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Phosphine-catalyzed asymmetric [4 + 1] annulation of Morita–Baylis–Hillman carbonates with dicyano-2-methylenebut-3-enoates†

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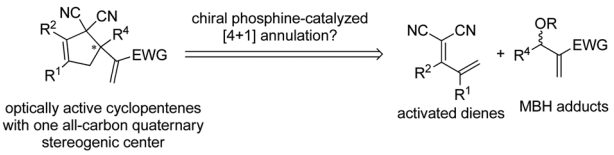
A novel asymmetric [4 + 1] annulation of MBH carbonates with dicyano-2-methylenebut-3-enoates has been developed for the first time, providing an efficient and enantioselective synthesis of highly functionalized cyclopentenes bearing one all-carbon quaternary stereogenic center.

Over the past decade, nucleophilic phosphine catalysis has attracted much research effort.[1] At the present stage, phosphine-mediated reactions have become a powerful tool in producing carbo- and heterocycles.[2] In particular, phosphine-catalyzed [3 + 2] and [4 + 2] annulations[3] of allenoates and imines/alkenes have been applied in the synthesis of several natural products.[4] Recently, Morita–Baylis–Hillman (MBH) acetates and carbonates as complementary and versatile substrates have emerged in nucleophilic phosphine catalysis since 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 a tertiary phosphine under mild conditions.[5] Then, several reports on asymmetric [3 + 2] annulations of MBH carbonates with electron-deficient olefins have been disclosed.[6] More recently, Zhang, Huang and He and their co-workers have also developed several MBH adducts involved in [4 + 1] annulations to give the annulation products in high yields, respectively, in which the MBH adducts served as a new kind of 1,1-dipolar synthon.[7] However, to the best of our knowledge, there is no report on the asymmetric version of this reaction. On the basis of these studies and our ongoing investigations on the phosphine catalyzed asymmetric annulations,[8] we envisioned that chiral phosphine-mediated [4 + 1] cyclization may be utilized to construct densely functionalized optically active cyclopentenes (Scheme 1).

The electron-deficient diene compounds necessary for the annulation reactions can be conveniently prepared from alkyl propiolates and α,α-dicyanoolefins.[9] Herein we wish to report

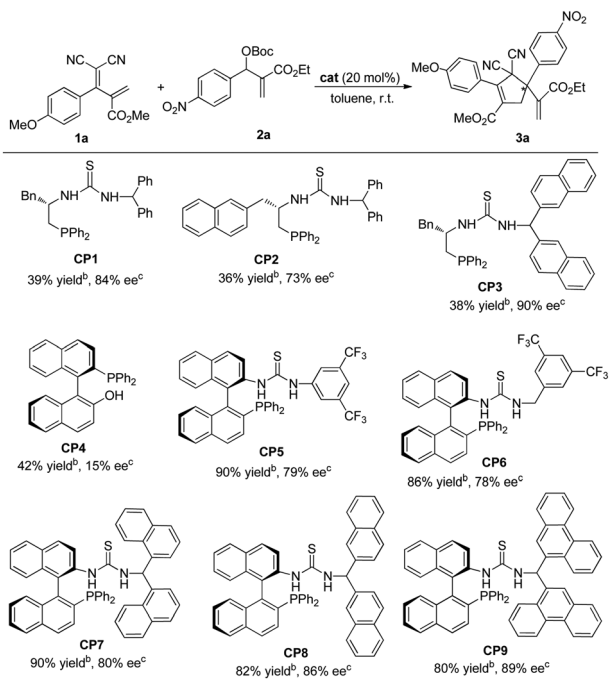


Scheme 1 A research proposal.

the first enantioselective [4 + 1] annulation of MBH acetates and carbonates with dicyano-2-methylenebut-3-enoates, providing a facile protocol to construct highly functionalized cyclopentenes bearing one all-carbon quaternary stereogenic center in good yields with excellent enantioselectivities.[10]

Based on our previous work on chiral phosphines as nucleophilic catalysts in asymmetric catalysis,[11] we initiated the study

Table 1 Screening of chiral phosphine catalysts[a]



[a] Reactions were performed with **1a** (0.10 mmol) and **2a** (0.15 mmol) in the presence of 20 mol% of **CP** in toluene (1 mL) at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

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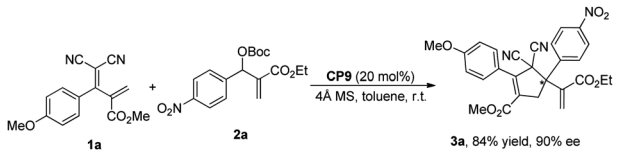


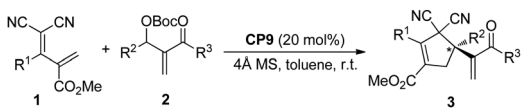
Scheme 2 Optimization of the reaction conditions.

by investigating the reaction between dicyano-2-methylenebut-3-enoate **1a** and MBH carbonate **2a** in the presence of multifunctional chiral thiourea–phosphine **CP1** (20 mol%) derived from L-phenylalanine in toluene at room temperature. To our delight, the desired annulation indeed took place, giving the corresponding product **3a** in 84% ee, albeit in only 39% yield (Table 1). Increasing the steric bulkiness of multifunctional thiourea–phosphines derived from natural amino acids, we consecutively examined the catalysts **CP2** and **CP3**, and identified that **CP3** was the more efficient catalyst, producing **3a** in 38% yield along with 90% ee value. Subsequently we examined several multifunctional chiral phosphines **CP4–CP9** having an axially chiral binaphthyl scaffold. Using **CP4** as the chiral phosphine **3a** was produced in 42% yield with 15% ee value. Notably, both yields and ee values of the product **3a** increased when multifunctional thiourea–phosphines **CP5–CP7** were employed, and revealed that **CP7** was the more effective catalyst, affording **3a** in 90% yield with 80% ee. Gratifyingly, an improvement was possible through a slight structural modification of catalyst **CP7** to give **CP8** and **CP9**, which could produce **3a** in better results. Finally, we found that **3a** could be obtained in 80% yield with 89% ee using **CP9** as catalyst (Table 1).

With the identification of the best catalyst in this reaction, we next attempted to further optimize reaction conditions by screening the solvent (Table S1, ESI†). The reaction outcomes revealed that using 20 mol% **CP9** as the catalyst with 4 Å MS as the additive (40 mg for 0.1 mmol of **1a** and 0.15 mmol of **2a**) and carrying out the reaction in toluene at room temperature for 2 days gave **3a** in 84% yield with 90% ee value, which served as the best reaction conditions in this reaction (Scheme 2). Using 10 mol% of **CP9** gave **3a** in 72% yield and 88% ee under identical conditions.

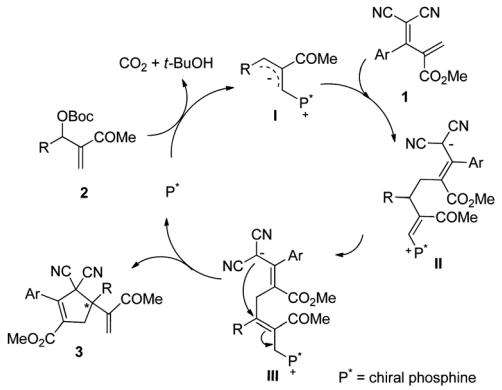
Having determined the optimal reaction conditions for the highly enantioselective formation of **3a**, we turned our attention to the substrate scope of this multifunctional chiral-phosphine-catalyzed asymmetric [4 + 1] annulation of dicyano-2-methylenebut-3-enoates with MBH carbonates and the results are summarized in Table 2. All reactions proceeded smoothly to give the corresponding products **3** in moderate to good yields with excellent enantioselectivities under the optimal reaction conditions (Table 2). Whether R^1 is an electron-rich or -deficient aromatic ring, the reactions proceeded smoothly to give the corresponding annulation products **3b–3i** in good yields with 77–90% ee values, respectively (Table 2, entries 1–8). Only in the case of *ortho*-$MeOC_6H_4$ dicyano-2-methylenebut-3-enoate **1b**, the corresponding adduct **3b** was obtained in good yield along with relatively lower ee value (77% ee), perhaps due to the steric influence (Table 2, entry 1). When R^1 is a heteroaromatic group (R^1 = funan-2-yl) or a sterically more bulky 2-naphthalene moiety or a more substituted aromatic group (R^1 = 3,4,5-$(MeO)_3C_6H_2$), the reactions also proceeded efficiently to afford the corresponding

Table 2 The substrate scope of [4 + 1] annulation of dienes **1** with MBH carbonates **2**[a]



Entry	R^1	R^2	R^3	Time (d)	Yield[b] (%)	ee[c] (%)
1	**1b** (*o*-$MeOC_6H_4$)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3b**, 80	77
2	**1c** (*m*-$MeOC_6H_4$)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3c**, 82	87
3	**1d** (*p*-MeC_6H_4)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3d**, 86	90
4	**1e** (*p*-FC_6H_4)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3e**, 80	89
5	**1f** (*p*-ClC_6H_4)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3f**, 79	90
6	**1g** (*p*-BrC_6H_4)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3g**, 70	90
7	**1h** (Ph)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3h**, 85	89
8	**1i** (*p*-$CF_3C_6H_4$)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3i**, 75	87
9	**1j** (furan-2-yl)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3j**, 81	91
10	**1k** (naphtha-2-yl)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3k**, 84	90
11	**1l** (3,4,5-$(MeO)_3C_6H_2$)	**2a** (*p*-$NO_2C_6H_4$)	**2a** (OEt)	2	**3l**, 70	90
12	**1d** (*p*-MeC_6H_4)	**2b** (*m*-$NO_2C_6H_4$)	**2b** (OEt)	2	**3m**, 76	92
13	**1d** (*p*-MeC_6H_4)	**2c** (*p*-ClC_6H_4)	**2c** (OEt)	7	**3n**, 42	85
14	**1d** (*p*-MeC_6H_4)	**2d** (Ph)	**2d** (OEt)	7	**3o**, 39	85
15	**1d** (*p*-MeC_6H_4)	**2e** (3-Br,4-FC_6H_3)	**2e** (OEt)	7	**3p**, 69	89
16	**1d** (*p*-MeC_6H_4)	**2f** (CH_3)	**2f** (OEt)	7	**3q**, 29	66
17	**1d** (*p*-MeC_6H_4)	**2g** (*p*-$NO_2C_6H_4$)	**2g** (O^tBu)	5	**3r**, 70	90
18	**1d** (*p*-MeC_6H_4)	**2h** (*p*-$NO_2C_6H_4$)	**2h** (OBn)	2	**3s**, 80	90
19	**1d** (*p*-MeC_6H_4)	**2i** (*m*-$NO_2C_6H_4$)	**2i** (CH_3)	2	**3t**, 90	90
20	**1d** (*p*-MeC_6H_4)	**2j** (*p*-$CF_3C_6H_4$)	**2j** (CH_3)	2	**3u**, 86	92
21	**1d** (*p*-MeC_6H_4)	**2k** (*p*-FC_6H_4)	**2k** (CH_3)	2	**3v**, 88	94
22	**1d** (*p*-MeC_6H_4)	**2l** (*o*-ClC_6H_4)	**2l** (CH_3)	4	**3w**, 41	93
23	**1d** (*p*-MeC_6H_4)	**2m** (*p*-ClC_6H_4)	**2m** (CH_3)	3	**3x**, 90	93
24	**1d** (*p*-MeC_6H_4)	**2n** (*p*-MeC_6H_4)	**2n** (CH_3)	4	**3y**, 86	98
25	**1d** (*p*-MeC_6H_4)	**2o** (3,4-$Cl_2C_6H_3$)	**2o** (CH_3)	3	**3z**, 92	90
26	**1d** (*p*-MeC_6H_4)	**2p** (thiophen-2-yl)	**2p** (CH_3)	3	**3aa**, 91	97

[a] Reactions were performed with **1** (0.10 mmol) and **2** (0.15 mmol) in the presence of 20 mol% of **CP9** in toluene (1 mL) at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis.



Scheme 3 Possible reaction mechanism for the formation of **3**.

products **3j–3l** in 70–84% yields with 90–91% ee values (Table 2, entries 9–11). Next, the investigation of the MBH carbonates was continued by using **1d** as a substrate (Table 2, entries 12–26). The reaction tolerated different aromatic moieties R^2 in the MBH carbonates **2**. Due to their lower reactivities, substrates with no substituent or halogen atom substituent on the aromatic ring of MBH carbonates resulted in reduced yields with high ee values upon prolonging the reaction time to 7 days (Table 2, entries 13–15). However, using MBH carbonate **2f** as a substrate, the reaction also proceeded efficiently, affording the cycloadduct **3q** in 29% yield along with 66% ee value. The reactions also worked well upon changing the ester groups in the MBH carbonates, providing the corresponding products **3r** and **3s** in 70% and 80% yields with identical 90% ee values, respectively (Table 2, entries 17 and 18). Notably, taking MBH carbonates derived from methyl vinyl ketone (MVK) as substrates, whether R^2 is an electron-rich or -deficient aromatic ring or a heteroaromatic group (R^2 = thiophen-2-yl), the reactions proceeded smoothly to give the corresponding annulation products **3t–3aa** in moderate to excellent yields (41–92%) with 90–98% ee values, respectively (Table 2, entries 19–26). Only in the case of *ortho*-ClC_6H_4 MBH carbonate **2l**, the corresponding adduct **3w** was obtained in 93% ee along with relatively lower yields (41% yield), perhaps due to the steric influence (Table 2, entry 22). The absolute configuration of **3d** has been assigned by X-ray diffraction as R-configuration. The ORTEP drawing and the CIF data are summarized in the ESI.†

On the basis of the above experimental results and previous work,[5a,c,12] a plausible reaction mechanism has been outlined in Scheme 3. The reaction might be initiated with the *in situ* formation of the phosphorus ylide **I** from **2** *via* an addition–elimination–deprotonation process. Then the nucleophilic attack of phosphorus ylide **I** to dicyano-2-methylenebut-3-enoate **1** with its C-1-terminal results in intermediate **II**, which isomerizes to intermediate **III** through a hydrogen transfer. Intermediate **III** produces the desired highly functionalized cyclopentene **3** and regenerates the chiral-phosphine catalyst *via* an intramolecular Michael addition followed by the elimination of catalyst. The possible transition state of this asymmetric [4 + 1] annulation is illustrated in Fig. S1 in the ESI.†

In conclusion, the asymmetric [4 + 1] annulation reactions utilizing MBH carbonates as C_1 synthons have been developed for the first time, which provide an efficient and enantioselective synthesis of highly functionalized cyclopentenes bearing one all-carbon quaternary stereogenic center. Further efforts are in progress to develop the use of this reaction in organic synthesis.

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