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Citation	Synlett, 2015, v. 26 n. 12, p. 1732-1736
Issued Date	2015
URL	http://hdl.handle.net/10722/234023
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Rasta Resin-TBD-Catalyzed γ -Selective Morita-Baylis-Hillman Reactions of α,γ -Disubstituted Allenones

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Received: The date will be inserted once the manuscript is accepted.

Abstract: Rasta resin-TBD (RR-TBD) was found to be an efficient organocatalyst for γ -selective Morita-Baylis-Hillman reactions between α,γ -disubstituted allenones and aryl aldehydes. In these reactions the heterogeneous nature of RR-TBD greatly facilitated product isolation since the catalyst could be separated simply by filtration.

Key words: allenones, Morita-Baylis-Hillman reactions, organocatalysis, polymer-supported catalysts, rasta resin

The Morita-Baylis-Hillman (MBH) reaction is a widely studied C-C bond forming transformation between an electron-withdrawing group activated alkene and an electrophile, typically an aldehyde or related compound, that is catalyzed by a nucleophilic organocatalyst.¹ Generally MBH reactions are α -selective, with the new C-C bond formed at the alkene position adjacent to the activating group (Scheme 1A). However, with activated allene substrates, the new C-C bond can be formed at the γ -position (Scheme 1B).² Recently Selig and co-workers have reported examples of such γ -selective MBH reactions involving allenates catalyzed by the organic superbases 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **1**, Figure 1) (Scheme 1C).⁴⁻⁶ Contemporaneous to this research, we were developing a heterogeneous polystyrene-based rasta resin-supported analogue of MTBD (RR-TBD, **2**, Figure 1) as an organocatalyst.⁷⁻⁹ Initially we studied the use of **2** in transesterification reactions such as biodiesel production,^{10,11} and once this research was completed, we next turned our attention to examining the utility **2** as a nucleophilic catalyst. Since we had extensive prior experience in developing polymer-supported nucleophilic phosphine catalysts for MBH reactions,¹² we attempted to use **2** in similar reactions and settled on allenone substrates. However, in light of the report by Selig et al.⁵ and the fact that Shi and co-workers originally studied only α -substituted allenones, we changed our focus to γ -selective MBH reactions of α,γ -disubstituted allenones catalyzed by **2**, and report our results herein.

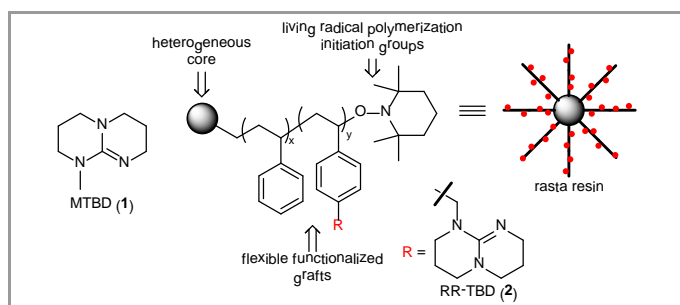
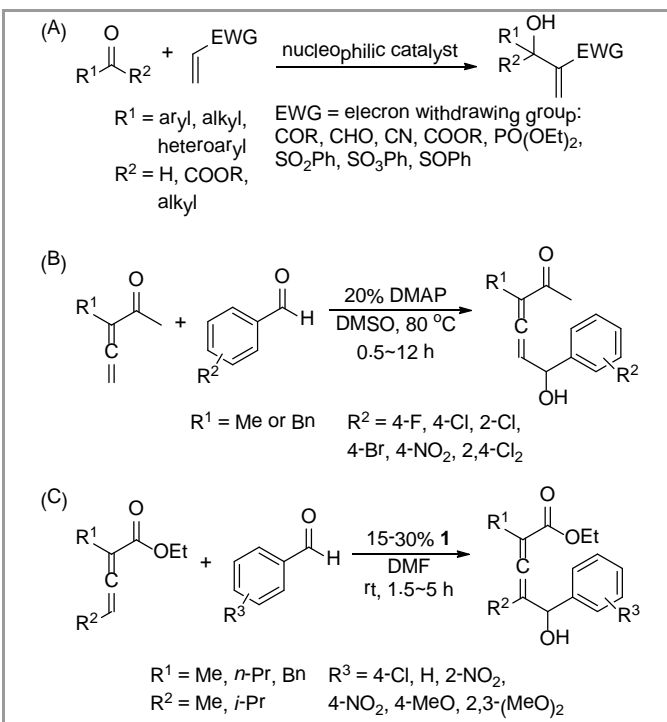
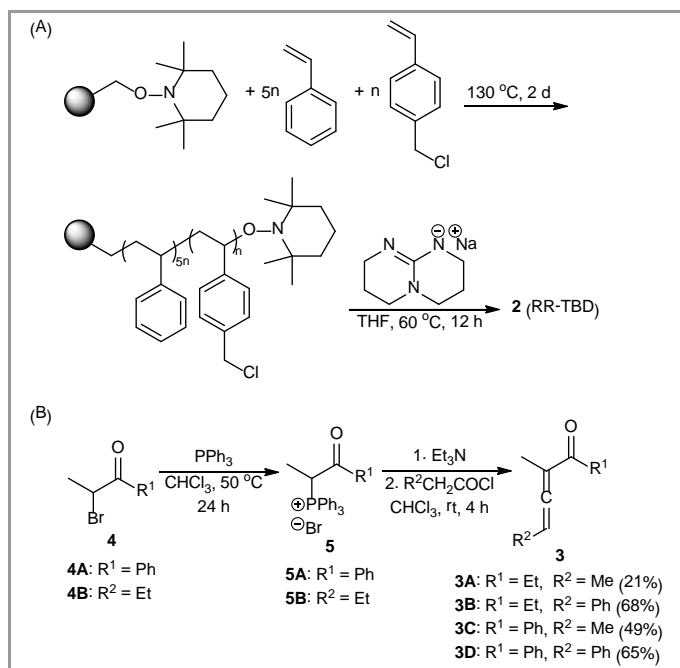


Figure 1 MTBD (**1**), the rasta resin concept, and RR-TBD (**2**)



Scheme 1 MBH reaction variations

Polymer **2** was synthesized as previously reported starting from the initiator functionalized heterogeneous core using a combination of styrene and 4-vinylbenzyl chloride (5:1 ratio) to install the functionalized grafts by a living radical polymerization process. (Scheme 2A).¹⁰ The benzyl chloride groups of the grafts were subsequently treated with deprotonated 1,5,7-triazabicyclo[4.4.0]dec-5-ene to install the catalytic MTBD group analogues. The allenone substrates **3A-D** were prepared by olefination of in situ generated ketenes according to literature procedure, starting from α -bromo ketones **4A-B** via phosphonium salt intermediates **5A-B**, in moderate overall yields (Scheme 2B).^{13,14}



Scheme 2 Synthesis of polymer **2** and allenones **3A-D**

With allenones **3A-D** in hand, we first investigated the possibility of their participation in γ -selective MBH reactions catalyzed by **1**. In the original report by Shi and co-workers, DMAP was used as the catalyst in reactions for which the solvent was DMSO.² We therefore applied similar reaction conditions in side-by-side reactions between **3A** and 4-chlorobenzaldehyde (**6a**) catalyzed by either DMAP or **1**, and observed that the later afforded higher yield of product **7Aa** as a nearly 1:1 mixture of diastereomers than did the former (Table 1, entries 1 and 2). Changing the solvent to NMP and increasing the amount of allenone **3A** relative to electrophile **6a** led to further yield enhancement (Table 1, entries 3-5).¹⁵ Unfortunately, when a 1:1 ratio of **3A** to **6a** was used, the reaction did not go to completion, and chromatographic purification of **7Aa** was required. On the other hand, using a 4-fold excess of the allenone substrate compared to the aldehyde was wasteful, made product purification tedious, and resulted only slightly higher yield. Thus, we chose to use a 2:1 ratio of allenone:aldehyde in future reactions.

We next turned our attention to examining catalyst **1** in a range of γ -selective MBH reactions using the optimized reaction conditions (Table 2). When allenone **3A** was reacted with other electron-withdrawing group substituted aldehydes **6b-c**, high yields of products **7Ab** and **7Ac** were obtained in short reaction times (entries 2 and 3). Very high yield of **7Ad** could even be obtained when unactivated benzaldehyde (**6d**) was used (entry 4). However, when electron rich 4-methoxybenzaldehyde (**6e**) was used, only relatively low yield of the corresponding product **7Ae** was obtained after a prolonged reaction (entry 5). Reactions using allenone **3B** that bears a phenyl group at the γ -position took longer and afforded lower product yields than did reactions with **3A** (entries 6 and 7), perhaps due to steric hindrance. Phenyl ketone substrates **3C** and **3D** showed similar reactivity patterns (entries 8-14). In all cases, the prod-

uct was obtained as a nearly 1:1 mixture of diastereomers.

Table 1 MBH reactions of **3A** with **6a**^a

Entry	Catalyst	Solvent	3A:6a	Time (h)	Combined Yield (%)
1	DMAP	DMSO	1:1	6	54
2	1	DMSO	1:1	6	67
3	1	NMP	1:1	5	71
4	1	NMP	2:1	4	85
5	1	NMP	4:1	4	89

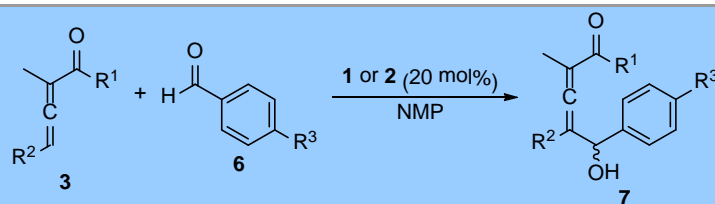
^a Reaction conditions: allenone **3A**, aldehyde **6a** (0.4 mmol), catalyst (0.08 mmol), and solvent (1.0 mL) were stirred at rt for the indicated time.

Having established the general utility of **1** as a catalyst for the reactions of interest, we next used **2** in an identical set of reactions (Table 2). Since we anticipated that the heterogeneous nature of **2** would lead to less efficient reactions, we performed these reactions at 50 °C rather than at room temperature. Even at this elevated temperature reaction times were much longer using **2** as the catalyst than with **1**, and product yields were slightly lower (entries 1-14). When a reaction using **2** between **3C** and **6b** was performed at room temperature, only 47% yield of **7Cb** was obtained after 24 h, compared to 81% yield of **7Cb** after 6 h at 50 °C (entry 15 vs. entry 8). Gratifyingly, when we used a macroporous polystyrene-supported TBD (PS-TBD, **8**) in which the catalytic groups are located in the interior of a heterogeneous polymer bead,^{16,17} much lower product yield of **7Ca** was obtained after a much longer reaction time (entry 16 vs. entry 10). This supports the notion that placing the catalytic groups on flexible grafts makes them more accessible to the substrate molecules and more efficient compared to having them located on the interior of a polystyrene bead, as we have observed in our previous studies.⁹ Unfortunately, we observed that polymer **2** was not an effective catalyst when reused (entries 17 and 18), and at this time the reasons for this are unclear. Reactivation of the catalytic groups by washing the polymer with base did not improve the situation.

In summary, we have found that both **1** and our previously reported polymer **2** based on the rasta resin architecture are able to effectively catalyze γ -selective MBH reactions between α,γ -disubstituted allenones and aryl aldehydes. Superbase **1** was found to be a more efficient catalyst than previously used DMAP, and while **2** was not reusable in these reactions, it did prove to be a more efficient catalyst than did a more traditional polystyrene-supported analogue. Importantly, the heterogeneous nature of **2** did facilitate product purification when

it was used. We are currently examining other applications for **2** and will report the results of these studies shortly.

Table 2 MBH reactions of **3** with **6** catalyzed by **1** or **2**^a



Entry	3	6	R ¹	R ²	R ³	7	1			2		
							Time (h)	Combined Yield (%)	ratio (major:minor)	Time (h)	Combined Yield (%)	ratio (major:minor)
1	3A	6a	Et	Me	Cl	7Aa	4	85	57:43	24	72	56:44
2	3A	6b	Et	Me	CN	7Ab	1.5	92	50:50	12	80	52:48
3	3A	6c	Et	Me	NO ₂	7Ac	3	87	51:49	18	70	50:50
4	3A	6d	Et	Me	H	7Ad	7	87	52:48	48	50	54:46
5	3A	6e	Et	Me	MeO	7Ae	18	64	56:44	60	11	50:50
6	3B	6b	Et	Ph	CN	7Bb	9	74	58:42	48	66	55:45
7	3B	6a	Et	Ph	Cl	7Ba	12	66	52:48	84	19	52:48
8	3C	6b	Ph	Me	CN	7Cb	0.5	91	53:47	6	81	50:50
9	3C	6c	Ph	Me	NO ₂	7Cc	1.5	95	55:45	10	81	51:49
10	3C	6a	Ph	Me	Cl	7Ca	3	89	50:50	12	81	56:44
11	3C	6d	Ph	Me	H	7Cd	5	79	59:41	48	64	55:45
12	3C	6e	Ph	Me	MeO	7Ce	10	48	50:50	48	40	54:46
13	3D	6b	Ph	Ph	CN	7Db	6	74	60:40	20	69	58:42
14	3D	6a	Ph	Ph	Cl	7Da	9	91	52:48	36	40	52:48
15 ^b	3C	6b	Ph	Me	CN	7Cb	-	-	-	24	47	50:50
16 ^c	3C	6a	Ph	Me	Cl	7Ca	-	-	-	24	33	50:50
17 ^d	3C	6a	Ph	Me	Cl	7Ca	-	-	-	12	49	56:44
18 ^e	3C	6a	Ph	Me	Cl	7Ca	-	-	-	12	0	-

^a Reaction conditions: allenone **3** (0.8 mmol), aldehyde **6** (0.4 mmol), **1** or **2** (0.08 mmol), and NMP (1.0 mL) were stirred at rt (with **1**) or 50 °C (with **2**) for the indicated time. ^b Reaction was carried out at room temperature. ^c Reaction was carried out using **8** at 50 °C. ^d First reuse of **2**. ^e Second reuse of **2**.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

Acknowledgement

This research was supported financially by the University of Hong Kong and the Research Grants Council of the Hong Kong S. A. R., P. R. of China (Project No. HKU 705510P).

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- (14) **General Procedure for the Synthesis of Allenones 3A-D:** α -Bromoketone **4A** or **4B** (20.0 mmol), PPh_3 (6.29 g, 24.0 mmol), and benzene (100 mL) were added to a 250-mL round-bottomed flask equipped with a magnetic stirrer and a condenser. The reaction flask was immersed in an oil bath, and the reaction mixture was refluxed for 2 days. After cooling to room temperature, the solvent was removed under reduced pressure to afford crude phosphonium salt **5A** or **5B** as a viscous oil. The crude salt dissolved in chloroform (65 mL) was transferred to a 100-mL round-bottomed flask equipped with a magnetic stirrer. The reaction mixture was cooled to 0 °C with an ice-water bath and then NEt_3 (6.1 mL, 44 mmol) was added dropwise. The ice-water bath was removed, and the reaction mixture was then stirred at room temperature for 3 hours. The reaction mixture was cooled to 0 °C and the appropriate acid chloride (18.0 mmol) was added dropwise. After 1 hour, the reaction mixture was warmed to room temperature and stirred for 10 hours more. The reaction mixture was transferred to a separation funnel and water (100 mL) was added. The organic layer was separated and washed with brine (50 mL) and then dried over MgSO_4 . The solvent was removed under reduced pressure to afford a yellow oil which was then purified by silica gel column chromatography using a mixture of dichloromethane and hexane as the eluent.
- 4-Methylhepta-4,5-dien-3-one (3A)**
 $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ ppm 5.50-5.43 (m, 1H), 2.71-2.59 (m, 2H), 1.79 (d, $J = 7.3$ Hz, 3H), 1.76 (d, $J = 2.7$ Hz, 3H), 1.07 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C-NMR}$ (101 MHz, CDCl_3) δ ppm 212.29, 202.88, 159.50, 138.13, 91.70, 88.92, 32.10, 13.49, 13.39, 8.99. HRMS for $\text{C}_8\text{H}_{12}\text{O}$: calc 124.0883, found 124.0881.
- (15) **General Procedure for the MBH Reactions:** Allenone **3A-D** (0.8 mmol), aldehyde **6a-e** (0.4 mmol), NMP (1.0 mL), and **1**, **2** or **8** (0.08 mmol) were added to a 10-mL round-bottomed flask equipped with a magnetic stirrer. The reaction mixture was stirred either at room temperature (when **1** was used as the catalyst) or at 50 °C (when **2** or **8** was used as the catalyst) for the reaction times indicated in Table 2. When **1** was used as the catalyst, solid NH_4Cl (0.006 g, 0.1 mmol) was added to the reaction mixture to quench the reaction. The reaction mixture was then transferred to a separation funnel, and then water (30 mL) and ethyl acetate (15 mL) were added. The organic layer was separated, washed with brine (30 mL), and dried over MgSO_4 . The solvent was evaporated under reduced pressure to afford an oil, which was purified by silica gel column chromatography using a mixture of ethyl acetate and hexane as the eluent. When **2** was used as the catalyst, the reaction mixture was merely filtered, and the crude product was purified by silica gel column chromatography.
- 7-(4-Chlorophenyl)-7-hydroxy-4,6-dimethylhepta-4,5-dien-3-one (7Aa)**
 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 7.37-7.29 (m, 4H, CH_{Ar} , both diastereomers), 5.26 (s, 1H, CHOH , major diastereomer), 5.24 (s, 1H, CHOH , minor diastereomer), 2.64-2.50 (m, 2H, COCH_2CH_3 , both diastereomers), 2.43 (s br, 1H, OH , major diastereomer), 2.37 (s, 1H, OH , minor diastereomer), 1.78 (s, 3H, $(\text{CH}_3)\text{CCOEt}$, both diastereomers), 1.74 (s, 3H, $(\text{CH}_3)\text{CCHOH}$, both diastereomers), 1.05 (t, $J = 7.4$ Hz, 3H, CH_2CH_3 , both diastereomers). $^{13}\text{C NMR}$ (major diastereomer, 101 MHz, CDCl_3) δ ppm 208.73 (s, $=\text{C}=\text{C}$), 202.80 (s, COEt), 140.12 (s, $\text{C}_{\text{Ar}}\text{CHOH}$), 133.73 (s, $\text{C}_{\text{Ar}}\text{Cl}$), 128.62 (s, $\text{C}_{\text{Ar}}\text{H}$), 127.67 (s, $\text{C}_{\text{Ar}}\text{H}$), 106.43 (s, CCHOH), 105.04 (s, CCOEt), 74.48 (s, CHOH), 32.43 (s, CH_2CH_3), 8.92 (s, CH_2CH_3). The signals for $(\text{CH}_3)\text{CCHOH}$ and $(\text{CH}_3)\text{CCO}$ (14.43, 14.20, 13.81) were not assigned due to overlapping signals. $^{13}\text{C NMR}$ (minor diastereomer, 101 MHz, CDCl_3) δ ppm 208.67 (s, $=\text{C}=\text{C}$), 202.86 (s, COEt), 140.09 (s, $\text{C}_{\text{Ar}}\text{CHOH}$), 133.80 (s, $\text{C}_{\text{Ar}}\text{Cl}$), 128.67 (s, $\text{C}_{\text{Ar}}\text{H}$), 127.74 (s, $\text{C}_{\text{Ar}}\text{H}$), 106.42 (s, CCHOH), 105.32 (s, CCOEt), 74.39 (s, CHOH), 32.43 (s, CH_2CH_3), 8.88 (s, CH_2CH_3). HRMS for $\text{C}_{15}\text{H}_{17}\text{ClO}_2$: calc 264.0912, found 264.0724.
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Graphical abstract

