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Highly Regio- and Diastereoselective Construction of Spirocyclopenteneoxindoles through Phosphine-Catalyzed [3 + 2] Annulation of Morita–Baylis–Hillman Carbonates with Isatylidene Malononitriles

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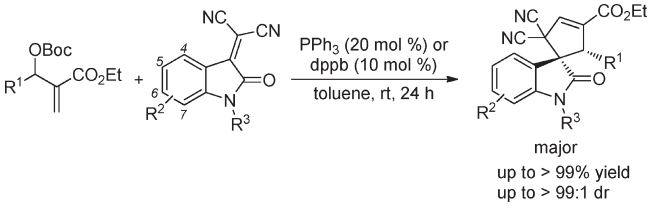
ABSTRACT



Phosphine-catalyzed highly regio- and diastereoselective [3 + 2] annulation of Morita–Baylis–Hillman (MBH) carbonates with isatylidene malononitriles has been disclosed to give the corresponding spirocyclopenteneoxindoles in excellent yields under mild conditions. A plausible reaction mechanism has also been proposed on the basis of previous literature.

Morita–Baylis–Hillman (MBH) acetates and carbonates as synthetically useful synthons have attracted significant attention from organic chemists.[1] The transformations of MBH acetates and carbonates have been directed toward the following three styles: substitution of MBH acetates and carbonates at the β- or β'-position with pronucleophiles (Scheme 1, eqs 1 and 2);[2,3] annulation of MBH acetates and carbonates with electron-deficient olefins in the presence of tertiary phosphine (Scheme 1,

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(3) Selected papers on the asymmetric substitution of MBH acetates and carbonates by nucleophiles: (a) Du, Y.-S.; Han, X.-L.; Lu, X.-Y. *Tetrahedron Lett.* **2004**, *45*, 4967. (b) van Steenis, D. J. V. C.; Marcelli, T.; Lutz, M.; Spek, A. L.; van Maarseveen, J. H.; Hiemstra, H. *Adv. Synth. Catal.* **2007**, *349*, 281. (c) Jiang, K.; Peng, J.; Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, *45*, 3955. (d) Cui, H.-L.; Peng, J.; Feng, X.; Du, W.; Jiang, K.; Chen, Y.-C. *Chem.—Eur. J.* **2009**, *15*, 1574. (e) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 720. (f) Peng, J.; Huang, X.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2010**, *12*, 4260. (g) Zhang, S.-J.; Cui, H.-L.; Jiang, K.; Li, R.; Ding, Z.-Y.; Chen, Y.-C. *Eur. J. Org. Chem.* **2009**, 5804. (h) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737. (i) Hu, Z.-K.; Cui, H.-L.; Jiang, K.; Chen, Y.-C. *Sci. Chin. Ser. B-Chem.* **2009**, *52*, 1309. (j) Feng, X.; Yuan, Y.-Q.; Cui, H.-L.; Jiang, K.; Chen, Y.-C. *Org. Biomol. Chem.* **2009**, *7*, 3660. (k) Hong, L.; Sun, W.-S.; Liu, C.-X.; Zhao, D.-P.; Wang, R. *Chem. Commun.* **2010**, *46*, 2856. (l) Sun, W.-S.; Hong, L.; Liu, C.-X.; Wang, R. *Org. Lett.* **2010**, *12*, 391. (m) Zhang, T.-Z.; Dai, L.-X.; Hou, X.-L. *Tetrahedron: Asymmetry* **2007**, *18*, 1990. (n) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (o) Ma, G.-N.; Cao, S.-H.; Shi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1086. (p) Deng, H.-P.; Wei, Y.; Shi, M. *Eur. J. Org. Chem.* **2011**, 1956. (q) Yang, Y.-L.; Pei, C.-K.; Shi, M. *Org. Biomol. Chem.* **2011**, *9*, 3349.

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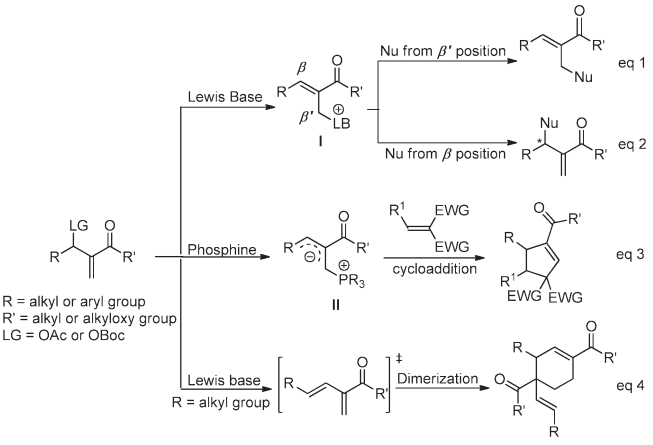
eq 3);[4] dimerization of MBH acetates and carbonates if R is an alkyl group in the presence of Lewis base (Scheme 1, eq 4).[5]

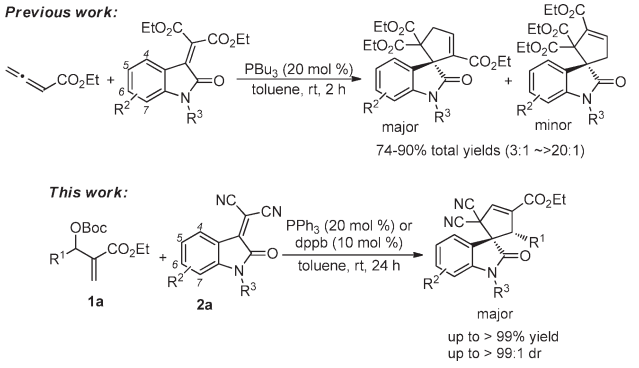
Scheme 1. Transformations of MBH Acetates or Carbonates



Among these transformations, annulation of MBH acetates and carbonates with electron-deficient olefins is an extremely useful synthetic method to construct multifunctional cyclic compounds because the in situ generated phosphorus ylides from MBH acetates and carbonates in the presence of tertiary phosphines are very reactive 1,3-dipoles in a variety of annulations. In this aspect, Lu and co-workers first reported a series of intra- and intermolecular [3 + *n*] annulations (n = 2, 4, 6) using MBH carbonates as 1,3-dipoles with various electron-deficient olefins catalyzed by tertiary phosphine, affording the corresponding cycloadducts in good yields and high regioselectivities under mild conditions.[4a−f] More recently, Zhang, Huang, and He and co-workers have also developed several MBH acetates and carbonates involved [4 + 1] annulations to give the annulation products in high yields, respectively.[6] Furthermore, Tang's group utilized spirobiindane-based chiral phosphines as catalysts to provide the corresponding intramolecular [3 + 2] annulation products in good yields along with high ee values in 2010.[7]

The prenylated indole alkaloids containing a spirocyclopenteneoxindole scaffold isolated from both terrestrial and marine fungi have attracted intense research efforts owing to their complex molecular structures and range of biological activities.[8] Recently, our group has reported an efficient method to construct this important structural motif through annulation of isatin-derived electron-deficient alkenes with allenoate in the presence of phosphine.[9] Herein, we to disclose a phosphine-catalyzed highly regio- and diastereoselective [3 + 2] annulation of MBH carbonates with isatylidene malononitriles to produce spirocyclopenteneoxindoles in good yields under mild conditions (Scheme 2). It should be also mentioned here that during our preparation of this manuscript, Barbas and his co-workers have reported a novel asymmetric [3 + 2] cycloaddition of MBH carbonates with methyleneindolinones in the presence of a chiral phosphine to give the corresponding spirocyclopentaneoxindoles, which have different regioselectivities from ours, in good yields and high ee values.[10]

Scheme 2. Phosphine-Catalyzed [3 + 2] Annulations of Isatylidenes To Construct Spirocyclopenteneoxindoles



We initially utilized 20 mol % of PPh_3 as catalyst and ethyl 2-((*tert*-butoxycarbonyloxy)(4-nitrophenyl)methyl)-acrylate **1a** (1.3 equiv) and 2-(1-benzyl-2-oxoindolin-3-ylidene)malononitrile **2a** (1.0 equiv) as substrates to investigate the influence of solvents on this annulation reaction. The results of these experiments are summarized in Table 1. It was found that toluene is the best solvent in this reaction, giving the corresponding annulation product **3a** in >99% yield along with >99:1 dr within 24 h (Table 1, entries 1−6). The relative configuration of major product

(4) (a) Du, Y.-S.; Lu, X.-Y.; Zhang, C.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Du, Y.-S.; Feng, J.-Q.; Lu, X.-Y. *Org. Lett.* **2005**, *7*, 1987. (c) Feng, J.-Q.; Lu, X.-Y.; Kong, A.-D.; Han, X.-L. *Tetrahedron* **2007**, *63*, 6035. (d) Zheng, S.-Q.; Lu, X.-Y. *Org. Lett.* **2008**, *10*, 4481. (e) Zheng, S.-Q.; Lu, X.-Y. *Tetrahedron Lett.* **2009**, *50*, 4532. (f) Zheng, S.-Q.; Lu, X.-Y. *Org. Lett.* **2009**, *11*, 3978. (g) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (h) Zhou, R.; Wang, J.-F.; Song, H.-B.; He, Z.-J. *Org. Lett.* **2011**, *13*, 580. (i) Cowen, B. J.; Miller, J. S. *Chem. Soc. Rev.* **2009**, *38*, 3102. (j) Wei, Y.; Shi, M *Acc. Chem. Res.* **2010**, *43*, 1005. (k) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174.

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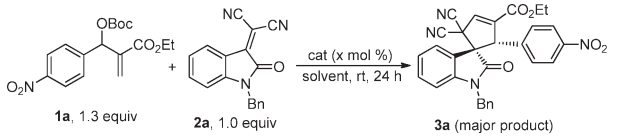
(10) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. The regiochemistry of the major product is different from that of **3a**.

Table 1. Screening of Solvents and Catalysts



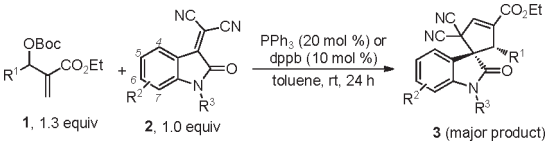
entry	cat	X	solvent	dr[a]	yield (%) of **3a**[b]
1	PPh_3	20	$CHCl_3$	7:1	88
2	PPh_3	20	toluene	>99:1	>99
3	PPh_3	20	DCM	3:1	62
4	PPh_3	20	THF	7:1	88
5	PPh_3	20	CH_3CN	2:1	42
6	PPh_3	20	DMF	1.5:1	38
7	PPh_2Me	20	toluene	14:1	93
8	dppb	10	toluene	49:1	98
9	$PPhMe_2$	20	toluene	3:1	66
10	PBu_3	20	toluene	4:1	72
11	DABCO	20	toluene		
12[c]	PPh_3	10	toluene	>99:1	>99
13[d]	PPh_3	5	toluene	>99:1	>99

[a] Determined by ^{1}H NMR spectroscopic data of crude products. [b] Yield was determined by ^{1}H NMR spectroscopic data of crude products using 1,3,5-trimethoxybenzene as a calibrated internal standard. [c] Reaction was carried out at room temperature for 30 h. [d] Reaction was carried out at room temperature for 48 h.

was determined by X-ray crystal structure.[11] Its ORTEP drawing is shown in the Supporting Information, and the corresponding CIF data are also presented in the Supporting Information. The examination of other phosphines such as PPh_2Me, $PPhMe_2$, dppb, or PBu_3 and 1,4-diazabicyclic-[2,2,2]octane (DABCO) revealed that PPh_3 was the best catalyst for this reaction and DABCO did not catalyze this reaction (Table 1, entries 7−11). Reducing the employed amounts of PPh_3 to 10 or 5 mol % also gave **3a** in 99% yield and >99:1 dr upon prolonging the reaction time (Table 1, entries 12 and 13).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this [3 + 2] annulation reaction, and the results are summarized in Table 2. Using isatylidene malononitrile **2a** as substrate, we examined its reaction with MBH carbonates **1b**−**k** derived from various aromatic or aliphatic aldehydes and found that the reactions of **2a** with MBH carbonates **1b**−**e** derived from electron-deficient aromatic aldehydes proceeded smoothly to give the corresponding products **3b**−**e** in excellent yields (90%→99%) along with high diastereoselectivities (dr = 10:1→99:1) (Table 2, entries 2−5). As for MBH carbonate **1f** having a chlorine substituent at the *ortho*-position of the benzene ring, MBH carbonate **1g** and MBH carbonates **1h** and **1i** bearing an electron-donating group on their benzene rings as well as MBH carbonates **1j** and **1k** derived from aliphatic aldehydes, the reactions became sluggish, presumably due to the steric or electronic effect, respectively. For example, using MBH carbonates **1f** and **1g** as substrates afforded the desired products **3f** and **3g** in 79% yield (dr = 8:1) and 94% yield (dr = 16:1), respectively, after 72 h (Table 2, entries 6 and 7). However, we found that when dppb (10 mol %) instead of PPh_3 (20 mol %) was used as catalyst, the reactions also proceeded efficiently, affording the cycloadducts **3g**−**k** in good yields along with good dr values within 24 h[12] (Table 2, entries 7−11). Using MBH carbonate **1c** as substrate, we next examined its reactions with isatylidene malononitriles **2b**−**g** bearing different substituents on their benzene rings or having different N-protecting groups, and it was found that all of the reactions proceeded smoothly to produce the corresponding products **3l**−**q** in excellent yields (88% → 99%) along with good to excellent dr values (8:1 → 99:1) (Table 2, entries 12−17).

Table 2. Substrate Scope for [3 + 2] Annulation of Isatylidene Malononitrile Derivatives with MBH Carbonates



entry	R^1	R^2	R^3	dr[a]	yield (%) of **3**[b]
1	**1a**, *p*-$NO_2C_6H_4$	**2a**, H	Bn	>99:1	**3a**, >99 (86)
2	**1b**, *m*-$NO_2C_6H_4$	H	Bn	19:1	**3b**, 95 (89)[c]
3	**1c**, *p*-CNC_6H_4	H	Bn	>99:1	**3c**, >99 (98)
4	**1d**, *p*-BrC_6H_4	H	Bn	12:1	**3d**, 92 (85)[c]
5	**1e**, *p*-ClC_6H_4	H	Bn	10:1	**3e**, 90 (81)[f]
6	**1f**, *o*-ClC_6H_4	H	Bn	8:1[d], 4:1[e]	**3f**, 79[d] (73)[c], 67[e]
7	**1g**, C_6H_5	H	Bn	16:1[d], 23:1[e]	**3g**, 94[d], 93[e] (84)[c]
8	**1h**, *p*-MeC_6H_4	H	Bn	22:1[e]	**3h**, 92[e] (86)[c]
9	**1i**, *p*-$MeOC_6H_4$	H	Bn	19:1[e]	**3i**, 94[e] (89)[c]
10	**1j**, H	H	Bn	12:1[e]	**3j**, 86[e] (81)[c]
11	**1k**, Me	H	Bn	2:1[e]	**3k**, 69[e] (56)[c]
12	*p*-CNC_6H_4	**2b**, 5-Br	Bn	49:1	**3l**, 98 (97)[c]
13	*p*-CNC_6H_4	**2c**, 5-Cl	Bn	99:1	**3m**, 99 (90)[c]
14	*p*-CNC_6H_4	**2d**, 5-Me	Bn	49:1	**3n**, 98 (90)[c]
15	*p*-CNC_6H_4	**2e**, 6-Br	Bn	>99:1	**3o**, >99 (85)[c]
16	*p*-CNC_6H_4	H	**2f**, allylic	24:1	**3p**, 96 (89)[c]
17	*p*-CNC_6H_4	H	**2g**, Me	8:1	**3q**, 88 (83)[c]

[a] Determined by ^{1} H NMR spectroscopic data of crude products. [b] Yield was determined by ^{1}H NMR spectroscopic data of crude products using 1,3,5-trimethoxybenzene as a calibrated internal standard. [c] Isolated yield of the major product. [d] Reactions were performed for 72 h. [e] Reactions were carried out for 24 h in the presence of dppb (10 mol %).

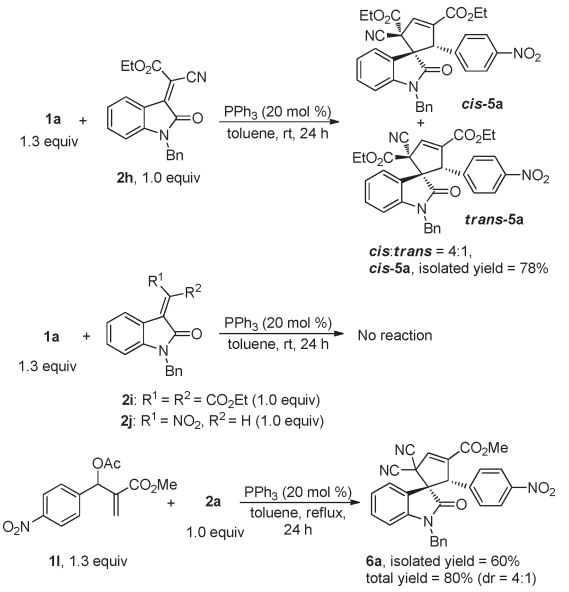
We have further explored the scope of isatylidenes **2** in this phosphine-catalyzed annulation under standard conditions and found that isatylidene cyanoacetate **2h** could also undergo this annulation reaction smoothly to give the corresponding cycloadduct *cis*-**5a** in 78% isolated yield along with a 4:1 dr (*cis*:*trans*) value (Scheme 3). The relative configuration of the major diastereomer *cis*-**5a** has been also determined by its X-ray crystal structure.[13] Its ORTEP drawing and the corresponding CIF data are presented in

(11) The crystal data of **3a** (major product) have been deposited in the CCDC with no. 805747.

(12) The dr value of **3j** was the ratio of two regioisomers.

(13) The crystal data of *cis*-**5a** have been deposited in the CCDC with no. 812838.

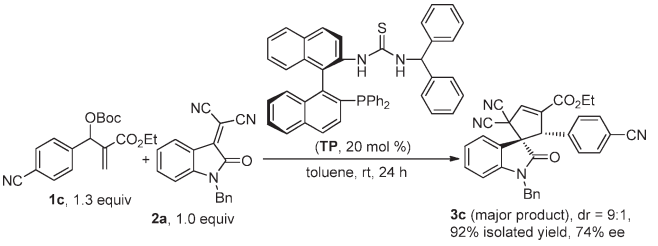
Scheme 3. [3 + 2] Annulation from MBH Carbonate **1a** or MBH Acetate **1l** with Other Isatylidene Derivatives



the Supporting Information. When isatylidene derivatives **2i** ($R^1 = R^2 = CO_2Et$) and **2j** ($R^1 = NO_2$, $R^2 = H$) were used as substrates, no reaction occurred under the standard conditions (Scheme 3). The reaction of MBH acetate **1l** with **2a** also proceeded smoothly to give the corresponding cycloadduct **6a** in 60% isolated yield along with 4:1 dr value in toluene under reflux for 24 h (Scheme 3).

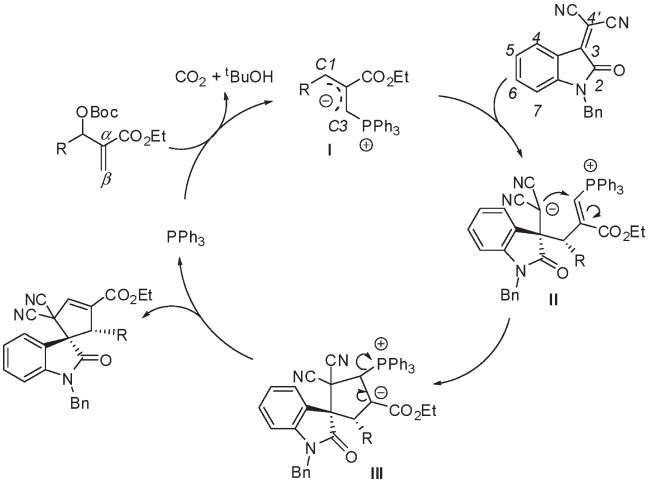
The chiral bifunctional thiourea–phosphine catalyst TP, which was an effective catalyst for the asymmetric allylic amination of MBH acetates,[3p] was also fairly effective in the [3 + 2] annulation of MBH carbonate **1c** with **2a** in toluene at room temperature, giving the corresponding major cycloadduct **3c** in 92% isolated yield along with 9:1 dr and 74% ee value (Scheme 4). The exploration of more effective chiral phosphines is undergoing.

Scheme 4. Asymmetric [3 + 2] Annulation Catalyzed by Chiral Bifunctional Thiourea-Phosphine Catalyst **TP**



On the basis of above experimental results and Lu's work,[4c] a plausible reaction mechanism has been outlined in Scheme 4. PPh_3 attacks from the β-position of MBH carbonate to take off carbon dioxide and *t*-BuOH, affording phosphorus ylide **I**. Then the nucleophilic attack of phosphorus ylide **I** at the 3-position of isatylidene malononitrile with its *C1*-terminal produces intermediate **II**, which undergoes Michael addition at the α-position of phosphorus cation to generate intermediate **III**. The elimination of PPh_3 along with the double bond formation furnishes the corresponding spirocyclopenteneoxindole product and completes the catalytic cycle. The diastereoselectivity of this reaction is perhaps controlled by steric effects as a stepwise process.

Scheme 5. Plausible Reaction Mechanism



In summary, we have found and developed an interesting phosphine-catalyzed highly regio- and diastereoselective [3 + 2] annulation of MBH carbonates with isatylidene malononitriles, affording the corresponding functionalized spirocyclopenteneoxindoles in good to excellent yields under mild conditions. A plausible reaction mechanism has also been proposed on the basis of previous literature and our own investigations (Scheme 5). Efforts are in progress toward the development of an asymmetric version of this reaction and in the application of this new methodology to synthesize interesting biologically active compounds.

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Supporting Information Available. Spectroscopic data and NMR charts of the compounds shown in Tables 1 and 2, Scheme 3, X-ray crystal data of major diastereomers **3a** and *cis*-**5a**, as well as detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.