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Highly Enantioselective Regiodivergent Allylic Alkylations of MBH Carbonates with Phthalides

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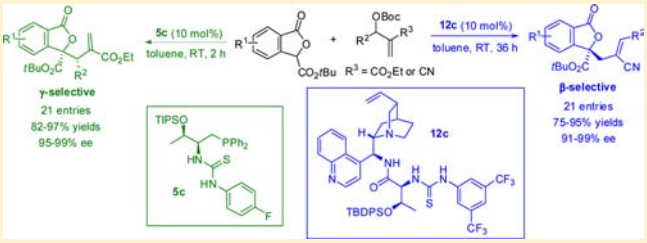
Supporting Information

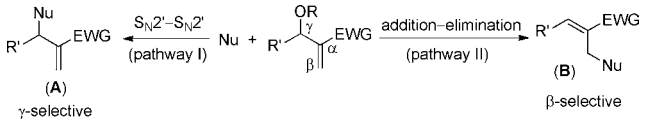
ABSTRACT: Phthalides were used for the first time in the allylic alkylation reactions with MBH carbonates for the creation of chiral 3,3-disubstituted phthalides. Highly enantioselective regiodivergent synthesis of γ-selective or β-selective allylic alkylation products was achieved by employing bifunctional chiral phosphines or multifunctional tertiary amine–thioureas as the catalyst, respectively. It was demonstrated that proper selection of catalysts and reaction conditions would differentiate an S_N2'–S_N2' pathway and an addition–elimination process, yielding different regioisomers of the allylic alkylation products in a highly enantiomerically pure form.



1. INTRODUCTION

Asymmetric allylic alkylation (AAA) is one of the most useful reactions in organic synthesis which allows easy access to chiral allylic intermediates. Approaches via transition metal catalysis have been intensively investigated and well-established for the AAA reaction.[1] Alternatively, organocatalytic methods utilizing Morita–Baylis–Hillman (MBH) adducts[2] as an electrophilic allylation reaction partner have recently emerged as a powerful strategy. The majority of reactions in this category made use of a cascade S_N2'–S_N2' pathway initiated by a nucleophilic phosphine[3] or amine catalyst.[4] On the other hand, the nucleophile can also attach to the β-carbon, usually via an addition–elimination pathway, leading to the formation of allylation products with different regioselectivity (Scheme 1).

Scheme 1. Regioselective Allylic Alkylation Reactions of the MBH Adducts



While the vast majority of literature examples described the formation of γ-products, methods for the construction of β-selective allylation products are scarce.[5] Given the high importance of the allylic alkylation products, versatile catalytic AAA reactions yielding different regioisomers are certainly very appealing and are of enormous synthetic value.

Enantiomerically pure 3,3-disubstituted phthalides are attractive structural motifs due to their wide occurrence in natural products and biologically important molecules[6] (Figure 1). However, asymmetric synthetic methods for phthalides with

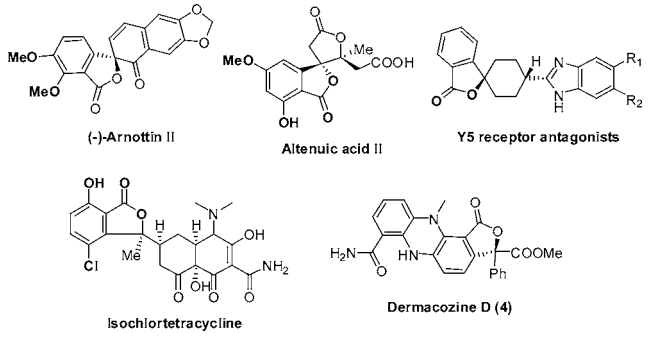


Figure 1. Selected examples of biologically important phthalides.

a 3-quaternary chiral center have met with limited success.[7] In conjunction with our continuous efforts for the creation of quaternary chiral centers,[8] we set out to explore the application of 3-substituted phthalides as a novel reaction partner with the MBH adducts in the AAA reaction. Herein, we document highly enantioselective and regiodivergent allylic alkylations of phthalides with the MBH carbonates, via either a Lewis base- or Brønsted base-catalyzed reaction pathway.

2. RESULTS AND DISCUSSION

2.1. γ-Selective Asymmetric Allylic Alkylation of Phthalides. We initiated our studies by examining the allylation reaction of MBH carbonates **2**, using 3-carboxylate phthalide **1a** as a prenucleophile. To selectively form the γ-selective allylic alkylation products, we reasoned nucleophilic phosphines might promote an S_N2'–S_N2' reaction sequence.

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We recently introduced a series of novel amino acid-derived chiral phosphines[9] in asymmetric catalysis. Our amino acid-based phosphines were found to be very powerful in a number of enantioselective organic transformations, including MBH reaction;[10a] aza-MBH reaction;[10b] [3 + 2] cycloaddition of allenoates with acrylates,[10c] imines,[10d] acrylamides,[10e] and maleimide;[10f] [4 + 2] annulation of allenoates with olefins;[10g] as well as [3 + 2] annulation using MBH adducts as a C3 synthon.[10h] The phosphine functional groups in these catalysts were highly nucleophilic, as they were connected to a primary carbon atom. The Brønsted acid moieties in the catalyst structures could be tuned easily to enable suitable interactions with substrates and thus contribute to the stereochemical control. Given their proven efficiency in asymmetric induction, we anticipated amino acid-based chiral phosphines may be very suitable for the projected enantioselective allylic alkylation of phthalides. The bifunctional phosphines investigated in this study are shown in Figure 2.

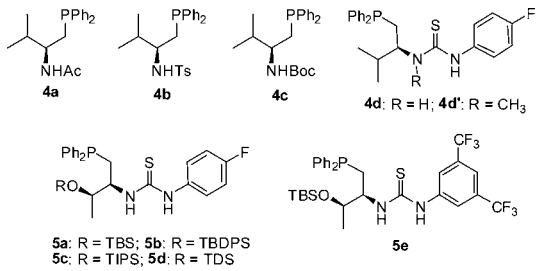
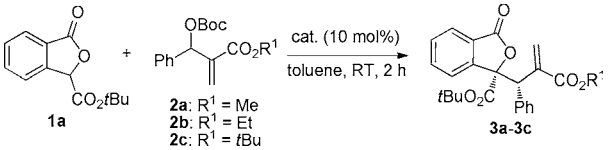


Figure 2. Amino acid-derived chiral phosphines examined.

All the phosphines examined were effective in promoting the reaction, affording the desired γ-selective products in excellent yields (Table 1). Among the various Brønsted acid moieties investigated, thioureas were found to be superior in stereochemical control (entries 1–4). Consistent with our previous findings, threonine-based catalysts proved to be privileged,[11] offering further improvement in enantioselectivity. The sterically hindered silyloxy groups were generally effective, and TIPS protection led to the best results (entries 5–8). Notably, the thiourea bearing a *p*-F-phenyl was slightly better than the thiourea with a 3,5-ditrifluoromethylphenyl group (entry 9). The ester moiety of the MBH carbonates also had influence on the reaction, and the ethyl ester gave the highest ee (entries 10–11). The reactions described proceeded rapidly to full conversion in 2 h, in contrast to much longer reaction time for the amine-catalyzed reactions.[4] Under the optimized reaction conditions, γ-selective allylation product **3a** was obtained in 96% yield and with 98% ee in a diasteromericallly pure form.

The generality of this γ-selective AAA reaction of MBH carbonates with phthalides **1** was next studied (Table 2). All the reactions were completed within 2 h, and the γ-allylic alkylation products were obtained in excellent yields. The aryl moieties in the MBH carbonates **2** were well-tolerated, regardless of their electronic nature and substitution pattern (entries 1–13). The heterocyclic rings and 2-naphthyl group were also suitable (entries 14–16). Moreover, the less reactive alkyl MBH carbonates could be employed, albeit with moderate diastereoselectivity (entries 17–18). It should be noted that alkyl MBH carbonates were found to be unsuitable substrates in related literature reports.[3,4] Substitutions on the aromatic ring of phthalides **1** could also be well-tolerated (entries 19–21). However, the trisubstituted alkenes such as the MBH adduct of cyclohexenone were found to be unsuitable for the reaction,

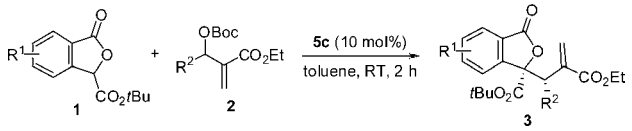
Table 1. Asymmetric Allylic Alkylation of MBH Carbonates 2 with Phthalide 1a Catalyzed by Bifunctional Phosphines[a]



entry	cat.	2	dr[b]	yield (%)[c]	ee (%)[d]
1	**4a**	**2a**	>99:1	94	25
2	**4b**	**2a**	>99:1	90	20
3	**4c**	**2a**	>99:1	91	3
4	**4d**	**2a**	>99:1	94	87
5	**5a**	**2a**	>99:1	92	96
6	**5b**	**2a**	>99:1	90	95
7	**5c**	**2a**	>99:1	92	97
8	**5d**	**2a**	>99:1	93	96
9	**5e**	**2a**	>99:1	91	94
10	**5c**	**2b**	>99:1	96	98
11	**5c**	**2c**	>99:1	90	88

[a]Reactions were performed with **1a** (0.05 mmol), **2** (0.075 mmol), and the catalyst (0.005 mmol) in toluene (0.5 mL) under argon. [b]Determined by ^{1}H NMR analysis of the crude products. [c]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

Table 2. Substrate Scope of the γ-Regioselective Allylic Alkylation Reaction of Phthalides[a]



entry	R^1/R^2 (3)	dr[b]	yield (%)[c]	ee (%)[d]
1	H/C_6H_5 (**3a**)	>99:1	96	98
2	H/4-Me-C_6H_4 (**3d**)	>99:1	95	99
3	H/4-Br-C_6H_4 (**3e**)	>99:1	92	98
4	H/4-F-C_6H_4 (**3f**)	>99:1	96	97
5	H/4-Cl-C_6H_4 (**3g**)	>99:1	93	99
6	H/4-CF_3-C_6H_4 (**3h**)	>99:1	97	98
7	H/4-NO_2-C_6H_4 (**3i**)	>99:1	91	98
8	H/4-CN-C_6H_4 (**3j**)	>99:1	92	98
9	H/3-Me-C_6H_4 (**3k**)	>99:1	92	95
10	H/3-Br-C_6H_4 (**3l**)	>99:1	93	98
11	H/2-Me-C_6H_4 (**3m**)	96:4	93	97
12	H/2-Br-C_6H_4 (**3n**)	>99:1	95	95
13	H/2,4-Cl-C_6H_3 (**3o**)	>99:1	92	97
14	H/2-thiophenyl (**3p**)	>99:1	94	96
15	H/3-furyl (**3q**)	97:3	92	97
16	H/2-nathphyl (**3r**)	>99:1	90	99
17	H/Me (**3s**)	67:33	82	99/30
18	H/*i*-Bu (**3t**)	75:25	92	98/53
19	5-Br/Ph (**3u**)	>99:1	93	>99
20	5-CN/Ph (**3v**)	>99:1	92	98
21	5-Br/2,4-Cl-C_6H_3 (**3w**)	>99:1	91	98

[a]Reactions were performed with **1** (0.05 mmol), **2** (0.075 mmol), and **5c** (0.005 mmol) in toluene (0.5 mL) under argon. [b]Determined by ^{1}H NMR analysis of the crude products. [c]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

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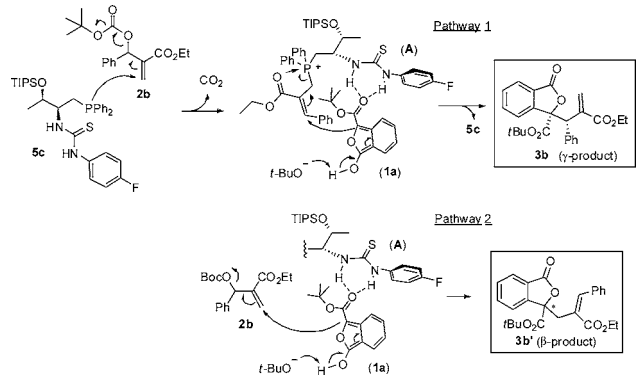
and no allylation product was observed. The absolute configuration of the allylation products was determined on the basis of X-ray crystal structural analysis of an acid derivative of **3w** (see the Supporting Information for details).

2.2. Mechanistic Considerations and Solvent Effects on Regioselectivity and Enantioselectivity. A mechanism involving a tandem S_N2'–S_N2' pathway was postulated to account for the formation of the observed γ-selectivity (Scheme 2, pathway 1). The first S_N2' reaction is initiated via

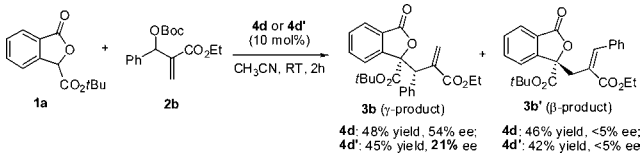
Scheme 2. Diverse Reaction Pathways



nucleophilic attack of phosphine **5c** on the MBH carbonate **2b**, and the phosphonium intermediate **A** is generated with concurrent release of CO_2. The *tert*-butoxide generated then deprotonates phthalide **1a**, which undergoes a second S_N2' with phosphonium **A** to yield γ-allylation product **3b**. We propose that the hydrogen bonding interactions between the thiourea moiety of the catalyst and the ester group of phthalide are crucial for the observed stereoselectivity.

Solvents are known to play important roles in organic reactions. Given the involvement of ionic intermediates in our reaction system, the solvent effect is thus anticipated to be profound. Intriguingly, when a phosphine **4d**-catalyzed reaction between phthalide **1a** and the MBH carbonate **2b** was carried out in CH_3CN, the β-product **3b′** and γ-selective **3b** were formed in a 1:1 ratio (Scheme 3). In stark contrast, the γ-

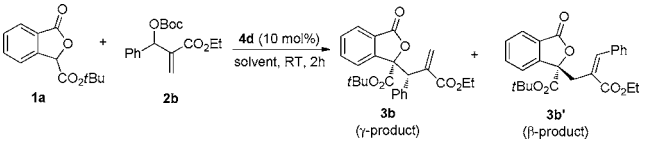
Scheme 3. AAA Reaction Catalyzed by 4d or 4d′ in CH_3CN



selective **3b** was the only product observed when toluene was used as the solvent (Table 1, entry 4). This experimental result suggested that another mechanism might be in operation with the simple switch of reaction medium from toluene to CH_3CN, which prompted us to further investigate the influence of solvents on our reaction.

We performed the allylation reaction between **1a** and **2b** catalyzed by bifunctional phosphine **4d** in a number of common aprotic organic solvents, and the results are summarized in Table 3. The ee values of the γ-products plotted against the β-selectivity of the reaction are illustrated in Figure 3. A clear correlation between regioselectivity and solvent polarity was observed. When solvents with low

Table 3. Influence of Various Aprotic Solvents on the Regioselectivities and Enantioselectivities[a]



entry	solvent	ε_r[b]	β/γ[c]	ee (γ)[d]
1	toluene	2.38	0:100	87
2	$CHCl_3$	4.89	0:100	87
3	THF	7.58	4.3:95.6	85
4	CH_2Cl_2	8.93	4.5:95.5	80
5	$ClCH_2CH_2Cl$	10.36	5.6:94.4	78
6	acetone	20.56	5.7:94.3	57
7	CH_3CN	35.90	46.0:54.0	54
8	DMSO	44.00	92.0:8.0	4

[a]Reactions were performed with **1a** (0.05 mmol), **2b** (0.075 mmol), and **4d** (0.005 mmol) in the solvent specified (0.5 mL) under argon. [b]Dielectric constant ε_r values are referred to as the empirical parameter of solvent polarity. [c]Evaluated by ^{1}H NMR analysis of the crude products. [d]The ee values of **3b**, determined by HPLC analysis on a chiral stationary phase. The ee values of **3b′** were all below 5%.

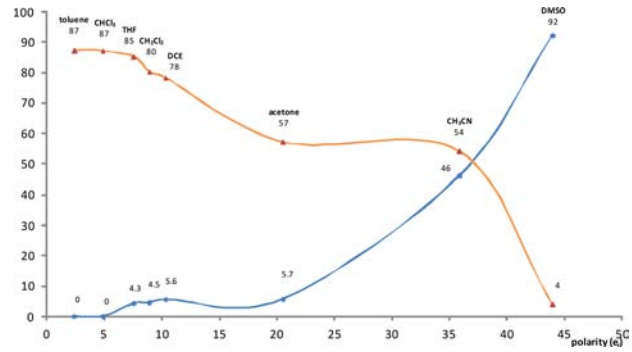


Figure 3. Correlation of the ee of the γ isomer (orange) and the $\beta/(\gamma + \beta)$ ratio (blue) with solvent polarity.

polarity[12] (e.g., toluene) were utilized, the γ-regioisomer **3b** was formed in high enantiomeric excess. The increase of solvent polarity favored the formation of the β-product **3b′**, but such an increase in β-selectivity was coupled with a decrease in enantioselectivity of the γ product. When the reaction was carried out in DMSO, a β (**3b′**) to γ (**3b**) ratio of 92:8 could be obtained; however, the γ-allylation product was formed with only 4% ee. It should also be noted that although more polar solvents favored the formation of β-products, such β-products were obtained in nearly racemic form.

The above results suggested that employment of more polar solvents resulted in a switch of reaction mechanism; a new β-selective and nonenantioselective pathway is likely in operation. When the in situ generated *tert*-butoxide abstracted the proton from the phthalide **1a**, the resulting anion could add to either intermediate **A** or the MBH carbonate **2b**. Intermediate **A** was a favored reaction partner when the reaction was run in toluene, due to the high electrophilicity of the phosphonium alkene **A** and the intramolecular like reaction facilitated by the hydrogen bonding interactions. However, when the polar aprotic solvent (e.g., DMSO) was used, the polar group of the solvent not only stabilized the phosphonium intermediate but also disrupted the hydrogen bonding interactions, and such a disruption resulted in decreased ee values of the γ-product formed. Indeed, when

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methylated thiourea phosphine **4d′** (Scheme 3) was employed, the ratio of γ to β products remained unchanged. Nevertheless, the ee of γ-product **3b** decreased to 21%, compared with 54% ee when thiourea−phosphine **4d** was used as a catalyst under otherwise same conditions. These results clearly showed the importance of hydrogen bonding interactions in stereochemical formation of a γ-product via pathway 1. When the solvent was switched to polar aprotic solvents, such as DMSO, the MBH carbonate **2b** became a predominant acceptor to trap the phthalide anion, yielding the β-allylic alkylation product **3b′**. Such an addition−elimination process is independent of steric or electronic control and, thus, is apparently nonstereoselective, affording nearly racemic products (Scheme 2, pathway 2).

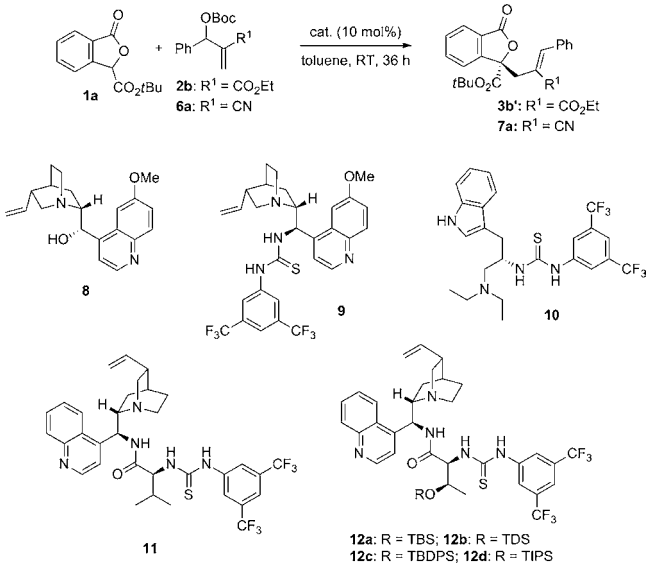
2.3. β-Selective Asymmetric Allylic Alkylation of Phthalides. Having established a stereoselective pathway for deriving γ-selective allylation products, we next focused on the formation of β-selective phthalides in an enantioselective manner. The aforementioned pathway 2 implies that a Brønsted base-initiated addition−elimination sequence may be utilized for selective formation of the β-product. Given the high acidity of the proton at the C3 position of phthalide, we reasoned an appropriate chiral Brønsted base may provide sufficient activation. We hypothesized that utilization of multifunctional tertiary amine-based catalysts may lead to an enantioselective variant of β-selective allylic alkylation of phthalides .

The reaction between phthalides **1a** and the MBH carbonates in the presence of tertiary amine−thiourea catalysts was examined, and the results are summarized in Table 4. Neither quinidine **8** nor quinidine-derived tertiary amine−thiourea **9** could effectively promote the reaction (entries 1−2). Suspecting the ester-containing MBH carbonate may not have sufficient reactivity, we then utilized carbonate **6a** as a reaction partner. Indeed, the allylation proceeded smoothly with **6a**, affording the β-selective product in excellent yield and with moderate ee (entry 3). To further improve the enantioselectivity of the reaction, a screening of catalysts was performed. Tryptophan-based catalyst **10** was ineffective (entry 4), and our previously developed trifunctional catalysts[8d] offered fantastic results (entries 5−9). Under the optimized reaction conditions,[13] threonine-incorporated **12c** promoted the allylation reaction of phthalide **1a** with **6a** in a highly enantioselective and regioselective manner, affording the β-product **7a** in 91% yield and with 98% ee (entry 8).

The above β-selective allylation reactions were general for MBH carbonates with different substituents (Table 5), including electron rich/poor aryls with different substitution patterns (entries 1−14), 1-naphthyl (entry 15), a heteroaromatic ring (entry 16), or a vinylic group (entry 17). Notably, in contrast to reported systems with substrates scope limited to aromatic substituted MBH adducts,[3,4] our current catalytic system also worked nicely for MBH carbonates with an aliphatic group (entry 18) or simply a hydrogen (derived from formaldehyde, entry 19). Moreover, different substituents on the aromatic part of phthalides **1** could also be tolerated (entries 20−21). In all cases, good to excellent Z/E ratios were attainable. The absolute configurations of products **7** were determined on the basis of X-ray crystal structural analysis of **7m** (see the Supporting Information for details).

We believe selective formation of the β-selective product resulted from a Brønsted base-initiated addition−elimination reaction sequence (Scheme 4, pathway B). It is postulated that the hydrogen bonding network between catalyst **12c** and the

Table 4. Reaction Condition Optimization for β-Selective Allylation Reaction of Phthalides[a]



entry	cat.	R^1	Z/E[b]	yield (%)[c]	ee (%)[d]
1	**8**	CO_2Et		<10	
2	**9**	CO_2Et		<10	
3	**9**	CN	15:1	94	72
4	**10**	CN	15:1	87	35
5	**11**	CN	14:1	90	85
6	**12a**	CN	17:1	90	93
7	**12b**	CN	17:1	92	93
8	**12c**	CN	18:1	91	98
9	**12d**	CN	18:1	92	94

[a]Reactions were performed with **1a** (0.05 mmol), **2b** or **6a** (0.075 mmol), and the catalyst (0.005 mmol) in toluene (0.5 mL) under argon. [b]Determined by ^{1}H NMR analysis of the crude products. [c]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

substrate was crucial for the observed enantioselectivity. However, it should be noted that the same product could also be formed via an S_N2'−S_N2 tandem reaction, in which tertiary amine catalysts serve as a nucleophilic catalyst (Scheme 4, pathway A).

To gain further mechanistic insights, we performed the same allylic alkylation experiment by utilizing the MBH acetate **6b** (Scheme 5). In the presence of 30 mol % **12c**, **7a** was obtained in 30% yield, in contrast to a 91% yield when the MBH carbonate **6a** was employed under otherwise identical reaction conditions. These experimental results support that pathway B is more likely for our reaction. Had the reaction proceeded via pathway A, the allylation product would not be formed, as the acetate anion is not basic enough to deprotonate **1a**. In pathway B, the in situ generated *tert*-butoxide deprotonates the ammonium species to regenerate the catalyst, hence making the reaction catalytic. When the MBH acetate was employed, the reaction was not catalytic any more, as the acetate was unable to facilitate the regeneration of the catalyst. The combination of the MBH acetate **6b** and the phosphine catalyst **5c** did not lead to the product formation, which clearly supported that the *tert*-butoxide was required for the deprotonation of phthalide in an S_N2'−S_N2' mechanism (Scheme 2). On the other hand, when carbonate **6a** was used in the presence of phosphine **5c**, only the β-product **7a**

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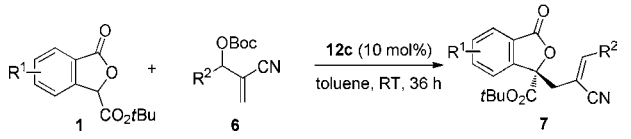
Table 5. Asymmetric β-Selective Allylic Alkylation of Phthalides[a]

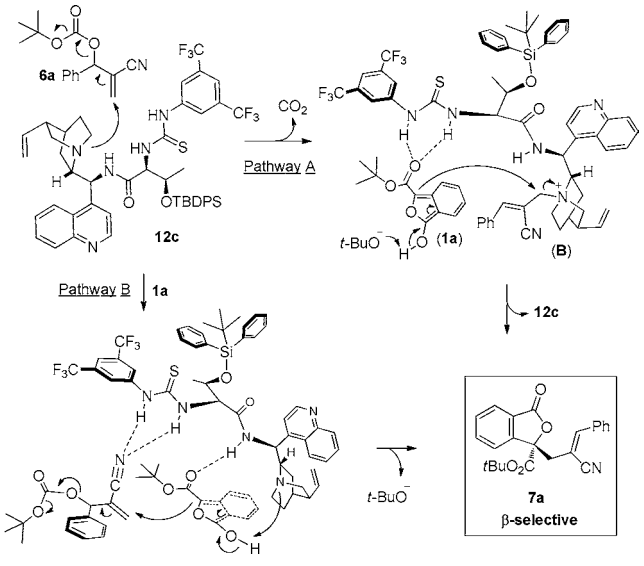


1 6 7

entry	R^1/R^2, 7	Z/E[b]	yield (%)[c]	ee (%)[d]
1	H/C_6H_5, **7a**	18:1	91	98
2	H/4-OMe-C_6H_4, **7b**	12:1	90	98
3	H/4-Cl-C_6H_4, **7c**	15:1	92	98
4	H/4-F-C_6H_4, **7d**	9:1	94	98
5	H/4-NO_2-C_6H_4, **7e**	9:1	95	98
6	H/3-CN-C_6H_4, **7f**	>25:1	93	98
7	H/3-Me-C_6H_4, **7g**	12:1	90	98
8	H/3-Br-C_6H_4, **7h**	10:1	95	98
9	H/3-Cl-C_6H_4, **7i**	18:1	92	99
10	H/3-F-C_6H_4, **7j**	21:1	93	97
11	H/2-Me-C_6H_4, **7k**	>25:1	92	97
12	H/2-Cl-C_6H_4, **7l**	11:1	91	96
13	H/3,4-Cl-C_6H_3, **7m**	11:1	86	98
14	H/3-NO_2-4-Cl-C_6H_3, **7n**	14:1	88	98
15	H/1-naphthyl, **7o**	7:1	92	97
16	H/2-thiophenyl, **7p**	25:1	80	91
17	H/(E)-PhCH=CH, **7q**	5:1	85	91
18	H/$C_6H_4CH_2CH_2$, **7r**	>25:1	75	95
19	H/H, **7s**		78	93
20	5-Br/4-Cl-C_6H_4, **7t**	>25:1	93	98
21	5-CN/C_6H_5, **7u**	10:1	88	97

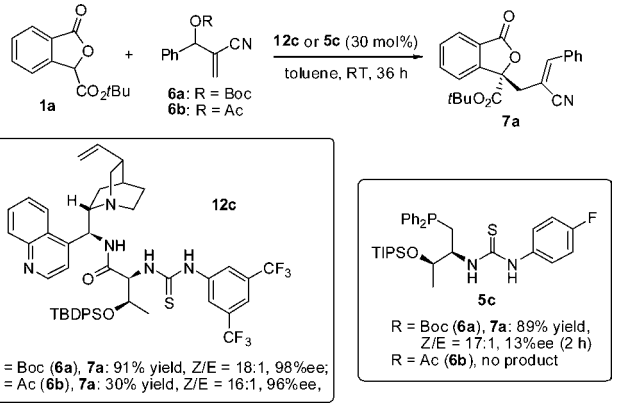
[a]Reactions were performed with **1** (0.05 mmol), **6** (0.075 mmol), and **12c** (0.005 mmol) in toluene (0.5 mL) under argon. [b]Determined by ^{1}H NMR analysis of the crude products. [c]Isolated yield. [d]Determined by HPLC analysis on a chiral stationary phase.

Scheme 4. Formation of β-Selective Allylation Product



was isolated. In contrast to γ-selectivity for carbonate **2b**, the observed β-selectivity with **6a** as a substrate under phosphine catalysis suggested that the cyano group in **6a** exerted a strong inductive effect and enhanced electrophilicity of the terminal alkene, and led to the formation of β-product.

Scheme 5. Employment of MBH Acetate in the Reaction



3. CONLUSIONS

In conclusion, we have used phthalides for the first time in the AAA reaction with MBH carbonates to access optically enriched 3,3-disubstituted phthalides. By employing bifunctional chiral phosphines or multifunctional tertiary amine–thioureas as the catalyst, we developed a highly regiodivergent approach to enantioselectively prepare γ-selective or β-selective allylic alkylation products, respectively. Our results also demonstrated that proper selection of catalysts and reaction conditions would differentiate an S_N2'–S_N2' pathway and an addition–elimination process, yielding different regioisomers of the allylic alkylation products in a highly enantiomerically pure form. Applications of the approaches described here to other allylation reactions, biological evaluation of our synthetic phthalides, and DFT calculations to understand our catalytic systems are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Representative experimental procedures, determinations of absolute configurations, X-ray crystallographic data, HPLC chromatograms, and NMR spectral data for all the compounds described. 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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