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Rasta Resin-TBD-Catalyzed γ-Selective Morita–Baylis–Hillman Reactions of α,γ-Disubstituted Allenones

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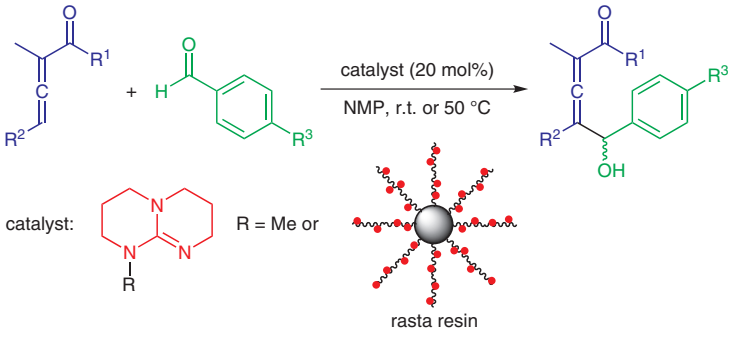

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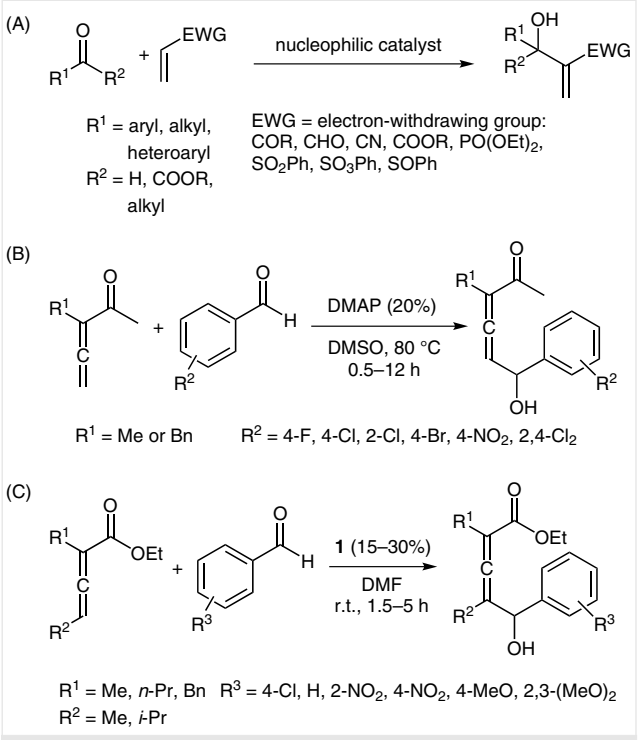
Abstract Rasta resin-TBD (RR-TBD) was found to be an efficient organocatalyst for γ-selective Morita–Baylis–Hillman reactions between α,γ-disubstituted allenones and aryl aldehydes. In these reactions the heterogeneous nature of RR-TBD greatly facilitated product isolation since the catalyst could be 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 1, A). However, with activated allene substrates, the new C–C bond can be formed at the γ-position (Scheme 1, B).[2] Recently Selig and co-workers have reported examples of such γ-selective MBH reactions involving allenoates catalyzed by the organic superbase[3] 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **1**, Figure 1 and Scheme 1, C).[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 of **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 allenoate 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.



Scheme 1 MBH reaction variations

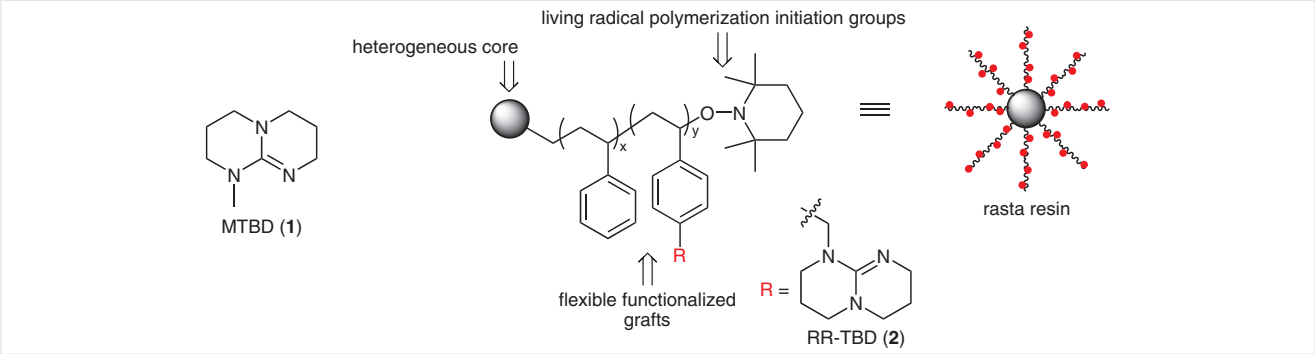
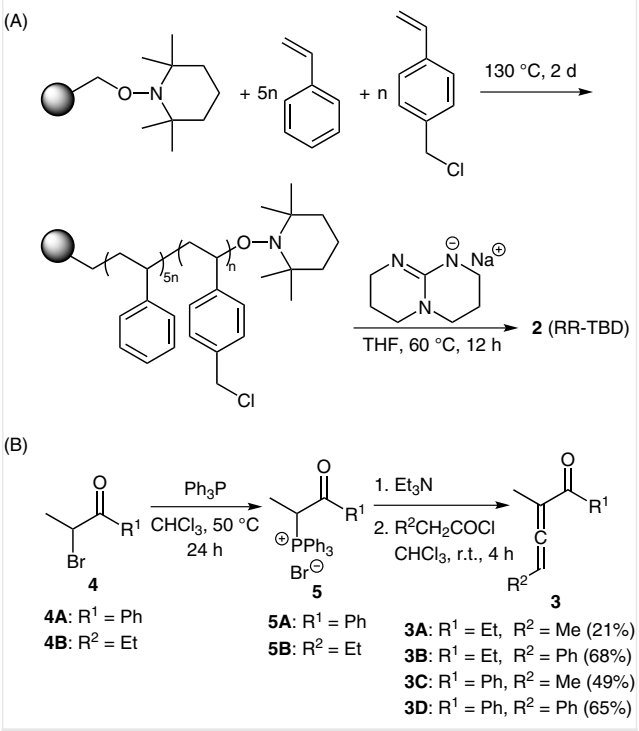


Figure 1 MTBD (**1**), the rasta resin concept, and RR-TBD (**2**)

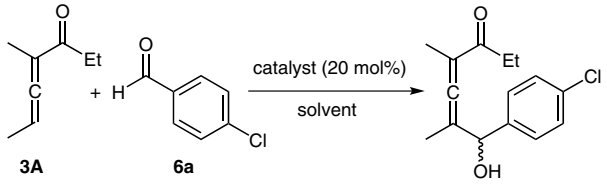
Polymer **2** was synthesized as previously reported starting from the initiator functionalized heterogenous core using a combination of styrene and 4-vinylbenzyl chloride (5:1 ratio) to install the functionalized grafts by a living radical polymerization process (Scheme 2, A).[10] The benzyl chloride 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 a literature procedure, starting from α-bromo ketones **4A**,**B** via phosphonium salt intermediates **5A**,**B**, in moderate overall yields (Scheme 2, B).[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 coworkers, 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 four-fold excess of the allenone substrate compared to the aldehyde was wasteful, made the product purification tedious, and resulted in only a slightly higher yield. Thus, we chose to use a 2:1 ratio of allenone to aldehyde in the subsequent reactions.

Table 1 MBH Reactions of **3A** with **6a**[a]



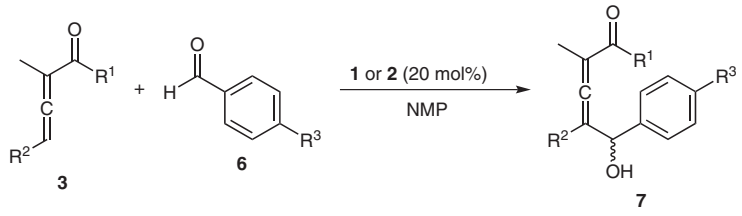
Entry	Catalyst	Solvent	**3A**/**6a**	Time (h)	Combined yield (%)
1	DMAP	DMSO	1:1	6	54
2	**1**	DMSO	1:1	6	67
3	**1**	NMP	1:1	5	71
4	**1**	NMP	2:1	4	85
5	**1**	NMP	4:1	4	89

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

We next turned our attention to examining the 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 be obtained even 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 the steric hindrance. Phenyl ketone substrates **3C** and **3D** showed similar reactivity patterns (entries 8–14). In all cases, the product was obtained as a nearly 1:1 mixture of diastereomers.

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 those with **1** and product yields were slightly lower (entries 1–14). When a reaction between **3C** and **6b** was performed using **2** at room temperature, only 47% yield of **7Cb** was obtained after 24 hours, compared to 81% yield of **7Cb** after six hours at 50 °C (entry 15 vs. entry 8). Gratifyingly, when we

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 r.t. (with **1**) or at 50 °C (with **2**) for the indicated time.
[b] Reaction was carried out at r.t.
[c] Reaction was carried out using **8** at 50 °C.
[d] First reuse of **2**.
[e] Second reuse of **2**.

used a macroporous polystyrene-supported TBD (PS-TBD, **8**) in which the catalytic groups are located on 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 a 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 the 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.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380691.

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(14) **General Procedure for the Synthesis of Allenones 3A–D**: α-Bromo ketone **4A** or **4B** (20.0 mmol), Ph_3P (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 d. After cooling to r.t., the solvent was removed under reduced pressure to afford the crude phosphonium salt **5A** or **5B** as a viscous oil. The crude salt dissolved in $CHCl_3$ (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 Et_3N (6.1 mL, 44 mmol) was added dropwise. The ice-water bath was removed, and the reaction mixture was then stirred at r.t. for 3 h. The reaction mixture was cooled to 0 °C and the appropriate acid chloride (18.0 mmol) was added dropwise. After 1 h, the reaction mixture was warmed to r.t. and stirred for a further 10 h. The reaction mixture was transferred to a separation funnel and H_2O (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 CH_2Cl_2 and hexane as the eluent.

4-Methylhepta-4,5-dien-3-one (3A): ^1H NMR (400 MHz,

$CDCl_3$): δ = 5.43–5.50 (m, 1 H), 2.59–2.71 (m, 2 H), 1.79 (d, *J* = 7.3 Hz, 3 H), 1.76 (d, *J* = 2.7 Hz, 3 H), 1.07 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 212.29, 202.88, 159.50, 138.13, 91.70, 88.92, 32.10, 13.49, 13.39, 8.99. HRMS: *m*/*z* calcd for $C_8H_{12}O$: 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 r.t. (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 H_2O (30 mL) and EtOAc (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 EtOAc 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): ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.37 (m, 4 H, CH_{Ar}, major + minor), 5.26 (s, 1 H, C*H*OH, major), 5.24 (s, 1 H, C*H*OH, minor), 2.50–2.64 (m, 2 H, $COCH_2CH_3$, major + minor), 2.43 (br s, 1 H, OH, major), 2.37 (s, 1 H, OH, minor), 1.78 [s, 3 H, (CH_3)CCOEt, major + minor], 1.74 [s, 3 H, (CH_3)CCHOH, major + minor], 1.05 (t, *J* = 7.4 Hz, 3 H, CH_2CH_3, major + minor). ^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$): δ = 208.73 (s, =C=), 202.80 (s, *C*OEt), 140.12 (s, C_{Ar}CHOH), 133.73 (s, C_{Ar}Cl), 128.62 (s, C_{Ar}H), 127.67 (s, C_{Ar}H), 106.43 (s, *C*CHOH), 105.04 (s, *C*COEt), 74.48 (s, CHOH), 32.43 (s, CH_2CH_3), 8.92 (s, CH_2CH_3). The signals for (CH_3)CCHOH and (CH_3)CCO (14.43, 14.20, 13.81) were not assigned due to overlapping signals. ^{13}C NMR (minor diastereomer, 101 MHz, $CDCl_3$): δ = 208.67 (s, =C=), 202.86 (s, *C*OEt), 140.09 (s, C_{Ar}CHOH), 133.80 (s, C_{Ar}Cl), 128.67 (s, C_{Ar}H), 127.74 (s, C_{Ar}H), 106.42 (s, *C*CHOH), 105.32 (s, *C*COEt), 74.39 (s, CHOH), 32.43 (s, CH_2CH_3), 8.88 (s, CH_2CH_3). HRMS: *m*/*z* calcd for $C_{15}H_{17}Cl_1O_2$: 264.0912; found: 264.0724.

(16) See reference 10 for details and a cartoon illustrating the structure of **8**. The polystyrene support used in **8** is commercially available and is the typical material used in polystyrene-supported reagents and catalysts.

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