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Morita–Baylis–Hillman Reaction of β,β-Disubstituted Enones: An Enantioselective Organocatalytic Approach for the Synthesis of Cyclopenta[*b*]annulated Arenes and Heteroarenes

*Bishnupada Satpathi and S. S. V. Ramasastry**

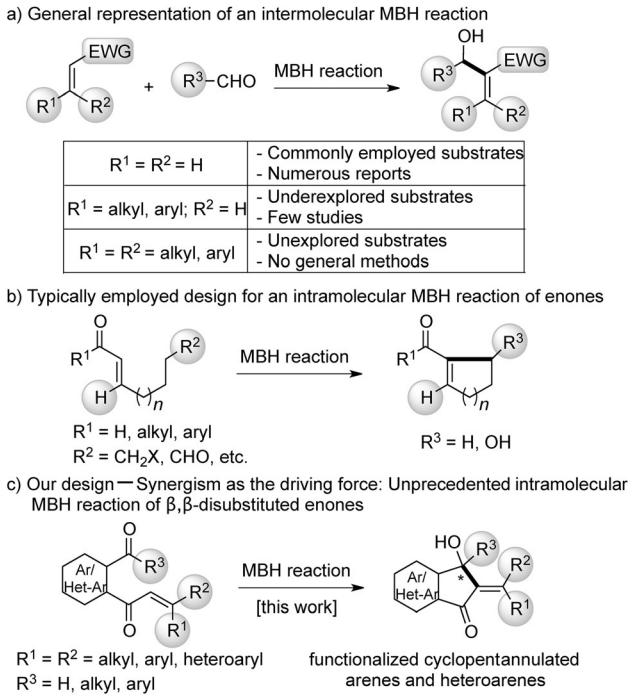
Dedicated to Professor S. Chandrasekaran on the occasion of his 70th birthday

Abstract: *The first enantioselective organocatalytic intramolecular Morita–Baylis–Hillman (MBH) reaction of sterically highly demanding β,β-disubstituted enones is presented. The MBH reaction of β,β-disubstituted-α,β-unsaturated electron-withdrawing systems was previously considered to be unfeasible. Towards this end, designer substrates, which under simple and practical reaction conditions generate a variety of cyclopenta[b]annulated arenes and heteroarenes in excellent enantiopurities and near-quantitative yields in remarkably short reaction times, are described. The reason for the unusually facile nature of this reaction is attributed to the synergy guided and entropically favored intramolecular reaction. Further, this strategy provides easy access to a substantial number of bioactive natural products and pharmaceutically significant compounds.*

The Morita–Baylis–Hillman (MBH) reaction is undoubtedly one of the most synthetically useful C–C bond-forming reactions.[1] The potential of this reaction has been exploited in the total synthesis of several natural products and other important targets.[2] The key attributes for the versatility of MBH reaction are its atom-economy, organocatalytic nature, and ease of transformation of the MBH adducts into synthetically attractive products.[3] Despite significant advancements witnessed in this field,[4] there still remain a few unresolved challenges. The reaction usually proceeds at a slow rate and in several instances it is sluggish because of its sensitivity to the steric and electronic nature of reactants and nucleophilic triggers, and thus eventually results in low conversions and long reaction times.

While the β-unsubstituted variants are the most commonly employed substrates in the MBH reaction, only a handful of successful studies have been realized with β-monosubstituted systems.[5] A major obstacle to the wider applicability of the MBH reaction is its failure with β,β-disubstituted substrates (Scheme 1 a).[1c,4c,6] Even the recent advancements in the entropically advantageous intramolecular MBH reaction[1,4,7] could not be established on the β,β-disubstituted systems (Scheme 1 b). With the desire to address this fundamental limitation of the MBH reaction, combined with our on-going research interests aimed at the development of novel strategies for the cyclopentannulation of arenes and heteroarenes,[8] we became interested in designing substrates amenable to an intramolecular MBH reaction.

A few important aspects pertaining the substrate design were considered prior to investigating the intriguing possibility of developing the MBH reaction of β,β-disubstituted systems: 1) to circumvent the high energy of activation imparted by the electronic and steric factors associated with β,β-disubstituted systems, an intramolecular MBH version (which benefits from less negative entropies) was considered, 2) tethering the enone and carbonyl functionalities *ortho* to each other could exert mutually beneficial electron-withdrawing effects (synergism or cooperativity), which could be a major driving force during nucleophile addition. An outline based on these hypotheses is depicted in Scheme 1 c.



Scheme 1. Significance of the present study.

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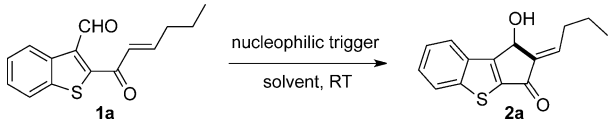
Since a MBH-reaction-based approach for the cyclopenta[*b*]annulation of heteroarenes has not been described thus far,[9] and since ready access to the proposed starting compounds (Scheme 1 c) can be achieved in a method described earlier by our research group,[10] we proceeded to identify optimized reaction conditions for β-monosubstituted enones appended to heteroaryl carbaldehydes. Accordingly, (*E*)-2-hexenoyl benzothiophene-3-carbaldehyde (**1a**) was chosen as the model substrate.[11] Various nucleophilic triggers and solvent combinations were investigated, and the results are summarized in Table 1. Initial assessment with typical

Table 1: Optimization of the reaction parameters.[a]



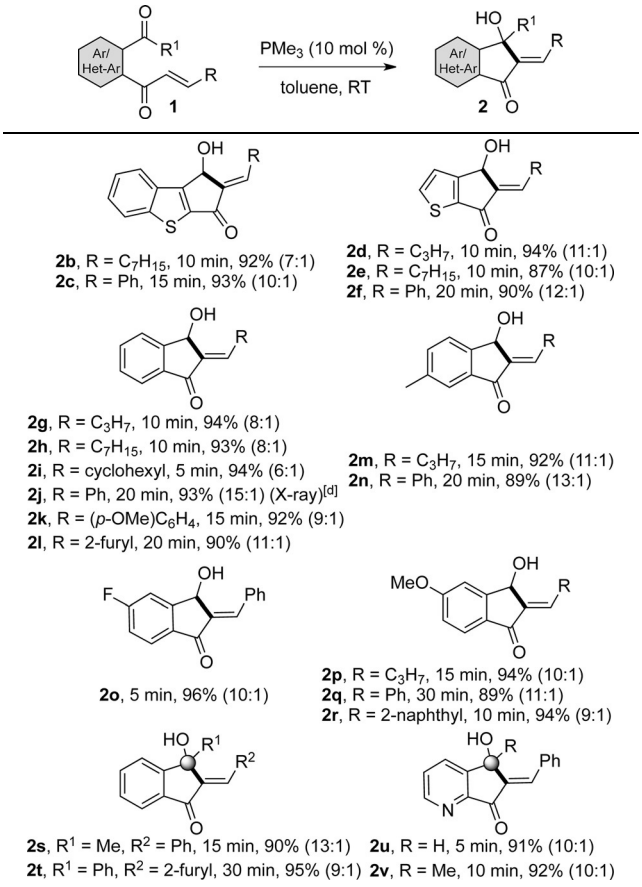
Entry	Nucleophilic trigger (mol%)	Solvent	*t*	Yield [%][b] (*E*/*Z*)[c]
1	DBU (20)	toluene	6 h	63 (6:1)
2	DABCO (20)	toluene	3 h	69 (8:1)
3	DABCO (20)	DMF	1.5 h	71 (7:1)
4	DMAP (20)	CH_2Cl_2	5 h	63 (7:1)
5	Imidazole (20)	toluene	7 h	79 (6:1)
6	PPh_3 (10)	CH_2Cl_2	48 h	–
7	PPh_2Et (10)	CH_2Cl_2	10 min	90 (8:1)
8	$PPhMe_2$ (10)	CH_2Cl_2	10 min	92 (11:1)
9	PCy_3 (10)	CH_2Cl_2	30 min	86 (8:1)
10	PMe_3 (10)	CH_2Cl_2	5 min	93 (10:1)
11	PMe_3 (10)	DMF	5 min	91 (9:1)
12	PMe_3 (10)	toluene	5 min	93 (10:1)
13	PMe_3 (10)	NMF	20 min	85 (10:1)
14	PMe_3 (10)	formamide	20 min	79 (9:1)
15	PMe_3 (10)	CH_3CN	10 min	89 (8:1)

[a] Reaction conditions: To a 5 mL glass vial filled with **1a** (0.1 mmol) in an appropriate solvent (1 mL), a catalyst (0.01 mmol) was introduced at room temperature (RT) under a nitrogen atmosphere. Stirring continued at RT until **1a** disappeared, as monitored by TLC. [b] Yield of product isolated after silica gel column chromatography. [c] Determined by ^{1}H NMR analysis on the crude reaction mixture. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, NMF = *N*-methylformamide.

amine-based Lewis bases was found to be very encouraging. The desired cyclopentannulated benzothiophene **2a** was formed in good yields (entries 1–5).[12] The structure of **2a** was deduced from the spectral data, and the predicted *E* geometry of the double bond was confirmed by single-crystal X-ray diffraction analysis (see below). In contrast, among the organophosphines screened, except PPh_3, a pronounced improvement in yield and reaction time were observed (entries 6–9). Strikingly, phosphines require only a few minutes for complete conversion, with PMe_3 delivering the best result (entry 10). Brief solvent screening (entries 11–15) prompted us to consider toluene in place of the volatile chlorinated solvent DCM for further studies.

With the optimal reaction conditions in hand, we sought to expand the substrate scope (Table 2). Cyclopentannulation

Table 2: Scope of β-monosubstituted enones.[a,b,c]

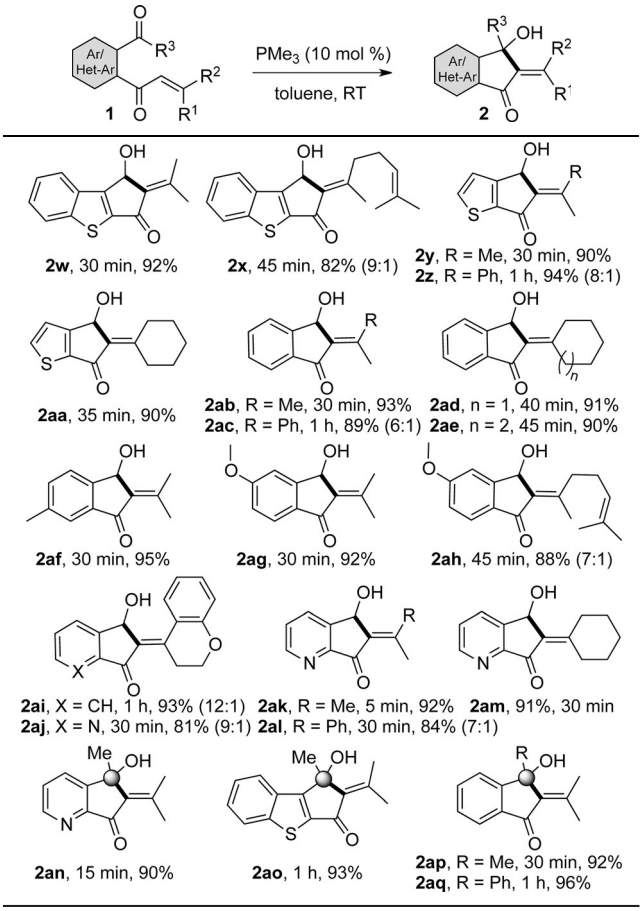


[a] Reaction conditions: To a 5 mL glass vial filled with **1** (0.1 mmol) in toluene (1 mL), PMe_3 (0.01 mmol) was introduced at room temperature (RT) under nitrogen atmosphere. Stirring continued at RT until **1** disappeared (by TLC). [b] Yield of product isolated after silica gel column chromatography. [c] *E*/*Z* ratios determined by ^{1}H NMR analysis of the crude reaction mixture. [d] See the Supporting Information.

of β-alkyl and β-aryl enones appended to benzothiophene- and thiophene-3-carbaldehydes proceeded smoothly in excellent yields (**2b–f**). Pleasingly, our attempts to extend this method for the synthesis of functionalized indanones and pyrindanones were also successful (**2g–v**). It is worth noting that the presence of electron-donating groups (such as -Me, -OMe) either on the aryl ring or on the β-substituents has no considerable impact on the efficiency of the reaction (for example, **2k–n** and **2p–r**). As a substantial advancement, indanones and pyrindanones possessing a tetrasubstituted carbon atom could also be efficiently generated within a few minutes by this method (**2s**, **2t**, and **2v**). Therefore, compounds possessing poor electrophiles such as ketones[13] were also demonstrated to be excellent substrates under these reaction conditions.

Having realized the extremely facile transformation of β-monosubstituted enones, we turned our attention to the previously unexplored β,β-disubstituted analogues. Towards this end, a wide variety of β,β-disubstituted enones tethered to heteroaryl and aryl carbaldehydes (**1w–aq**) were synthesized. From the results shown in Table 3, it can be realized that the

Table 3: Scope of β,β-disubstituted enones.[a,b,c]



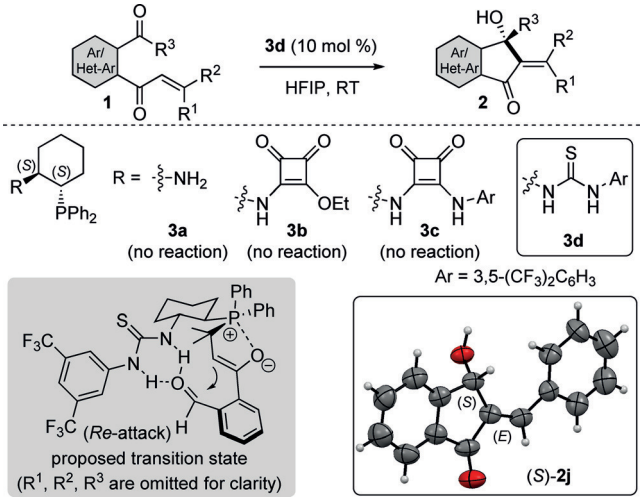
[a] Reaction conditions: As described in Table 2. [b] Yield of the product isolated after silica gel column chromatography. [c] *E*/*Z* ratios determined by ^{1}H NMR analysis of the crude reaction mixture.

substrate scope of this protocol is remarkably broad. In general, consistently short turnaround times and excellent yields were achieved irrespective of the steric or electronic factors. Otherwise difficult to access cycloalkylidene, alkylidene and arylidene cyclopenta[*b*]annulated benzothiophenes, thiophenes, indanones, and pyrindanones can be readily assembled (**2w**–**aq**). Notably, substrates with electron-donating groups on the aryl ring showed no noticeable impact on the overall result (**2af**–**aj**). Of particular interest, the formation of β,β-disubstituted pyrindanones (**2aj**–**an**) in a significantly short reaction time highlights the role of an electron-deficient pyridine backbone on the rate enhancement. Versatility of this method is furthered with the synthesis of cyclopentannulated arenes and heteroarenes, having a stereogenic tetrasubstituted carbon atom, in excellent yields in less than one hour (**2an**–**aq**).[13]

After establishing a general, practical, and highly efficient method for the synthesis of unprecedented β,β-disubstituted MBH adducts, we next focused on the development of an enantioselective organocatalytic version. For this purpose, several catalyst, ligand, and solvent combinations were evaluated with **1j** and **1ab** as model substrates (see the Supporting Information for details). To our delight, the bifunctional organocatalyst **3d** (for structure see Table 4) only in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) delivered the desired products in excellent enantiomeric excesses and yields. While the prominence of bifunctional organocatalysts in the asymmetric MBH reaction is gaining ground,[14] dramatic influence of fluorinated solvents, especially on MBH reactions, has been realized,[15] but in this instance it is noteworthy since the enantioinduction could be observed only in HFIP solvent. These results further suggest an extraordinary level of synergism between the substrate, catalyst, and more importantly, the fluorinated solvent.[15,16] Table 4 depicts the substrate scope under the optimized reaction conditions. The results presented herein constitute the first examples of enantioselective organocatalytic cyclopenta[*b*]annulations of either β-mono- or β,β-disubstituted enones by a MBH reaction.

All the β-monosubstituted enones generated the respective products consistently with excellent enantioselectivities

Table 4: Enantioselective organocatalytic intramolecular MBH reaction of β-mono- and β,β-disubstituted enones.[a]



Entry	Substrate	Product	*t* [h]	Yield [%][b] (*E*/*Z*)[c]	*ee* [%]
1	**1c**	**2c**	5	92 (11:1)	98
2	**1d**	**2d**	20	92 (10:1)	91
3	**1e**	**2e**	24	92 (11:1)	91
4	**1f**	**2f**	23	92 (12:1)	97
5	**1h**	**2h**	5	93 (9:1)	98
6	**1i**	**2i**	7	97 (15:1)	94
7	**1j**	**2j**	7	95 (13:1)	98
8	**1k**	**2k**	8	92 (10:1)	98
9	**1l**	**2l**	10	90 (10:1)	95
10	**1o**	**2o**	5	96 (20:1)	>99
11	**1q**	**2q**	10	93 (12:1)	96
12	**1r**	**2r**	6	94 (10:1)	92
13	**1u**	**2u**	1	92 (16:1)	98
14[d]	**1y**	**2y**	160	80	80
15[e]	**1ab**	**2ab**	96	87	77
16	**1ak**	**2ak**	6	91	85

[a] Reaction conditions: To a 5 mL glass vial filled with **1** (0.1 mmol) in HFIP (0.5 mL), **3d** (0.01 mmol) was introduced at room temperature (RT) under argon atmosphere. Stirring continued at RT until **1** disappeared (by TLC). [b] Yield of product isolated after silica gel column chromatography. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Yield based on starting material recovery. [e] At 10 °C.

and near-quantitative yields (Table 4, entries 1–13). Even dramatic improvement in the *E*/*Z* ratios was realized when compared to the respective racemic variants. The absolute stereochemistry of **2j** was determined by X-ray diffraction analysis and assigned to other products in analogy.[17,18] In contrast, initial evaluation of the β,β-disubstituted enones was very promising. For example, the cyclopenta[*b*]thiophene **2y** and indanone **2ab** were obtained in good yields and enantiopurities (entries 14 and 15). The case of the pyridine derivative **1ak** is especially interesting as the reaction is complete within six hours and generates the pyrindanone **2ak** in 91% yield and 85% *ee* (entry 16).

In summary, we present the first enantioselective organocatalytic MBH reaction of β,β-disubstituted enones for the synthesis of cyclopenta[*b*]annulated arenes and heteroarenes. The success of this reaction can be attributed to an extraordinary level of synergism between the *ortho* functionalities, bifunctional catalyst, and the fluorinated solvent. Some of the salient features of this method are: 1) simple, practical, and efficient, 2) broad substrate scope, 3) short reaction times and excellent yields, and 4) easily accessible starting compounds. Efforts to expand the substrate scope, studies to elucidate the role of solvents in the enantioinduction process, and elaboration of this methodology to new classes of compounds are underway in our laboratory.

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[16] The exact role of HFIP in the dramatic enhancement of enantioselectivity has not yet been completely understood. In general, it is attributed to its acidity ($pK_a \approx 9.3$) and strong hydrogen-bond donating ability which can potentially stabilize the transition states. Also see Reference [15].

[17] CCDC 1429346 (for racemic **2j**) and 1429345 (for chiral **2j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[18] The absolute stereochemistry was further verified by a literature report. See: T. Suzuki, Y. Ishizaka, K. Ghozati, D.-Y. Zhou, K. Asano, H. Sasai, *Synthesis* **2013**, 2134.

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