Asymmetric Synthesis

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Highly Enantioselective [3+2] Annulation of Morita–Baylis–Hillman Adducts Mediated by L-Threonine-Derived Phosphines: Synthesis of 3-Spirocyclopentene-2-oxindoles having Two Contiguous Quaternary Centers**

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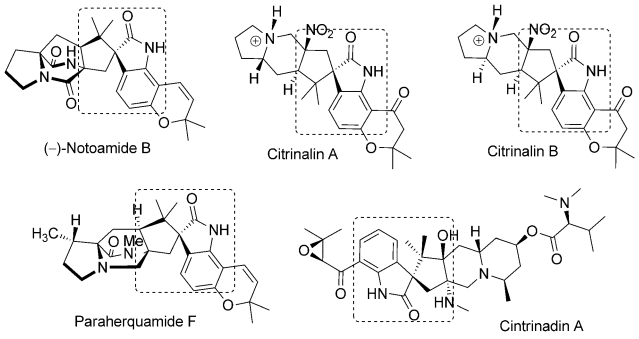
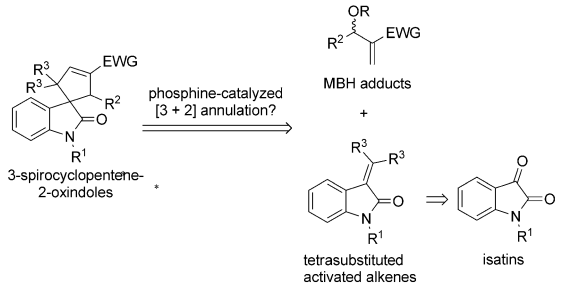
Spirocyclic oxindoles[1] are the structural motifs frequently found in many natural products and biologically active molecules.[2] Among many spirooxindole cores, the 3,3′-pyrrolidinyl spirooxindole units are well known for their strong bioactivity profiles, thus synthetic studies toward this fused heterocyclic system have been pursued intensively. Oxindoles having spiral carbocyclic rings are also important substructures that are widely present in numerous bioactive natural products. In this context, 3-spirocyclopentane-2-oxindoles containing two adjacent quaternary centers are particularly striking structural motifs[3] (Scheme 1), and their efficient asymmetric constructions are formidable synthetic tasks.[4] To the best of our knowledge, there were only two catalytic asymmetric syntheses in the literature dealing with similar structural scaffolds. Trost and co-workers reported an enantioselective construction of spirocyclic oxindolic cyclopentanes by using a palladium-catalyzed [3+2] cycloaddition of trimethylenemethane.[5] Very recently, Marinetti et al. disclosed an organocatalytic asymmetric [3+2] cyclization between 3-alkylideneindolin-2-ones and allenes for the synthesis of spirooxindoles.[6]



Scheme 1. Spirocyclicpentane oxindole structures having two contiguous quaternary centers.

Nucleophilic catalysis employing chiral phosphines is an intensively explored research area in asymmetric catalysis.[7] For the construction of five-membered ring systems, phosphine-mediated [3+2] annulations represents one of the most efficient approaches.[8] As part of our research program toward the development of asymmetric synthetic methods catalyzed by amino-acid-based organocatalysts,[9] we recently focused on the development of novel chiral phosphines from amino acids. We showed that dipeptide-derived novel phosphines were powerful catalysts for the enantioselective allene–acrylate [3+2] cycloadditions.[8n] More recently, we also derived a series of phosphine sulfonamide bifunctional catalysts and demonstrated their effectiveness in the enantioselective aza-Morita–Baylis–Hillman (aza-MBH) reactions.[10] We envisioned that phosphine-mediated [3+2] cyclizations may be utilized to construct spirooxindole cores (Scheme 2). The electron-deficient alkene components necessary for the annulation reactions can be conveniently derived from isatins. Notably, such tetrasubstituted activated alkenes are unexplored substrates in the asymmetric [3+2] cyclization processes, and their successful elaboration in the cycloaddition reaction may create two contiguous quaternary centers. Allenes and alkynes are commonly employed as C_3 synthons in the annulation reactions, and in this context, employment of more readily available and versatile C_3 synthons in the annulations is certainly ideal. The MBH reaction is one of the most atom-economic reactions for the construction of densely functionalized products,[11] and the



Scheme 2. Construction of 3-spirocyclopentene-2-oxindoles through phosphine-catalyzed [3+2] cycloadditions of MBH adducts. EWG = electron-withdrawing group.

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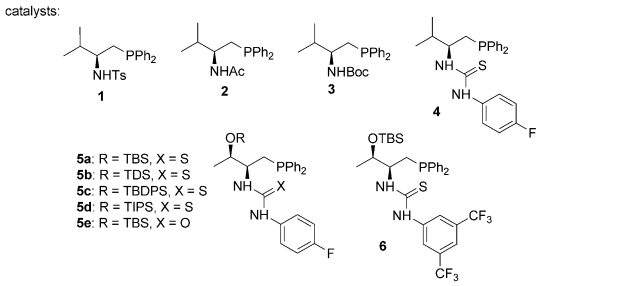
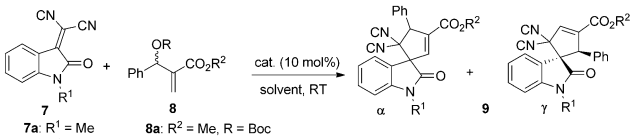
MBH adducts are tremendously useful intermediates in organic synthesis. In the past few years, Lu and co-workers pioneered the use of the MBH adducts in [3+2] cyclizations and various cycloadditions.[12] However, an asymmetric cycloaddition employing the MBH adducts is yet to be developed.[13] Compared with allenes and alkynes, the MBH adducts are much more challenging substrates for such annulations; their lower reactivity makes the development of an asymmetric catalytic annulation process particularly difficult. Given the high nucleophilicity observed for our amino-acid-derived chiral phosphines,[8n,10] we reasoned that our catalysts may be suitable for such an activation. Herein, we document the first highly enantioselective [3+2] cycloaddition between the MBH carbonates and isatin-derived tetrasubstituted activated alkenes, thereby creating 3-spirocyclopentene-2-oxindoles containing two contiguous quaternary centers.

The [3+2] cycloaddition between isatin-derived α,α-dicyanoalkene[14] **7** and the MBH carbonate **8** was selected as a model reaction, and the catalytic effects of various amino-acid-derived phosphines were examined (Table 1). To induce effective stereochemical control, potential interactions of the catalyst with the hydrogen-bond acceptor groups in the isatin derivatives seem to be important, thus, a number of amino-acid-based phosphines having various Brønsted acid moieties were prepared. L-Valine-derived phosphine sulfonamide **1** showed poor catalytic activity (entry 1). In the presence of valine-derived amide **2** or carbamate **3**, the reaction proceeded smoothly, thus affording the desired cyclization product in excellent yield, albeit with low stereoselectivity (entries 2 and 3). Valine-derived phosphine thiourea **4** displayed much-improved catalytic effects, and the products were obtained in excellent yield and with moderate enantioselectivity. However, the ratio of the α to γ regioisomer remained very poor (entry 4). With our previous success in threonine-based catalytic systems,[9] we then focused on threonine-derived phosphine thiourea catalysts. To our delight, the enantioselectivity was significantly improved when the threonine core was introduced, and only one diastereomer was observed. Common sterically hindered silyloxy groups[15] all proved to be effective, and the catalyst **5d** having a TIPS group gave slightly better results (entries 5–8). Replacement of the thiourea moiety in the catalyst with a urea resulted in a faster reaction, but with slightly decreased enantioselectivity (entry 9). Notably, the thiourea catalyst containing a 3,5-di-trifluoromethylphenyl group was not more effective than 4-fluorophenyl-derived thiourea, and the latter was thus chosen as it is more economical (entry 5 versus 10). To improve the regioselectivity of the reaction, we next employed oxindoles with different N-alkyl groups. Gratifyingly, the introduction of a benzyl group on the oxindole nitrogen atom led to substantially enhanced regioselectivity (entry 11). When the *N-para*-methoxybenzyl (PMB) was employed, the cyclization products were formed with an γ to α ratio of 14:1 (entry 12). The utilization of N-trityl substrate **7d**, however, resulted in very poor conversion, probably as a result of the steric hindrance introduced by the trityl group (entry 13). Variation of the ester groups in the MBH adducts led to further improvement; ethyl ester proved to be superior to the methyl ester (entry 14), and the utilization of the MBH adduct with the *tert*-butyl ester further increased the *ee* value of the cyclization product to 85% (entry 15). The carbonate group in the MBH adducts is important for the observed reactivity, since the corresponding MBH acetate was found to be inactive in the cycloaddition (entry 16). The addition of 3 Å molecular sieves to the

Table 1: Asymmetric [3+2] annulations of MBH adducts with isatin-derived activated alkenes.[a]

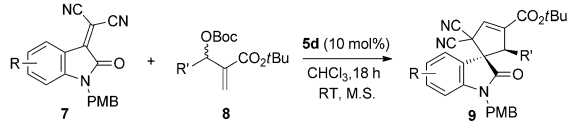




Entry	Cat.	7	8	Solvent	*t* [h]	Yield [%][b]	γ/α[c]	*ee* [%][d]
1	**1**	**7a**	**8a**	THF	12	<30	–	–
2	**2**	**7a**	**8a**	THF	12	90	1.5:1	10
3	**3**	**7a**	**8a**	THF	12	92	1.5:1	16
4	**4**	**7a**	**8a**	THF	12	94	1.5:1	35
5	**5a**	**7a**	**8a**	THF	12	93	2:1	71
6	**5b**	**7a**	**8a**	THF	12	89	2:1	70
7	**5c**	**7a**	**8a**	THF	12	83	2:1	69
8	**5d**	**7a**	**8a**	THF	12	93	2:1	74
9	**5e**	**7a**	**8a**	THF	6	92	2:1	68
10	**6**	**7a**	**8a**	THF	12	89	2:1	70
11	**5d**	**7b**	**8a**	THF	18	86	13:1	75
12	**5d**	**7c**	**8a**	THF	18	84	14:1	77
13	**5d**	**7d**	**8a**	THF	48	<30	–	–
14	**5d**	**7c**	**8b**	THF	18	83	14:1	80
15	**5d**	**7c**	**8c**	THF	48	90	13:1	85
16	**5d**	**7c**	**8d**	THF	48	n.r.	–	–
17[e]	**5d**	**7c**	**8c**	THF	18	92	14:1	86
18[e]	**5d**	**7c**	**8c**	CH_2Cl_2	18	89	7:1	88
19[e]	**5d**	**7c**	**8c**	CH_3CN	18	70	2:1	63
20[e]	**5d**	**7c**	**8c**	toluene	18	90	>20:1	90
21[e]	**5d**	**7c**	**8c**	DMF	48	trace	–	–
22[e]	**5d**	**7c**	**8c**	Et_2O	18	91	>20:1	85
23[e]	**5d**	**7c**	**8c**	CH_3OH	48	trace	–	–
24[e]	**5d**	**7c**	**8c**	$CHCl_3$	18	93	13:1	96

[a] Reactions conditions: **7** (0.05 mmol), **8** (0.075 mmol), catalyst (0.005 mmol), and solvent (0.5 mL) under Ar. [b] Yield of the isolated product. [c] The γ/α ratios were determined by ^{1}H NMR analysis of the crude products. [d] The *ee* value of the major regioisomer was determined by HPLC analysis using a chiral stationary phase. [e] 3 Å molecular sieves (30 mg) were added. Boc = *tert*-butoxycarbonyl, DMF = *N*,*N*′-dimethylformamide, n.r. = no reaction, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TDS = thexyldimethylsilyl, THF = tetrahydrofuran, TIPS = triisopropylsilyl, Trt = trityl.

Table 2: Substrate scope.[a]



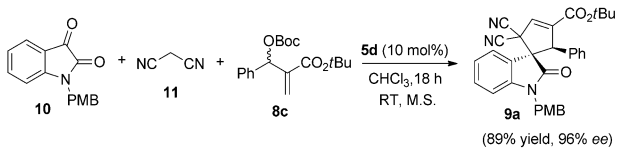
Entry	R′, R (**9**)	Yield [%][b]	γ/α[c]	*ee* [%][d]
1	Ph, H (**9a**)	93	13:1	96
2	4-FC_6H_4, H (**9b**)	92	17:1	94
3	4-ClC_6H_4, H (**9c**)	96	21:1	94
4	4-BrC_6H_4, H (**9d**)	96	23:1	94
5	4-$CF_3C_6H_4$, H (**9e**)	90	16:1	93
6	4-CNC_6H_4, H (**9f**)	92	14:1	93
7	4-MeC_6H_4, H (**9g**)	94	12:1	94
8	3-ClC_6H_4, H (**9h**)	95	13:1	95
9	3-BrC_6H_4, H (**9i**)	91	12:1	94
10	3-MeC_6H_4, H (**9j**)	92	15:1	95
11	3-CNC_6H_4, H (**9k**)	93	15:1	92
12	2-FC_6H_4, H (**9l**)	89	4:1	87
13[e]	3,5-$(CF_3)_2$-C_6H_3, H (**9m**)	78	14:1	91
14	2-naphthyl, H (**9n**)	94	16:1	94
15	3-furyl, H (**9o**)	91	4:1	87
16[f]	2-thiophenyl, H (**9p**)	91	1:1	90
17[g]	(*E*)-PhCH=CH, H (**9q**)	94	25:1	75
18[h]	$PhCH_2CH_2$, H (**9r**)	83	1:2	65
19[i]	CO_2Et, H (**9s**)	92	1:1	96
20	Ph, 5-Me (**9t**)	89	12:1	99
21	Ph, 5,7-Me (**9u**)	86	10:1	96
22	Ph, 7-Cl (**9v**)	82	7:1	91
23	Ph, 7-F (**9w**)	85	7:1	94

[a] Reactions conditions: **7** (0.05 mmol), **8** (0.075 mmol), **5d** (0.005 mmol), and 3 Å molecular sieves (30 mg) in $CHCl_3$ (0.5 mL) under Ar. [b] Yield of the isolated product. [c] The γ/α ratios were determined by ^{1}H NMR analysis of the crude products, and the two isomers could be easily separated. [d] The *ee* value of γ-regioisomer was determined by HPLC analysis using a chiral stationary phase. [e] The reaction time was 36 h. [f] The *ee* value of the α isomer was 53%. [g] The reaction was performed with 10 mol% of **5e** in toluene (1.0 mL) at 80°C for 10 min. [h] The reaction was performed with 20 mol% of **5e** at 0°C for 48 h and the *ee* value of the α isomer was 67%. [i] The reaction was performed at 0°C for 1 h and the *ee* value of the α isomer was 54%. M.S. = molecular sieves.

reaction mixture was beneficial, as the reaction rate was significantly enhanced and a better enantioselectivity was attainable (entry 17). A solvent screening was subsequently performed, and chloroform was identified to be the best solvent for the reaction (entries 18–24). Under the optimized conditions, the diastereomerically pure spirooxindole **9** was regioselectively formed in 93% yield and with 96% *ee*.

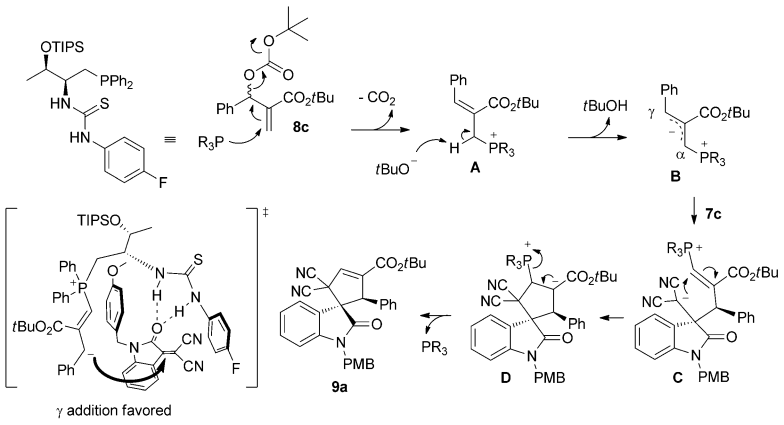
The scope of **5d**-mediated [3+2] annulations between a variety of 2-(2-oxoindolin-3-ylidene)malononitriles **7** and different MBH carbonates **8** was evaluated, and the results are summarized in Table 2. In general, excellent yields and selectivities were attainable for all the examples examined. The reaction tolerated different aromatic moieties in the MBH carbonates **8**. Notably, the presence of *ortho*-substituted aryls in **8** resulted in reduced regioselectivity and enantioselectivity (entry 12). The reaction also worked well for the 2-naphthyl-, 3-furyl-, and 2-thiophenyl-containing MBH carbonates (entries 14–16). When the MBH adduct with a vinylic substituent was used, good enantioselectivity could be obtained (entry 17).[16] The MBH carbonate bearing an alkyl group could also be employed, although the *ee* value was only modest (entry 18). It should be noted the alkyl-substituted MBH adducts are intrinsically difficult C_3 synthons for the asymmetric [3+2] annulation,[12c] and our results represent one of the only two successful examples reported in the literature.[13] Moreover, the reaction worked well for different isatin-derived α,α-dicyanoalkenes, and both good regioselectivities and enantioselectivities were observed (entries 20–23). The absolute configurations of the cycloaddition products were determined based on X-ray crystal structural analysis of an amide derivative of **9d** (see the Supporting Information for details).[17]

The 2-(2-oxoindolin-3-ylidene)malononitriles utilized in this study were prepared from isatins and malononitrile **11**. To make our method more synthetically appealing, the feasibility of carrying out the reaction in one pot was examined. The one-pot protocol proved to be equally effective; simply mixing isatin **10**, malononitrile **11**, and the MBH carbonate **8c** in the presence of **5d** resulted in a smooth annulation reaction, thus delivering the spirooxindole **9a** in 89% yield and with 96% *ee* (Scheme 3).



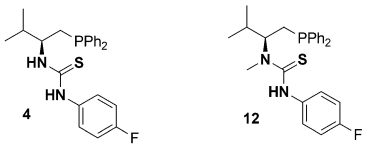
Scheme 3. One-pot construction of a 3-spirocyclopentene-2-oxindole.

A plausible reaction mechanism is proposed in Scheme 4. The reaction is initiated by the nucleophilic attack of the phosphine on the MBH carbonate **8c** to yield the phosphonium salt **A**. The in situ generated *tert*-butoxide anion deprotonates **A** to give the ylide **B**, which then undergoes γ addition to alkene **7c** to give the intermediate **C**. Subsequent intramolecular cyclization then delivers **D**, and the



Scheme 4. Proposed mechanism.

elimination of the phosphine moiety then regenerates the catalyst and affords the final cycloaddition product. The in situ generated *tert*-butoxide anion is crucial for the reaction, as the cyclization did not occur when the MBH acetate was employed (Table 1, entry 16). The observed γ selectivity may be attributed to the steric hindrance induced by the N-PMB group of **7** in the key cycloaddition step, and the potential aromatic interactions cannot be excluded at this stage. We believe the hydrogen-bonding interactions between the thiourea moiety of the catalyst and the isatins play a crucial role in asymmetric induction. Such an assumption has been supported experimentally; the methylated phosphine thiourea[18] **12** was able to catalyze the [3+2] annulation between **7c** and **8c**, however, an γ to α ratio of 2:1 and 11% *ee* (for the γ isomer of **9a**) were obtained. In comparison a 12:1 regioselectivity and 83% *ee* were observed when **4** was used under otherwise identical conditions (Scheme 5).



(**9a**: 95% yield, γ/α = 12:1, 83% *ee*) (**9a**: 93% yield, γ/α = 2:1, 11% *ee*)

Scheme 5. The [3+2] annulation of **7c** and **8c** promoted by **4** or **12**.

In conclusion, we have utilized the MBH carbonates as C_3 synthons in asymmetric [3+2] annulation reactions for the first time. These MBH carbonates, compared to allenes and alkynes, are more readily available and versatile, thus they are expected to have applications in asymmetric synthesis. We have also developed a threonine-derived phosphine thiourea catalyst for the promotion of the stereoselective [3+2] cycloaddition process between the MBH carbonates and isatin-derived tetrasubstituted alkenes. This strategy allows facile enantioselective preparation of biologically important 3-spirocyclopentene-2-oxindoles with two contiguous quaternary centers. Biological evaluations of our synthetic spirooxindoles, further applications of the MBH adducts in other asymmetric organic reactions, and mechanistic investigations of this novel [3+2] annulation are underway in our laboratory.

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