**5g**	41	89
6	*p*−Br−Ph	**5h**	80	94
7	*p*−Me−Ph	**5i**	78	95
8	*m*−Me−Ph	**5j**	84	93
9	*p*−MeO−Ph	**5k**	84	91
10	2−thienyl	**5l**	84	68
11[d]	*n*−propyl	**5m**	70	57
12	cyclohexyl	**5n**	52	91
13	*i*−propyl	**5o**	35 (63)[e]	96 (91)[e]
14[f]	Ph	**5p**	74	92

[a] At 0.1 mmol scale in 0.5 mL *m*-xylene, **2a**/**3**/**1h** = 1:1.5:0.1. [b] Isolated yield for two steps. [c] Determined by HPLC analysis. The absolute configuration of the products was assigned by analogy to **5c**. [d] At −40 °C for 84 h. [e] Data in parentheses is related to in situ formed imine at 4 °C for 60 h, see Supporting Information. [f] *N*-Cbz benzaldimine was used.

isolated yields were obtained for *N*-Boc aryl imines bearing various electron-withdrawing or -donating substitutions (entries 1−9), while modest ee was observed for imine with a 2-thienyl group (entry 10). Importantly α-enolizable alkyl imines could be successfully applied, and remarkable ee values were attained for branched substrates (entries 11−13). Moreover, the reaction with in situ formed alkyl imine in the presence of aqueous Cs_2CO_3 solution was promising,[18] and better yield with high ee was gained (entry 13, data in parentheses). It should be stated that alkyl imines have not been effectively utilized in the normal asymmetric aza-MBH reaction.[2] In addition, good results could be achieved for *N*-Cbz benzaldimine (entry 14). It was noteworthy that catalyst **1h** could be recovered by FC and reused in the Mannich-type reaction without any effects on its efficacy (for **5a**, second use, 81% yield, 89% ee; third use, 85% yield, 90% ee).

In conclusion, we have presented the first asymmetric Mannich-type reaction of stabilized phosphorus ylides and Boc-protected aldimines by employing readily available and recyclable bisthiourea organocatalysts. Subsequent reaction with formaldehyde provides a facile access to chiral *N*-Boc-β-amino-α-methylene carboxylic esters in good to excellent enantioselectivities. This methodology presented herein may potentially open avenues for the application of phosphorus ylides in asymmetric synthesis. Currently mechanism exploration and reaction expansion of the related ylides are under way in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures, structural proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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