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Phosphine-mediated enantioselective [1 + 4]-annulation of Morita–Baylis–Hillman carbonates with 2-enoylpyridines†

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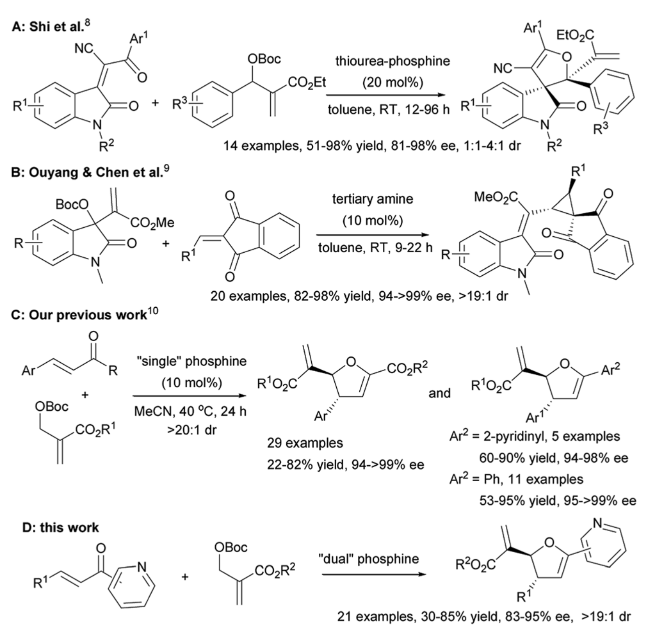
This work describes a phosphine-catalyzed asymmetric [1 + 4] annulation of Morita–Baylis–Hillman carbonates with 2-enoylpyridines for constructing the enantiomerically enriched 2,3-dihydrofuran motif. In the presence of (−)-1,2-bis[(2R,5R)-2,5-dimethylphospholano]benzene, a series of Morita–Baylis–Hillman carbonates reacted with 2-enoylpyridines smoothly to afford a wide range of optically active 2,3-dihydrofurans featuring pyridine motifs in high yields with excellent asymmetric induction.

Recently Morita–Baylis–Hillman (MBH) carbonates have been proved to be diverse reaction partners for the synthesis of a wide variety of carbo- and heterocyclic compounds.[1] In particular, MBH carbonates have been successfully employed as C1 synthons in many cyclization reactions for the construction of diverse heterocycles.[2] In terms of [1 + 4] annulations between MBH carbonates and α,β-unsaturated carbonyl compounds, Zhang *et al.* firstly reported a PPh_3 catalyzed [1 + 4] annulation of MBH carbonates with activated α,β-unsaturated ketones (enones) to furnish a series of racemic 2,3-dihydrofurans.[3] The substituent (*e.g.*, alkyne moiety) at the α-position of the enone was necessary to improve the reactivity of the enone by lowering the energy of the LUMO, which was critical for obtaining a high yield. Two years later, Huang *et al.* realized the catalyst dosage controlling the product distribution between 2,3-dihydrofurans and biaryls from the phosphine mediated [1 + 4] annulation of MBH carbonates and β,γ-unsaturated α-keto esters.[4] In 2014, Shi *et al.* reported a tunable phosphine-triggered cascade reaction of MBH carbonates and 3-acyl-2*H*-chromen-2-ones for the synthesis of diverse chromenones.[5] Different from [1 + 4] annulation, He *et al.* disclosed that the PBu_3-mediated reactions between MBH carbonates and chalcones underwent either [3 + 2] or [2 + 2 + 1] annulations depending on the substituent variation of both reactants.[6] However, in sharp contrast, the reports on enantioselective catalytic annulation of MBH carbonate as C1-synthon are very limited.[7] The landmark study reported by Shi and co-workers presented thiourea-phosphines that were efficient catalysts for the asymmetric [1 + 4] annulation of MBH carbonates with activated α,β-unsaturated ketones, although the reaction of MBH carbonates bearing an electron-donating substituent on their aromatic group remained a challenge (Scheme 1A).[8] In 2016, Ouyang and Chen *et al.* remarkably disclosed the first highly enantio- and diastereoselective [1 + 2] annulation reactions of MBH carbonates and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones (Scheme 1B).[9] Despite their elegant examples, the organocatalytic asymmetric annulations of MBH carbonates as C1-synthons are still far from well-developed.[10]



Scheme 1 Limited examples of enantioselective annulation of MBH carbonates with α,β-unsaturated ketones.

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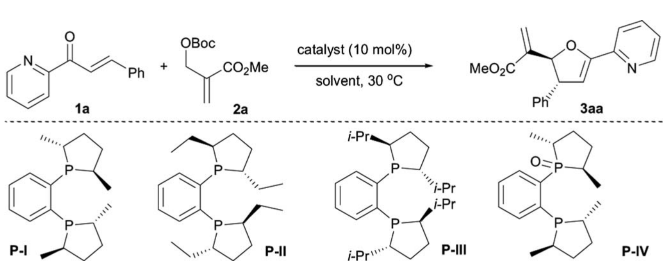
Very recently, we overcame the restriction to successfully develop a chiral phosphine catalysed [1 + 4] annulation of MBH carbonates with electron-deficient olefins for constructing optitally active 2,3-dihydrofurans (Scheme 1C).[11] Furthermore, several cases of 2-enoylpyridines furnished the corresponding products in 60–90% yield with 94–98% ee and >20 : 1 dr. Although the ubiquitous nature of 2-enoylpyridines in enantioselective reactions,[12] the systematic study on asymmetric [1 + 4] annulation of MBH carbonates with 2-enoylpyridines has not been reported so far. Therefore, developing efficient strategy for the asymmetric [1 + 4] annulation of MBH carbonates with 2-enoylpyridines is highly desirable. Herein, we report comprehensive results from the phosphine-catalyzed asymmetric [1 + 4] annulation of MBH carbonates with 2-enoylpyridines (Scheme 1D).

To achieve better yields without compromising the asymmetric induction of the [1 + 4] annulation of MBH carbonates and 2-enoylpyridines, we revisited the prototypical catalyst system (Table 1). Choosing the [1 + 4] annulation of 2-(methoxycarbonyl)allyl *tert*-butyl carbonate **2a** and 3-phenyl-1-(pyridin-2-yl)prop-2-en-1-one **1a** as model reaction, we screened a series of phosphine catalysts.[13] It was found that (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene **P-I** mediated reaction generated the better results, furnishing the desired product **3aa** in 79% yield with 91% ee and >19 : 1 dr (Table 1, entry 1). Increasing the steric hindrance of catalyst resulted in lowering yields and enantioselectivities (Table 1, entries 2 and 3). The investigations of reaction media indicated that solvent affected the reaction in terms of yield and stereoselectivity (Table 1, entries 5–9), and MeCN was more suitable for the transformation to afford the product **3aa** in 77% yield with 94% ee and >19 : 1 dr (Table 1, entry 10). Further optimization of the conditions including reaction temperature, ratio of reactants, and reaction time enabled the formation of **3aa** in 81% yield with 95% ee and >20 : 1 dr (Table 1, entries 11–14).

With the optimal reaction conditions determined, we then investigated the substrate scope of this asymmetric [1 + 4] annulation and the results were summarized in Table 2. It was found that the ester group of the MBH carbonates affected the yield of the reaction without any discernible impact on the asymmetric induction. Increasing the size of the ester group led to a decrease in the yield (Table 2, entries 1–3). The substrate scope of 2-enoylpyridines **1** was examined by reactions with MBH carbonate **2a**. Importantly, this catalytic strategy was applicable to various substituted 2-enoylpyridines bearing different types of substituents. Both electron-withdrawing (F, Cl, Br, CF_3) and electron-donating (MeO) groups were well tolerated to afford the corresponding products **3ba–ja** in 75–85% yields with 91–94% ee and >19 : 1 dr (Table 2, entries 4–12). Substrates 3-(4-nitrophenyl)-1-(pyridin-2-yl)prop-2-en-1-one **1k**

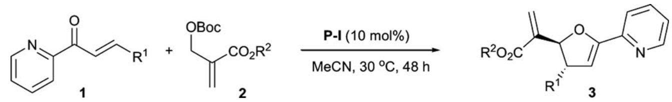
Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Solvent	*t* (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**P-I**	CH_2Cl_2	24	79	>19 : 1	91
2	**P-II**	CH_2Cl_2	24	55	>19 : 1	−78
3	**P-III**	CH_2Cl_2	24	28	>19 : 1	−48
4	**P-IV**	CH_2Cl_2	24	40	>19 : 1	93
5	**P-I**	$CHCl_3$	24	56	>19 : 1	90
6	**P-I**	THF	24	38	>19 : 1	84
7	**P-I**	Toluene	24	65	>19 : 1	85
8	**P-I**	EtOAc	24	51	>19 : 1	90
9	**P-I**	$(CH_2Cl)_2$	24	71	>19 : 1	91
10	**P-I**	MeCN	24	77	>19 : 1	94
11[e]	**P-I**	MeCN	24	69	>19 : 1	93
12[f]	**P-I**	MeCN	24	57	>19 : 1	94
13[g]	**P-I**	MeCN	24	69	>19 : 1	93
14	**P-I**	MeCN	48	81	>19 : 1	95

[a] Reaction conditions: unless noted, a mixture of **1a** (0.2 mmol), **2a** (0.24 mmol), and catalyst (10 mol%) in the solvent (1.0 mL) was stirred at 30 °C for the time given. [b] Isolated yield. [c] dr = diastereomeric ratio, determined by ^1H NMR. [d] Enantiomeric excess (ee) of major enantiomer, determined by chiral HPLC analysis. [e] Performed at 40 °C. [f] Performed at 0 °C. [g] **2a** (0.3 mmol) was used.

Table 2 Substrate scope[a]

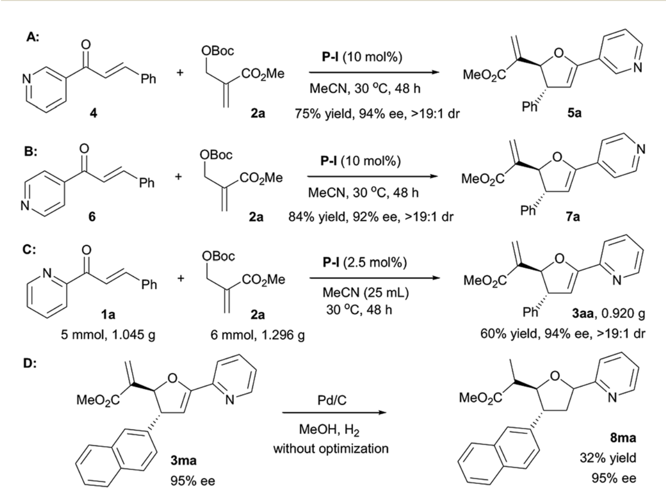


Entry	R^1	R^2	3	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph	Me	**3aa**	81	>19 : 1	95
2	Ph	Et	**3ab**	72	>19 : 1	94
3	Ph	Bn	**3ac**	54	>19 : 1	94
4	2-BrC_6H_4	Me	**3ba**	76	>19 : 1	91
5	2-$MeOC_6H_4$	Me	**3ca**	75	>19 : 1	94
6	3-ClC_6H_4	Me	**3da**	82	>19 : 1	91
7	3-BrC_6H_4	Me	**3ea**	79	>19 : 1	92
8	3-$MeOC_6H_4$	Me	**3fa**	79	>19 : 1	94
9	4-FC_6H_4	Me	**3ga**	79	>19 : 1	93
10	4-ClC_6H_4	Me	**3ha**	80	>19 : 1	93
11	4-BrC_6H_4	Me	**3ia**	78	>19 : 1	92
12	4-$CF_3C_6H_4$	Me	**3ja**	85	>19 : 1	91
13	4-$NO_2C_6H_4$	Me	**3ka**	30	>19 : 1	91
14	4-MeC_6H_4	Me	**3la**	52	>19 : 1	92
15	2-Naphthyl	Me	**3ma**	85	>19 : 1	83
16	2-Thienyl	Me	**3na**	63	>19 : 1	94
17	2-Pyridinyl	Me	**3oa**	60	>19 : 1	94
18	PhCH=CH	Me	**3pa**	64	>19 : 1	92
19	Me	Me	**3qa**	61	>19 : 1	92
20[e]	Ph	Me	**3ad**	—	—	—

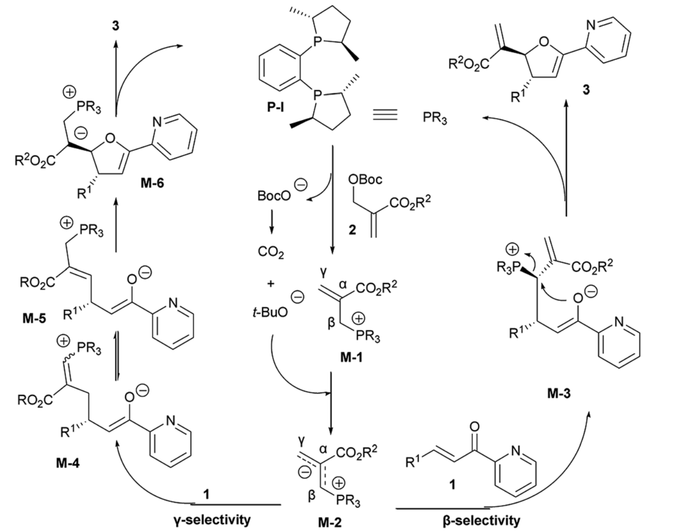
[a] Reaction conditions: unless noted, a mixture of **1** (0.2 mmol), **2** (0.24 mmol), and **P-I** (10 mol%) in MeCN (1.0 mL) was stirred at 30 °C for 48 h. [b] Isolated yield. [c] dr = diastereomeric ratio, determined by ^1H NMR. [d] Enantiomeric excess (ee) of major enantiomer, determined by chiral HPLC analysis. [e] Instead of **2a**, 2-(methoxycarbonyl)-1-phenylallyl *tert*-butyl carbonate was used.

and 1-(pyridin-2-yl)-3-*p*-tolylprop-2-en-1-one **1l** were found to react with **2a** slowly to furnish **3ka** in 30% yield with 91% ee (Table 2, entry 13) and **3la** in 52% yield with 92% ee (Table 2, entry 14), respectively. Pleasingly, 3-(naphthalen-3-yl)-1-(pyridin-2-yl)prop-2-en-1-one **1m** reacted with **2a** smoothly to afford product **3ma** in 85% yield with 83% ee and >19 : 1 dr (Table 2, entry 15). In addition, the heteroaromatic **1n-o** were also compatible to afford the corresponding adducts **3na-oa** in 60–63% yield with 94% ee and >19 : 1 dr (Table 2, entries 16 and 17). Notably, adduct **3pa** was obtained in 64% yield with 92% ee and >19 : 1 dr from the annulation of **2a** with 5-phenyl-1-(pyridin-2-yl)penta-2,4-dien-1-one (Table 2, entry 18). Importantly, the annulation of aliphatic 2-enoylpyridine **1q** was also compatible and afforded the desired product **3qa** in 61% yield with 92% ee (Table 2, entry 19). It was found that 2-(methoxycarbonyl)-1-phenylallyl *tert*-butyl carbonate was not compatible and no desired product was obtained (Table 2, entry 20). Taken altogether, our results demonstrate that catalyst **P-I** is broadly applicable in the asymmetric [1 + 4] annulation of MBH carbonates and 2-enoylpyridines.

In order to further explore the scope of the [1 + 4] annulation, other α,β-unsaturated pyridinyl ketones were also surveyed (Scheme 2). Under the standard conditions, 3-phenyl-1-(pyridin-3-yl)prop-2-en-1-one **4** reacted with MBH carbonate **2a** smoothly to afford the product **5a** in 75% yield with 94% ee and >19 : 1 dr (Scheme 2A). The **P-I** mediated [1 + 4] annulation of MBH carbonate **2a** with 3-phenyl-1-(pyridin-4-yl)prop-2-en-1-one **6** also furnished the desired **7a** in 84% yield with 92% ee and >19 : 1 dr (Scheme 2B). Notably, these results indicated that the pyridinyl group of α,β-unsaturated ketones has no effect on the stereoselectivity of the reaction. To highlight the synthetic potential of the catalytic system, we also evaluated the gram-scale synthesis of **3aa**. In the presence of **P-I** with a loading of 2.5 mol% in MeCN of 25 mL at 30 °C for 48 h, 5.0 mmol of **1a** (1.045 g) reacted smoothly with 6.0 mmol of **2a** (1.296 g), affording **3aa** in 60% yield (0.920 g) with 94% ee and >19 : 1 dr (Scheme 2C). As mentioned in our previous work,[10] the product **3ma** could be hydrogenated and tetrahydrofuran **8ma** was obtained in 32% yield with 95% ee (Scheme 2D).



Scheme 2 Further investigations of [1 + 4] annulation.



Scheme 3 Proposed reaction mechanism.

The absolute configurations of chiral 2,3-dihydrofurans **3** were confirmed according to the products from the [1 + 4] annulation between MBH carbonates and α,β-unsaturated ketones under the same conditions.[10] Accordingly, two proposed reaction pathways were shown in Scheme 3. An initial S_N2 attack of nucleophilic chiral phosphine catalyst **P-I** on the MBH carbonate **2** triggered the elimination of the leaving group ($BocO^-$) delivering the chiral phosphonium salt intermediate **M-1**, which was then deprotonated by an *in situ*-generated base ($BocO^- = CO_2 + t\text{-}BuO^-$) to give chiral allylic phosphorus ylide **M-2**. The β-selective reaction of **M-2** with 2-enoylpyridine **1** furnished intermediate **M-3**, followed by cyclization to generate the desired product **3**.[9] Alternatively, the ylide **M-2** reacted with **1** *via* γ-selectivity to afford intermediate **M-4**, which interconverts with intermediate **M-5**.[2b,2d,7b] Then an intramolecular Michael addition of **M-5** afforded intermediate **M-6**. Finally, **M-6** engaged in elimination of the chiral phosphine **P-I** to give the annulation product **3**.

In conclusion, we have successfully developed an efficient organocatalytic asymmetric [1 + 4] annulation of MBH carbonates and 2-enoylpyridines. With (−)-1,2-bis[(2*R*,5*R*)-2,5-dimethylphospholano]benzene as catalyst, the reactions proceed well to furnish a series of chiral 2,3-dihydrofurans featuring pyridine motifs in high yields and excellent stereoselectivities. Importantly, the reaction was successfully extended to other α,β-unsaturated pyridinyl ketones without compromising the yields and asymmetric induction.

Conflicts of interest

There are no conflicts to declare.

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