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Enantioselective Allylic Amination of Morita-Baylis-Hillman Acetates Catalyzed by Chiral Thiourea-Phosphine

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The enantioselective allylic amination of Morita-Baylis-Hillman acetates catalyzed by chiral cyclohexane-based thiourea-phosphine catalysts was investigated. In the presence of 20 mol% rosin-derived thiourea-phosphine **3j**, the chiral amines were obtained in up to 88% yield and up to 85% *ee*.

Keywords allylic amination, chiral phosphine, enantioselective organocatalysis, Morita-Baylis-Hillman acetate, phthalimide

Introduction

The asymmetric allylic substitution reaction, which is a powerful tool in organic synthesis for the construction of carbon-carbon and carbon-heteroatom bonds with a carbon-stereogenic center, allows easy access to diverse allylic compounds.[1,2] The substitution with nitrogen-containing nucleophiles, as known as allylic amination, is one of the straightforward method of synthesizing α-methylene-β-amino compounds, which is widely applied in the synthesis of natural products and biologically active pharmaceuticals.[3] Over the past decade, great progress has been made in the chiral amine-catalyzed allylic amination,[4,5] and the *N*-nucleophiles involve 4-methyl benzene-sulfonamide,[5a] phthalimide,[5b,5c] indole,[5d] cyanopyrrole,[5d,5i] enamide,[5e] benzophenone imine,[5f] carbamate and tosylcarbamate,[5g,5k] allylic amine,[5h] isatin[5j] and hydrazine[5l] in the allylic amination of allylic alcohols or their derivatives. However, there are only a few examples of enantioselective allylic amination using nucleophilic chiral tertiary phosphine as catalyst.[6] In 2004, Krische[6a] demonstrated the first chiral phosphine-catalyzed enantioselective allylic amination of phthalimide with Morita-Baylis-Hillman (MBH) acetate in 80% yield and in 56% *ee*, using (*R*)-Cl-MeO-BIPHEP as a chiral catalyst. Hou and co-workers[6b] reported the allylic amination of MBH acetates catalyzed by planar-chiral [2,2] paracyclophane monophosphines in 2007. Later on, Shi and co-workers[6c] developed a chiral BINOL-derived amide-phosphine for this reaction, giving the chiral amines in good yields (70%—95%) and up to 78% *ee*. The corresponding thiourea-phosphine was also applied in the enantioselective allylic amination of MBH acetates by Shi's group[6d] in 2011, and the desired products were provided in up to 99% yield and up to 90% *ee* by using 25 mol% of chiral organocatalyst at 10 ℃. Considering the variety of chiral phosphine catalysts in other asymmetric reactions,[7] the exploration of efficient chiral phosphine-based organocatalysts for allylic amination remains necessary.

In our previous works, we have found the chiral cyclohexane-based phosphine compounds are highly efficient organocatalysts in several enantioselective reactions, such as allylic alkylation,[8a] [4+2] cycloaddition,[8b] and MBH-type reactions.[8c-8k] As a part of our continuing efforts to expand the application of these phosphine organocatalysts, herein we report the enantioselective allylic amination of MBH adducts catalyzed by the chiral cyclohexane-based phosphines.

Experimental

General procedure for the enantioselective allylic amination

To a solution of chiral catalyst **3j** (0.04 mmol) in 1 mL $CHCl_3$ was added the MBH adduct **5** (0.2 mmol), phthalimide (0.4 mmol) and triethylamine (0.04 mmol) at 25 ℃. The corresponding mixture was stirred at this temperature until the completion of the reaction (monitored by TLC). The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography on silica gel to afford the desired products. The *ee* values were determined by HPLC analysis with a chiral column.

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Results and Discussion

Initially, we chose allylic amination of phthalimide with the MBH acetate **5a** derived from methyl vinyl ketone as a model reaction to evaluate the chiral cyclohexane-based phosphine catalysts (Figure 1). The reaction could not take place in the absence of a basic additive. Considering that the pK_a value of pronucleophile phthalimide (pK_a 8.3) is larger than that of acetic acid (pK_a 4.8), which should not allow the acetate to deprotonate the phthalimide.[6d] To achieve the deprotonation of phthalimide, triethylamine was added to the reaction system. With the same loading of triethylamine and chiral catalyst, allylic amination was performed at 25 ℃ in $CHCl_3$, and the results are summarized in Table 1. Firstly chiral bifunctional organocatalysts bearing different H-bonding donors were investigated. The results indicated that the thiourea-phosphine **3f** provided higher yield than the corresponding amide-phosphine **1** and squaramide-phosphine **2** (Entry 8 vs. 1 and 2). Therefore, chiral cyclohexane-based thiourea-phosphines containing different scaffolds were evaluated. All the thiourea-phosphines screened achieved good-to-excellent yields in the allylic amination (Entries 3—9). Among them, organocatalyst **3f** provided the best enantioselectivity. The additional chiral group in the alkyl thiourea moiety would improve the enantioselectivity, especially the thiourea-phosphines **3j** and **4** containing a dehydroabietic amine unit (Entries 10—13).[9] The rosin-derived thiourea-phosphine **3j** was proved to be the best catalyst for the allylic amination achieving 88% yield with 85% *ee* (Entry 12), probably due to good chiral match between the chiral cyclohexyl backbone and dehydroabietic amine unit. By comparing the optical rotation value with that reported in the literature,[6d] the absolute configuration of the allylic amination products was assigned as "*R*".

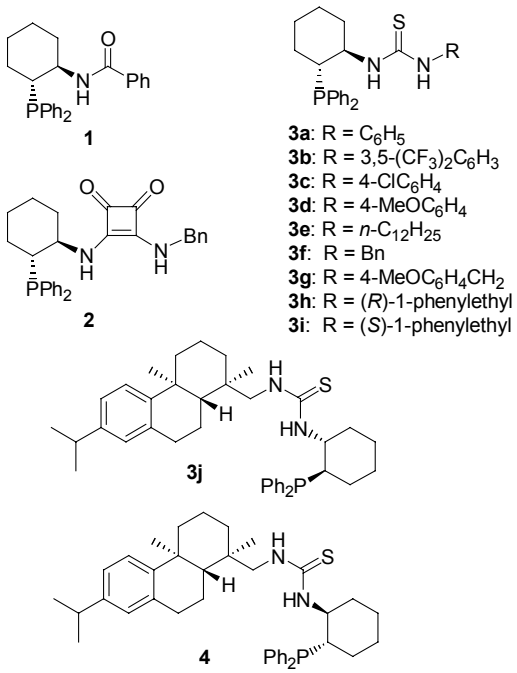
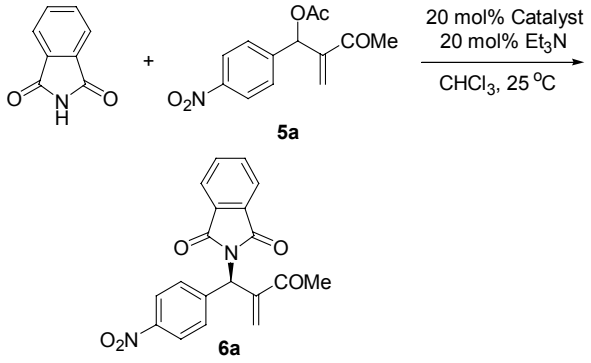


Figure 1 Structures of the chiral phosphine organocatalysts screened.

Table 1 Screening of chiral organocatalysts for the allylic amination between phthalimide and MBH acetate **5a**[a]



Entry	Catalyst	Time/d	Yield[b]/%	*ee*[c]/%
1	**1**	4	70	56
2	**2**	4	72	55
3	**3a**	1	86	55
4	**3b**	2	80	48
5	**3c**	1.5	95	50
6	**3d**	4.5	96	55
7	**3e**	1.2	95	34
8	**3f**	1.2	89	64
9	**3g**	3.5	95	55
10	**3h**	3	87	68
11	**3i**	3	83	77
12	**3j**	3	88	85
13	**4**	3	87	−80

[a] The reactions were carried out with substrate **5a** (0.2 mmol), phthalimide (2 equiv.), 20 mol% Et_3N and 20 mol% of chiral catalyst in $CHCl_3$ (1.0 mL) at 25 ℃. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC.

Next, the effect of reaction solvent was investigated using 20 mol% **3j** as a catalyst (Table 2). The allylic amination is sluggish in non-polar solvent such as toluene, and only 72% yield and 70% *ee* were obtained even after 7 d (Entry 1). Halogen solvents such as $CHCl_3$ and CH_2Cl_2 resulted in good yields and enantioselectivities (Entries 2 and 3), and so did 1,4-dioxane (Entry 4). In the case of ether, good yield was achieved while a longer time was required due to the slow reaction rate (Entry 5). Complex by-products were generated in THF, EtOAc and CH_3CN (especially in CH_3CN), so the chemical yields of allylic amination decreased obviously (Entries 6—8). In non-protonic polar solvent DMSO, catalyst **3j** was inefficient for the allylic amination (Entriy 9). Then $CHCl_3$ was selected as a solvent for the subsequent optimization.

Among the bases screened, triethylamine was the

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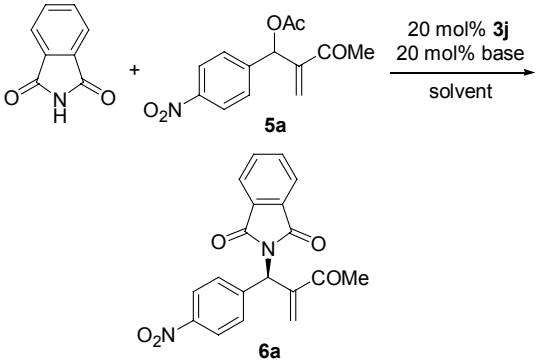
Table 2 Optimization of the reaction conditions[a]



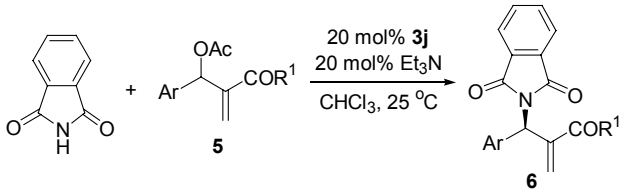
Entry	Solvent	Base	Time/d	Yield[b]/%	*ee*[c]/%
1	Toluene	Et_3N	7	72	70
2	$CHCl_3$	Et_3N	3	88	85
3	CH_2Cl_2	Et_3N	3	85	84
4	Dioxane	Et_3N	3	87	82
5	Ether	Et_3N	6	84	75
6	THF	Et_3N	3.5	59	67
7	EtOAc	Et_3N	3.5	73	69
8	CH_3CN	Et_3N	3	23	68
9	DMSO	Et_3N	5	trace	nd[d]
10	$CHCl_3$	C_6H_5N	3	49	55
11	$CHCl_3$	DIPEA	3	81	57
12	$CHCl_3$	DMAP	1.5	90	8
13	$CHCl_3$	DBU	3	65	34
14[e]	$CHCl_3$	Et_3N	1.5	86	35
15[f]	$CHCl_3$	Et_3N	3	86	81
16[g]	$CHCl_3$	Et_3N	3	84	83
17[h]	$CHCl_3$	Et_3N	3	86	75
18[i]	$CHCl_3$	Et_3N	4.5	75	82
19[j]	$CHCl_3$	Et_3N	7	55	85
20[k]	$CHCl_3$	Et_3N	1.5	89	77
21[l]	$CHCl_3$	Et_3N	6	85	84

[a] Unless stated otherwise the reactions were carried out with substrate **5a** (0.2 mmol), phthalimide (2 equiv.), 20 mol% base and 20 mol% chiral catalyst **3j** in solvent (1.0 mL) at 25 ℃. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC. [d] Not determined. [e] The amount of triethylamine was 100 mol%. [f] The reaction was conducted with 1 equiv. of phthalimide. [g] The reaction was conducted with 3 equiv. of phthalimide. [h] The reaction was carried out in 2.0 mL $CHCl_3$. [i] The reaction was carried out in 0.67 mL $CHCl_3$. [j] The reaction temperature was 0 ℃. [k] The reaction temperature was 40 ℃. [l] The catalyst loading was 10 mol%.

optimal one for both yield and enantioselectivity (Entry 2 vs. 10—13). Using 1 equiv. of triethylamine could accelerate the reaction but with a negative effect on the enantioselectivity (Entry 14 vs. 2). The ratio of phthalimide to MBH acetate had a slight effect on the chemical yield and enantioselectivity (Entries 2, 15 and 16). With the concentration of MBH acetate ranging from 0.1 to 0.3 mol/L in $CHCl_3$, the lower concentration (0.1 mol/L) led to an obvious decrement of the enantioselectivity, while the higher concentration (0.3 mol/L) caused a lower yield (Entries 17 and 18 vs. 2). Moreover, the higher temperature sped up the reaction, but resulted in lower enantioselectivity (Entries 2, 19 and 20). When the catalyst loading of **3j** was reduced from 20 mol% to 10 mol%, the yield and enantioselectivity were slightly decreased (Entry 21 vs. 2).

Under the established optimal reaction condition (20 mol% catalyst **3j**, 2 equiv. of phthalimide in $CHCl_3$ at 25 ℃), the substrate scope of allylic amination was surveyed. The results are summarized in Table 3. The MBH acetates with electron-withdrawing group at the *para*- or *meta*-position of the phenyl group could afford better yields than those with electron-donating group or without substituent on the aromatic ring (Entries 1, 2 and 4—10 vs. 11 and 12). Moreover, the MBH acetates containing strong electron-withdrawing group provided higher enantioselectivities (Entries 1, 2, 4 and 6). However, the MBH acetate bearing a nitro group at the *ortho*-position of the phenyl ring could not generate the product (Entry 3), probably due to the *ortho*-effect. The MBH acetates with two electron-withdrawing groups at both 3- and 4-positions of the phenyl group also gave

Table 3 Substrate scope of the enantioselective allylic amination[a]



Entry	R^1	Ar	Time/d	Product	Yield[b]/%	*ee*[c]/%
1	Me	4-$NO_2C_6H_4$	3	**6a**	88	85
2	Me	3-$NO_2C_6H_4$	4	**6b**	78	84
3	Me	2-$NO_2C_6H_4$	5	—	trace	nd[d]
4	Me	4-CNC_6H_4	1.5	**6c**	80	81
5	Me	3-CNC_6H_4	1.5	**6d**	73	61
6	Me	4-$CF_3C_6H_4$	2	**6e**	81	80
7	Me	4-BrC_6H_4	3.5	**6f**	71	77
8	Me	4-ClC_6H_4	3.5	**6g**	76	79
9	Me	3-ClC_6H_4	4	**6h**	74	76
10	Me	4-FC_6H_4	3.5	**6i**	67	65
11	Me	C_6H_5	4	**6j**	58	74
12	Me	4-MeC_6H_4	5	**6k**	57	68
13	Me	3,4-$Cl_2C_6H_3$	3.5	**6l**	75	79
14	Me	3,4-$F_2C_6H_3$	3.5	**6m**	66	74
15	MeO	4-$NO_2C_6H_4$	5	**6n**	24	67

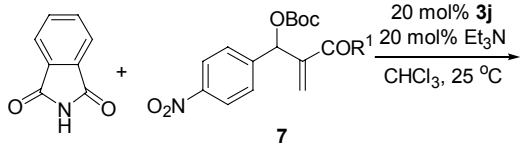
[a] The reactions were carried out with substrate **5** (0.2 mmol), phthalimide (2 equiv.), 20 mol% Et_3N and 20 mol% chiral catalyst **3j** (0.04 mmol) in $CHCl_3$ (1.0 mL) at 25 ℃. [b] Isolated yield. [c] The *ee* values were determined by chiral HPLC. [d] Not determined.

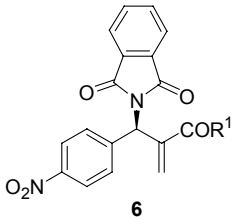
the corresponding amines in moderate yields with enantioselectivities (Entries 13 and 14).

This asymmetric catalytic system is not suitable for the MBH acetate derived from methyl acrylate, which exhibited a lower yield and enantioselectivity than the MBH acetate derived from methyl vinyl ketone under the identical conditions (Entry 15 vs. 1). Except phthalimide, other *N*-nucleophiles such as aniline, benzylamine and *p*-toluene-sulfonamide could not react with the MBH acetates under this catalytic system.

We also examined MBH carbonates as electrophile in the allylic amination (Scheme 1). To our surprise, MBH carbonate **7a** derived from methyl vinyl ketone afforded racemic product in good yield. The MBH carbonate **7b** derived from methyl acrylate provided the desired product in better yield than the corresponding MBH acetate, and the addition of triethylamine led to a decrease of enantioselectivity.

Scheme 1 The allylic amination of MBH carbonates





6a: 85% yield, racemic (82% yield, racemic, without Et_3N)
6n: 77% yield, 54% *ee* (72% yield, 78% *ee*, without Et_3N)

According to the above-mentioned experimental results and the related reports,[6a,6d] a probable transition-state structure was proposed as shown in Figure 2. A nucleophilic addition of the phosphine to the MBH adduct and the following leaving of AcO^- group generate a cationic enone intermediate, which would be preferentially formed as the *E* isomer and stabilized by the hydrogen-bonding interactions between the thiourea moiety and the carbonyl group. Triethylamine deprotonates the acidic NH group of phthalimide to give a nucleophile. The steric repulsion between the chiral catalyst and deprotonated phthalimide forces the nucleophile to attack the cationic intermediate from the *Re*-face to generate the product with an (*R*)-configuration.

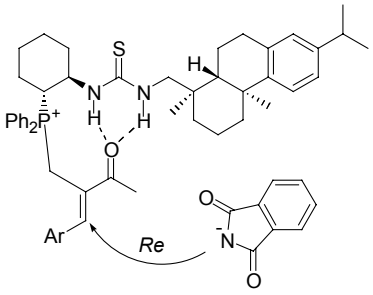


Figure 2 Proposed transition state

Conclusions

In summary, the chiral cyclohexane-based thiourea-phosphine **3j** was an efficient organocatalyst for the enantioselective allylic amination of phthalimide with MBH adducts. With 20 mol% organocatalyst **3j** and 20 mol% triethylamine in $CHCl_3$, the enantioselective allylic amination could provide the chiral amines in up to 85% *ee* and moderate-to-good yields.

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