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Asymmetric Construction of Functionalized Bicyclic Imides via [3 + 2] Annulation of MBH Carbonates Catalyzed by Dipeptide-Based Phosphines

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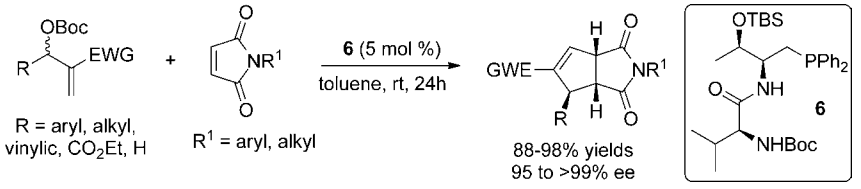
ABSTRACT



A highly enantioselective [3 + 2] annulation of MBH carbonates and maleimides catalyzed by chiral phosphines has been developed. In the presence of 5 mol % of L-Thr-L-Val-derived phosphine 6, functionalized bicyclic imides were prepared in excellent yields, and with high diastereoselectivities and nearly perfect enantioselectivities.

Synthesis of enantiomerically pure imide derivatives is of significant importance because of the wide occurrence of optically active imide moieties in natural products and biologically active molecules.[1] For instance, imides are the key building blocks for thalidomide,[2a] ethosuximide,[2b] phensuximide,[2c] and andrimid.[2d] Not surprisingly, considerable effort has been devoted to the construction of these structure motifs in the past decades.[3] However, apart from the Diels–Alder reaction of maleimides,[4] enantioselective preparation of bicyclic imides employing maleimides has rarely been explored,[5] despite the fact that such a structural scaffold is ubiquitous in many natural products and pharmaceutical agents (Figure 1).[6]

Nucleophilic phosphine catalysis represents one of the most straightforward methods for efficient assembly of cyclic compounds.[7] In particular, phosphine-triggered [3 + 2] annulations are extremely useful for the creation of cyclopentene ring structures.[8] Our group has been actively investigating in this research area in recent years.[9] We have developed a

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series of amino acid based[10] bifunctional phosphine catalysts and demonstrated that they are remarkably effective in a wide range of enantioselective organic transformations.[11] By utilizing L-threonine-derived bifunctional phosphines, we[11h] recently successfully applied Morita–Baylis–Hillman (MBH) carbonates as a C_3 synthon in the asymmetric [3 + 2] cycloaddition reaction.[12] Given the ready availability and strutural variation of the MBH carbonates, they are undoubtedly valuable reaction partners in the cylizations. We envisioned that a phosphine catalyzed [3 + 2] annulation of MBH carbonates with maleimides can lead to a facile access to bicyclic imides bearing three contiguous tertiary stereogenic centers (Scheme 1). Herein, we document a highly enantioselective [3 + 2] annulation mediated by dipeptide-based phosphines, furnishing bicyclic imides in excellent yields and nearly perfect enantioselectivities.

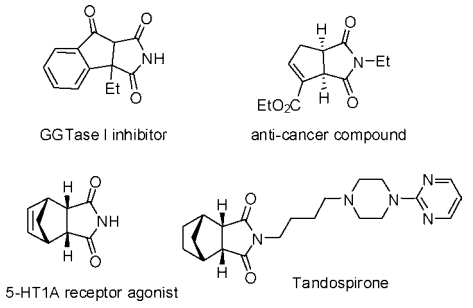
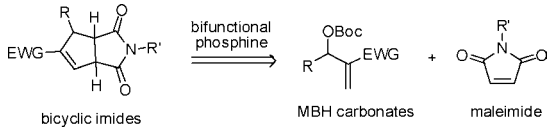


Figure 1. Selected bioactive bicyclic imides.

Scheme 1. Construction of Bicyclic Imides via Phosphine Catalyzed [3 + 2] Annulation



We began our investigation by examining the catalytic effects of various amino acid derived chiral phosphines in the [3 + 2] annulation reaction between MBH carbonate **1a** and *N*-phenyl maleimide **2a**, and the results are summarized in Table 1. Different L-Valine derived phosphines **4a**–**d** were effective, and the reaction proceeded smoothly at room temperature (entries 1–4). The influence of different Brønsted acid moieties was found to be significant. Employment of amide-bearing **4b** led to the formation of products with high enantioselectivity, but with no diastereoselectivity (entry 2). Catalyst **4c** with a carbamate group resulted in the formation of a single diastereomer (entry 3). Turning to our privileged threonine core[13] offered remarkable improvement. In the presence of L-Thr-derived **5**, the annulation took place to yield a single diastereomer with excellent enantioselectivity. The chemical yield of the reaction, however, was modest (entry 5). To make further improvement, we next examined dipeptide-based phosphines, which were recently developed by us for several enantioselective annulation processes.[11c–g] To our delight, L-Thr-L-Val-derived phosphine **6** and L-Thr-L-*tert*-Leu-derived phosphine **8** worked remarkably well for the reaction, affording the desired product in excellent yield, in a diastereomerically pure form and with a very high enantiomeric excess (entries 6 and 8). Contrary to our previous report,[11c] L-Thr-D-Val-derived phosphine **7** led to the products with a 1:1 diastereomeric ratio (entry 7), which again proved the vital importance of chirality matching in our stereoselective catalytic processes. Variation of the ester moiety in MBH carbonate **1** offered a slight improvement in ee (entry 9). Different solvents were examined, and none were found to be superior to toluene (entries 10–12). Notably, we were able to reduce the catalyst loading to 5 mol %, and both the chemical yield and stereoselectivities of the reaction were maintained (entry 13).

With the optimized reaction conditions in hand, the generality of phosphine **6** catalyzed [3 + 2] annulations

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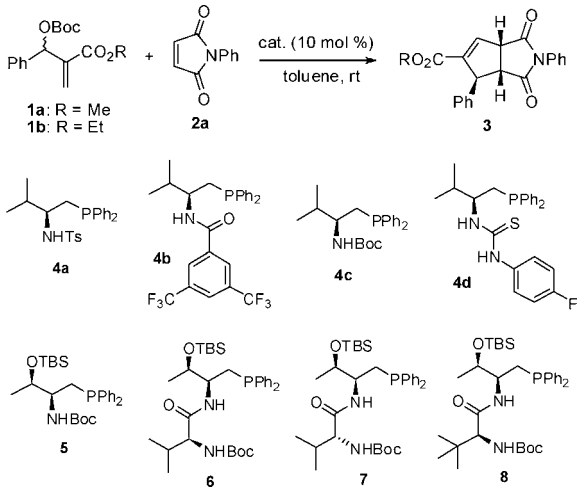
Table 1. Screening of Chiral Phosphines for the [3 + 2] Annulation of MBH Carbonates **1** with Maleimide **2a**[a]

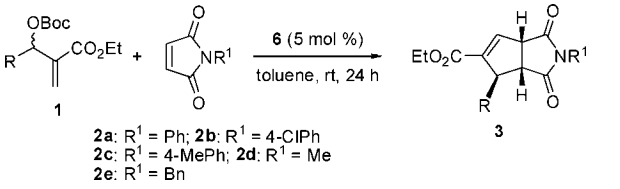


entry[a]	1	cat.	t (h)	dr[b]	yield (%)[c]	ee (%)[d]
1	**1a**	**4a**	24	1:1.3	<50	–
2	**1a**	**4b**	3	1:1	76	87
3	**1a**	**4c**	3	>25:1	71	51
4	**1a**	**4d**	3	2:1	62	41
5	**1a**	**5**	3	>25:1	73	92
6	**1a**	**6**	3	>25:1	92	98
7	**1a**	**7**	3	1:1.2	93	97
8	**1a**	**8**	3	>25:1	94	99
9	**1b**	**6**	3	>25:1	94	99
10[e]	**1b**	**6**	12	>25:1	65	99
11[f]	**1b**	**6**	24	–	<30	–
12[g]	**1b**	**6**	24	–	<10	–
13[h]	**1b**	**6**	24	>25:1	93	99

[a] Reactions were performed with **1** (0.06 mmol), **2a** (0.05 mmol), and catalyst (0.005 mmol) in toluene (0.5 mL). [b] Determined by ^{1}H NMR analysis of the crude products. [c] Isolated yield. [d] Determined by HPLC analysis on a chiral stationary phase. [e] Reaction was performed in $CHCl_3$ (0.5 mL). [f] Reaction was performed in CH_2Cl_2 (0.5 mL). [g] Reaction was performed in THF (0.5 mL). [h] The catalyst loading was 5 mol %.

was subsequently studied (Table 2). In all the examples evaluated, excellent yields and extremely high enantiomeric excesses were attainable. The reaction was applicable to MBH carbonates bearing different aromatic groups, regardless of their substitution pattern and electronic nature (entries 1–10). 2-Naphthyl and 2-thiophenyl-containing MBH substrates could also be used (entries 11–12). Moreover, MBH carbonates with a vinylic group, an ester, or a methyl group, as well as a hydrogen atom (MBH carbonate derived from formaldehyde), were all suitable for the reaction, albeit diastereoselectivities dropped in a few cases (entries 13–16). Furthermore, maleimides containing different *N*-substituents, including both aryl and alkyl groups, were all found to work wonderfully for the annulation reaction (entries 17–21). The absolute configurations of the bicyclic imides were determined based on X-ray crystal structural analysis of **3r** (see the Supporting Information for details).

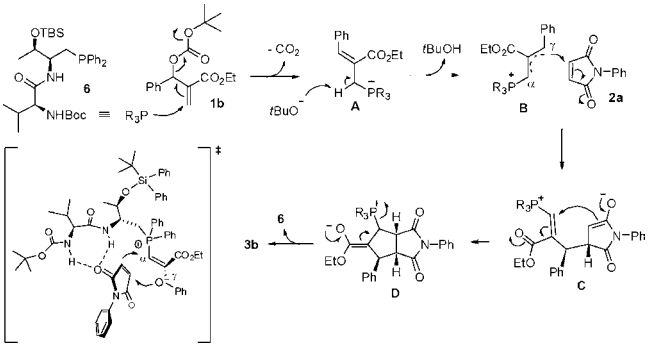
Table 2. Scope of the Reaction[a]



entry	R	2	3	dr[b]	yield (%)[c]	ee (%)[d]
1[e]	Ph	**2a**	**3a**	>25:1	91	99
2	Ph	**2a**	**3b**	>25:1	93	99
3	4-MeC_6H_4	**2a**	**3c**	>25:1	95	>99
4	4-$NO_2C_6H_4$	**2a**	**3d**	>25:1	93	98
5	4-FC_6H_4	**2a**	**3e**	>25:1	95	>99
6	4-CNC_6H_4	**2a**	**3f**	>25:1	93	98
7	3-BrC_6H_4	**2a**	**3g**	>25:1	96	99
8	3-ClC_6H_4	**2a**	**3h**	>25:1	93	>99
9	2-BrC_6H_4	**2a**	**3i**	>25:1	98	>99
10	2,4-ClC_6H_3	**2a**	**3j**	>25:1	93	99
11	2-thiophenyl	**2a**	**3k**	18:1	95	>99
12	2-naphthyl	**2a**	**3l**	>25:1	98	>99
13[f]	(*E*)-PhCH=CH	**2a**	**3m**	3:1	92	99
14	CO_2Et	**2a**	**3n**	12:1	95	>99
15[g]	Me	**2a**	**3o**	9:1	93	>99
16[g]	H	**2a**	**3p**	>25:1	88	95
17[h]	Ph	**2a**	**3q**	>25:1	90	>99
18	4-ClC_6H_4	**2b**	**3r**	>25:1	92	>99
19	Ph	**2c**	**3s**	>25:1	94	>99
20	Ph	**2d**	**3t**	13:1	93	>99
21	Ph	**2e**	**3u**	15:1	92	>99

[a] Reactions were performed with **1** (0.06 mmol), **2** (0.05 mmol), and **6** (0.0025 mmol) in toluene (0.5 mL). [b] Determined by ^{1}H NMR analysis of the crude products. [c] Isolated yield. [d] Determined by HPLC analysis on a chiral stationary phase. [e] CO_2Me was used in **1**. [f] When catalyst **5** (0.005 mmol) was used, **3m** was isolated in 93% yield and with 12:1 dr and 91% ee. [g] The catalyst loading was 10 mol %. [h] C(O)Me was used in **1**.

Scheme 2. Proposed Mechanism



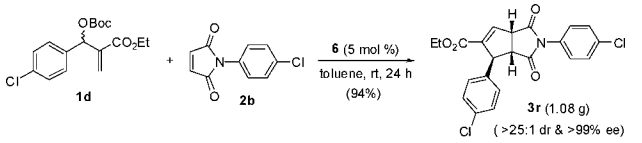
A plausible reaction mechanism is depicted in Scheme 2. The nucleophilic attack of phosphine **6** to MBH carbonate **1b** gives rise to intermediate **A**, with cocurrent release of CO_2. The in situ generated *tert*-butoxide deprotonates **A** to afford ylide **B**, which then undergoes γ-addition to

maleimide **2a** to furnish intermediate **C**. Intramolecular cyclization of **C**, followed by β-elimination, yields final product **3b** and regenerates catalyst **6**. To account for the observed stereochemical outcome, we propose a transition state model as shown in Scheme 2. Hydrogen bonding interactions between the maleimide and phosphonium intermediate not only lock the position of the maleimide, contributing to the stereoselectivity of the reaction, but also make γ-attack from the phosphonium enolate more favorable due to the activation of an oxygen atom in imide.

In view of the biological significance of chiral bicyclic imides, and to demonstrate the practicality of our method, we performed the annulation reaction at the gram scale. As shown in Scheme 3, when maleimide **2b** was treated with MBH carbonate **1d** under the optimal reaction conditions, the reaction proceeded smoothly to afford the desired imide **3r** at the gram scale without loss of reactivity or enantioselectivity (Scheme 3).

In summary, we have developed a highly stereoselective [3 + 2] annulation of MBH carbonates with maleimides. By utilizing dipeptide-based bifunctional phosphines, diastereomerically pure and highly enantiomerically enriched bicyclic imides (≥98% ee in most cases) could be readily prepared in excellent yields under mild reaction conditions. Biological evaluations of our synthetic chiral bicyclic imides are underway in our laboratory.

Scheme 3. Gram Scale [3 + 2] Annulation between MBH Carbonate **1d** and Maleimide **2b**



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Supporting Information Available. Representative experimental procedures, determination of absolute configurations, X-ray structure of **3r**, HPLC chromatogram, and NMR spectra of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.