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Bifunctional Polymeric Organocatalysts and Their Application in the Cooperative Catalysis of Morita–Baylis–Hillman Reactions

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Abstract: A series of soluble, non-cross-linked polystyrene-supported triphenylphosphane and 4-dimethylaminopyridine reagents were prepared. Some of these polymeric reagents contained either alkyl alcohol or phenol groups on the polymer backbone. The use of these materials as organocatalysts in a range of Morita–Baylis–Hillman reactions indicated that hydroxyl groups could participate in the reactions and accelerate product formation. In the cases examined, phenol groups were more effective than alkyl alcohol groups for catalyzing the reactions. This article is one of the first reports of the synthesis and use of non-natural, bifunctional polymeric reagents for use in organic synthesis in which both functional groups can cooperatively participate in the catalysis of reactions.

Keywords: amines · Lewis bases · Morita–Baylis–Hillman reactions · organocatalysis · phosphanes

Introduction

The use of polymer-supported reagents and catalysts in organic synthesis is now commonplace and many such reagents are either commercially available or have been reported in the literature.[1] This technology has evolved to the stage where it is now possible to use polymer-assisted synthesis for molecules as complex as epothilone C[2] and (+)-plicamine[3] by using polymeric reagents or catalysts in every synthetic step. However, one limitation of currently available supported reagents and catalysts is that they generally contain only a single functional group that can actively participate in a reaction. One exception is the recently reported example of cooperative catalysis by using a series of general acid and base bifunctional mesoporous silica-supported materials that were used in aldol, Henry, and cyanosilylation reactions.[4–7] The only other successful reports in the literature concerning multifunctional supported reagents involve the immobilization of a visualization dye onto the polymer in addition to the reagent group,[8] systems in which both the substrate and the catalyst are attached to the same polymer support,[9] or polymers containing both aza crown ethers and a fluorescent tag.[10] The fundamental drawback of the limited reactivity of monofunctional supported reagents, and our interest in developing organic polymer-supported reagents and catalysts,[11] led us to design multipolymer reaction systems in which multiple supported reagents are used simultaneously to affect the desired reaction.[12] For example, we have recently reported a Mitsunobu reaction system in which the phosphane and the azo reagents are immobilized on different polymer backbones and these supported reagents are used together.[13] However, in many applications it would perhaps be preferable to use a single polymeric reagent rather than multiple ones.

Because, to our knowledge, only the polyfunctional mesoporous silica-supported materials previously mentioned have been reported, we sought to develop a simple and general method for the preparation of analogous organic polymer-supported materials based on radical polymerization. Specifically, we wanted to prepare bifunctional polystyrene-supported organocatalysts[14] for use in Morita–Baylis–Hillman (MBH) reactions.[15,16] Recent investigations into the mechanisms of MBH reactions indicated that they may be accelerated by the presence of weak acids or hydrogen-bond-donating groups, such as alkyl alcohols or phenols,[17] and that alcoholic solvents are often used to perform these reactions.[18]

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Furthermore, the use of bifunctional organocatalysts to perform MBH reactions has long been established. 3-Quinuclidinol was identified as a very efficient catalyst for MBH reactions of a range of substrates (Figure 1).[19] It was proposed that the hydroxyl group accelerated the reactions by hydrogen bonding with either the Michael acceptor carbonyl oxygen or the enolate intermediate of the reaction. This observation led to the use of chiral bifunctional amino alcohols, such as quinidine, cinchonine, *N*-methyl ephedrine, and *N*-methyl prolinol, as chiral catalysts for asymmetric MBH reactions.[20] Subsequently, Hatakeyama et al. reported the use of β-isocupreidine[21] and Sasai et al. described the use of chiral binapthol/3-dialkylaminopyridine and binapthinol/triphenylphosphane bifunctional catalysts[22] in highly enantioselective MBH reactions, and this work inspired our efforts to develop chiral bifunctional catalysts for asymmetric MBH reactions.[23] A monoprotonated Sharpless ligand,[24] a chiral binapthyl-derived amine/thiourea compound,[25] and an ionic liquid bearing both an amine and an alcohol moiety[26] have also been reported to act as bifunctional MBH reaction catalysts. These facts, coupled with our experience in studying intermolecular,[27] intramolecular,[28] and aza[29] variations of the MBH reaction, and the use of polymer-supported catalysts to perform them,[30] led us to design and evaluate new polymers that are functionalized with triphenylphosphane (**1a–e**) or 4-dimethylaminopyridine (DMAP, **2a–f**) groups, and that are attached to hydroxyl-group-bearing polystyrene supports that are reported herein.

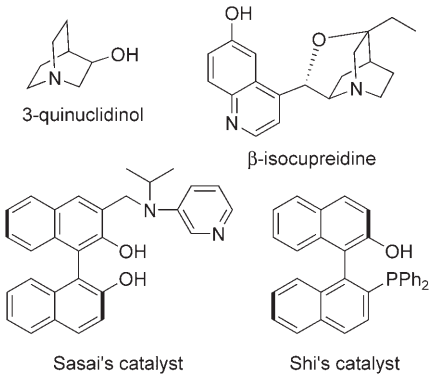
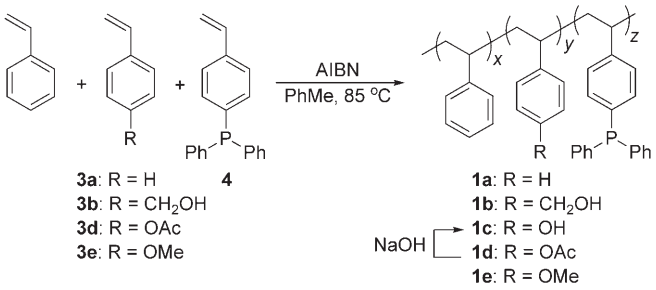


Figure 1. Bifunctional MBH reaction catalysts.

Results and Discussion

We previously reported the synthesis of soluble, non-cross-linked-polystyrene-supported triphenylphosphane (NCPS–PPh_3, **1a**) by means of copolymerization of styrene (**3a**) with 4-vinyltriphenylphosphane (**4**) (Scheme 1).[11a] Therefore, we



Scheme 1. Synthesis of NCPS-supported PPh_3 reagents **1a–e** (AIBN = azobisisobutyronitrile).

used this methodology to prepare related reagents that contained hydroxyl functional groups, both alkyl (**1b**) and aryl (**1c**), to examine if the addition of the hydroxyl groups renders these new materials more effective than **1a** at catalyzing various MBH reactions. The synthesis of **1b** and **1c** was accomplished by using monomer **3b**[31] and commercially available **3d**, respectively, in the radical polymerization reaction of **3a** with **4**. It is important to note that in the preparation of these new polymer-supported reagents, we purposely prepared materials with a PPh_3 loading level of approximately 1.0 mmol g^{-1} and incorporated approximately two equivalents of the hydroxyl functional group for every phosphane group (Table 1). We limited the number of hydroxyl groups so that the resulting polymers would remain hydrophobic and could be precipitated with solvents such as methanol or diethyl ether; this was accomplished by using the appropriate quantity of **3a** to dilute the functionalized monomers. The synthesis of **1c** was accomplished by means of the saponification of **1d**. In addition to **1a–d**, which contain phenyl, benzyl alcohol, phenol, and phenyl acetate groups, respectively, on the polymer backbone, we used **3e** to prepare **1e**, which contains anisole groups.

For all of the polymerization reactions, the observed loading of the phosphane groups in the products were determined by using both elemental analysis (EA) and ^{1}H NMR spectroscopy, and were similar to the theoretical values calculated based on monomer input. The biggest discrepancy observed was with **1e**, in which the EA loading value was approximately 30% greater than the NMR loading value, and the average of these two was 50% higher than the theoretical value (Table 1, entry 5). However, this result is not

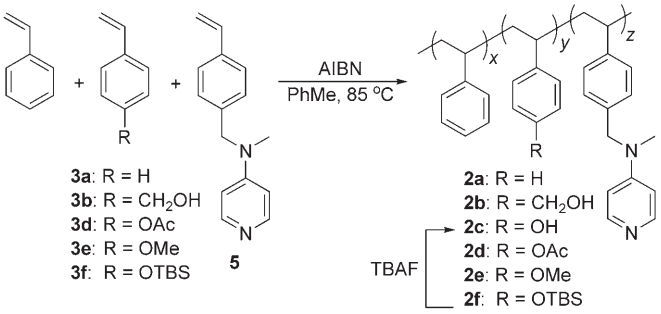
Table 1. Synthesis of NCPS-supported PPh_3 reagents **1a–e**.

Entry	Reagent	Monomer mixture [mmol]			Yield [%]	P Content [%]		Loading level [mmol g^{-1}]				**3*x*:4**[c]
		3*x*	**4**	**3a**		theor[a]	obsd[b]	theor[a]	EA[b]	NMR[c]	av[d]	
1	**1a**	–	5.8	34.6	61	3.3	3.9	1.1	1.3	1.1	1.2	–
2	**1b**	10.4	5.2	20.8	52	3.1	3.8	1.1	1.2	1.1	1.2	2.0
3	**1c**	–[e]	–[e]	–[e]	77	3.2	3.7	1.1	1.2	1.1	1.0	1.9
4	**1d**	15.3	7.6	30.5	70	2.8	4.1	1.0	1.3	1.1	1.2	1.9
5	**1e**	13.9	7.0	27.8	53	3.1	5.1	1.0	1.7	1.3	1.5	1.2

[a] Theoretical P content based on monomer mixture. [b] Observed P content determined by means of EA. [c] Determined by means of ^{1}H NMR spectroscopic analysis. [d] Average EA + NMR loading values that were used in subsequent reactions. [e] Reagent **1c** was prepared from reagent **1d**.

significant because **1e** does not contain hydrogen-bond-donating groups and was designed as an experimental control for comparison with **1c**. Furthermore, **1e** was also the only polymer in which the observed monomer incorporation deviated significantly from the theoretical **3/4** ratio of 2:1, which was also determined by means of ^{1}H NMR spectroscopy. Importantly, both ^{1}H and ^{31}P NMR spectroscopies indicated that no oxidation of the phosphane group occurred for any of the polymers **1a–e**, and thus, the loading levels observed represent the amount of nucleophilic triphenylphosphane groups present.

For the synthesis of the polystyrene-supported DMAP organocatalysts, monomer **5** was prepared according to literature methods from 4-vinylbenzyl chloride and 4-(*N*-methylamino)pyridine.[32] This monomer was then copolymerized under the same conditions as those for **3a**, **3b**, and **3d–f** to prepare **2a, 2b**, and **2d–f**, respectively, in moderate to good yields (Scheme 2, Table 2). Monomer **3f** was prepared according to literature methods from 4-hydroxybenzaldehyde,[33] and **2f** was converted into **2c** by treatment with fluoride. Deprotection of silyl ether groups was chosen for the synthesis of **2c**, rather than saponification, to ensure that the amine groups remained unprotonated, and thus, retained their nucleophilicity.



Scheme 2. Synthesis of NCPS-supported DMAP reagents **2a–f** (TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutyl ammonium fluoride).

Table 2. Synthesis of NCPS-supported DMAP reagents **2a–f**.

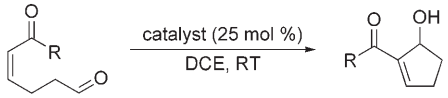
Entry	Reagent	Monomer mixture [mmol]			Yield [%]	N Content [%]		Loading level [mmol g^{-1}]				**3x**:**5**[c]
		3x	**5**	**3a**		theor[a]	obsd [b]	theor[a]	EA[b]	NMR[c]	av[d]	
1	**2a**	–	16.6	99.8	45	2.8	4.5	1.2	1.6	1.6	1.6	–
2	**2b**	10.7	5.4	53.5	50	1.8	2.7	0.7	1.0	1.1	1.0	1.8
3	**2c**	–[e]	–[e]	–[e]	80	3.2	2.8	1.1	1.0	1.2	1.1	1.9
4	**2d**	12.9	6.5	25.9	31	2.9	2.6	1.0	0.9	1.1	1.0	2.0
5	**2e**	17.8	8.9	35.7	40	3.1	3.0	1.0	1.1	1.0	1.1	2.2
6	**2f**	17.8	8.9	35.7	33	–[f]	–[f]	0.9	–[f]	0.9	–[f]	2.0

[a] Theoretical N content based on monomer mixture. [b] Observed N content determined by means of EA. [c] Determined by means of ^{1}H NMR spectroscopic analysis. [d] Average EA + NMR loading values that were used in subsequent reactions. [e] Reagent **2c** was prepared from reagent **2f**. [f] Not determined.

As before, the DMAP loading levels of these polymers were calculated to be approximately 1.0 mmol g^{-1}, and they contained approximately two equivalents of the functional monomer group per DMAP group (Table 2). The actual loading levels of the polymers were again determined by means of EA, to obtain the nitrogen content, and integration of their ^{1}H NMR spectra. The only observed polymer loading level that deviated significantly from the theoretical value was that for **2a**, in which the observed value was approximately 33% greater than expected. However, as the loading values for **2a** obtained by means of EA and NMR were identical, we have confidence in the value and used it for the MBH reactions. Furthermore, polymers **2a–f** all exhibited almost the theoretical **3/5** ratio of 2:1.

With the bifunctional polymer-supported reagents in hand, we examined the use of **1a–e** as catalysts for intramolecular MBH reactions of *Z* enones **6a–f**, which contain pendant electrophilic aldehyde groups (Table 3). These substrates, which contain both alkyl and aryl substituents, were chosen because it has been previously observed that PPh_3 is a good catalyst for the cyclization of these starting materials,[18t,28] and we already had these materials and authentic product samples in hand. Parallel reactions were performed in which all five catalysts were used individually for the same substrates. The reactions were performed at room temperature and allowed to proceed until one reaction was almost complete, as determined by means of TLC analysis. At this time, all of the reactions were stopped and the isolated yields of pure product were determined. It should be noted that the reactions gave only the desired product, and that products **7a–f** were identical to authentic samples (see the Supporting Information).[28]

Table 3. Intramolecular MBH reactions catalyzed by **1a–e**.



6a-f **7a-f**

Entry	Substrate	Yield [%][a]				
		1a	**1b**	**1c**	**1d**	**1e**
1[b]	**6a**: R = –Et	2	26	72	21	12
2[b]	**6b**: R = –Bu	37	55	84	33	15
3[c]	**6c**: R = –Ph	33	77	84	31	27
4[c]	**6d**: R = –C_6H_4-4-Cl	53	67	75	63	59
5[c]	**6e**: R = –C_6H_4-3-Me	35	53	60	46	38
6[c]	**6f**: R = –C_6H_4-4-Me	31	44	52	39	35

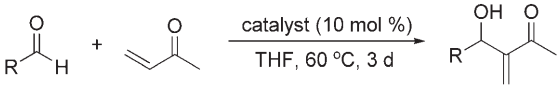
[a] Average isolated yield from at least two experiments. [b] Reactions were performed for 36 h. [c] Reactions were performed for 18 h.

Table 3 shows that the best catalyst for all six substrates in the parallel reactions was phenol-substituted **1c**, which led to isolated yields of the product ranging from 52–84%. The second best catalyst was methanol-substituted **1b**, which afforded slightly to significantly lower yields (26–77%) for the

same substrates. The other three catalysts, **1a**, **1d**, and **1e**, were comparable in performance, and all afforded lower yields than **1b** and **1c**. The most dramatic difference in product yields between hydroxylated catalysts **1b** and **1c**, and the non-hydroxylated ones can be seen with phenyl-substituted substrate **6c** (Table 3, entry 3). The smallest difference in product yields was observed with the most electron poor, and therefore, most activated substrate **6d**, which afforded good yields with all catalysts (Table 3, entry 4). Less-reactive alkyl-substituted substrates **6a** and **6b** also exhibited substantially higher yields with the hydroxylated catalysts than with the non-hydroxylated ones (Table 3, entries 1 and 2).

Subsequently, we examined the use of **2a–e** as catalysts for intermolecular MBH reactions between aryl aldehydes **8a–h** and methyl vinyl ketone (**9**) (Table 4). The reactions

Table 4. MBH reactions of methyl vinyl ketone catalyzed by **2a–e**.



8a-h **9** **10a-h**

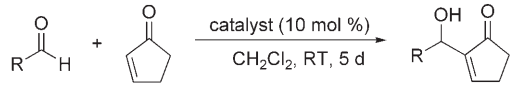
Entry	Aldehyde	Yield [%][a]				
		2a	**2b**	**2c**	**2d**	**2e**
1	**8a**: R = −Ph	trace	19	28	trace	trace
2	**8b**: R = $-C_6H_4$-4-Br	24	36	41	28	32
3	**8c**: R = $-C_6H_4$-2-Cl	12	27	35	17	19
4	**8d**: R = $-C_6H_4$-4-Cl	31	42	50	35	38
5	**8e**: R = $-C_6H_4$-4-F	47	67	74	53	57
6	**8f**: R = $-C_6H_4$-3-NO_2	37	55	64	44	47
7	**8g**: R = $-C_6H_4$-4-NO_2	42	62	71	45	51
8	**8h**: R = $-C_6H_3$-2,4-Cl_2	33	49	56	41	45

[a] Average isolated yield from at least two experiments.

were performed in parallel as before, except that it was necessary to use electron-deficient aldehydes for these reactions to achieve good to moderate yields after 3 d at 60 °C in THF. When benzaldehyde (**8a**) was used as the electrophile, significant amounts of product **10a** were only observed by using hydroxylated catalysts **2b** and **2c**, with the latter affording a higher yield (Table 4, entry 1). In fact, **2c** afforded the highest yields (28–74 %) of all the catalysts for the reactions of the aldehyde electrophiles with Michael acceptor **9**, and **2b** afforded the second highest yields (19–67 %). As before, non-hydroxylated catalysts **2a**, **2d**, and **2e** performed similarly, and were less efficient than the hydroxylated ones, to afford at most a 57 % yield of the desired product (Table 4, entry 5).

Similar reactivity patterns were observed by using these same catalysts to perform MBH reactions of both 2-cyclopenten-1-one (**11**) and 2-cyclohexen-1-one (**13**), and various electron-deficient aldehydes (Tables 5 and 6, respectively). In these reactions, aldehyde **8j**, functionalized with two electron-withdrawing nitro groups, afforded the highest yields of all those examined (entry 4 in both Tables 5 and 6), and catalyst **2c** functionalized with a phenol group afforded the

Table 5. MBH reactions of 2-cyclopenten-1-one catalyzed by **2a-e**.

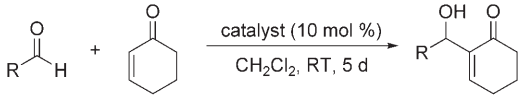


8f,g,i-k **11** **12a-e**

Entry	Aldehyde	Yield [%][a]				
		2a	**2b**	**2c**	**2d**	**2e**
1	**8f**: R = $-C_6H_4$-3-NO_2	7	27	32	17	8
2	**8g**: R = $-C_6H_4$-4-NO_2	30	69	81	31	56
3	**8i**: R = $-C_6H_4$-2-NO_2	4	27	33	8	10
4	**8j**: R = $-C_6H_3$-2,4-$(NO_2)_2$	36	61	87	43	44
5	**8k**: R = $-C_6H_4$-4-CN	8	29	66	10	8

[a] Average isolated yield from at least two experiments.

Table 6. MBH reactions of 2-cyclohexen-1-one catalyzed by **2a–e**.



8f,g,i-k **13** **14a-e**

Entry	Aldehyde	Yield [%][a]				
		2a	**2b**	**2c**	**2d**	**2e**
1	**8f**: R = $-C_6H_4$-3-NO_2	2	9	49	7	0
2	**8g**: R = $-C_6H_4$-4-NO_2	6	14	72	10	7
3	**8i**: R = $-C_6H_4$-2-NO_2	2	4	27	4	2
4	**8j**: R = $-C_6H_3$-2,4-$(NO_2)_2$	42	52	79	36	36
5	**8k**: R = $-C_6H_4$-4-CN	3	13	67	3	3

[a] Average isolated yield from at least two experiments.

highest yields in reactions with all substrates (32–87 %) amongst all of the catalysts screened. Methanol-functionalized catalyst **2b** was again the second best catalyst for all reactions; **2a**, **2d**, and **2e** all performed similarly. Interestingly, reactions of Michael acceptor **13** afforded some of the largest differences in catalytic efficiency between **2a–e** observed in this study. For reactions of **13** with aldehydes **8f, 8g**, **8i**, and **8k**, catalyst **2c** afforded approximately 5-fold more product than **2b**, and 10- to 20-fold more product than non-hydroxylated catalysts **2a**, **2d**, and **2e**.

It should be noted that for all of the reactions performed with catalysts **2a–e**, products **10a–h, 12a–c**, and **14a–c** have all been reported previously,[17f,18h,p,34] or were characterized by means of ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectral analysis (see the Supporting Information). Only compounds **12d–e** and **14d–e** have not been previously described in the literature.

Taken as a whole, the data clearly indicate that the hydroxylated catalysts are better than the non-hydroxylated ones, and that of the former, phenol-substituted **1c** and **2c** are more efficient than methanol-substituted **1b** and **2b**. The methoxy- and acetoxy-functionalized catalysts performed similarly to the unfunctionalized polystyrene-supported catalysts. Thus, the reactivity pattern for both sets of catalysts were similar: **1c** and **2c** > **1b** and **2b** > **1a** and **2a** ≈ **1d** and **2d** ≈ **1e** and **2e**.

Conclusion

In summary, we have prepared two series of bifunctional polymeric nucleophilic organocatalysts that contain either PPh_3 (**1a–e**) or DMAP (**2a–e**) groups. It was found that of these materials, those functionalized with hydroxyl groups (**1b, 1c**, **2b**, and **2c**) are more efficient at catalyzing both intra- and intermolecular MBH reactions than those that are unfunctionalized (**1a** and **2a**) or functionalized with methoxy (**1d** and **2d**) or acetoxy groups (**1e** and **2e**). It is proposed that these hydroxylated materials are able to cooperatively catalyze the reactions studied either by hydrogen-bond activation of the Michael acceptor (Figure 2, **A**) or by stabilization of the enolate intermediate that is formed in the reactions (Figure 2, **B**). This hypothesis is supported by the results of many previous examples of bifunctional small-molecule organocatalysts, especially chiral ones, and the fact that the more acidic phenol-functionalized reagents **1c** and **2c** afforded higher product yields in all reactions than methanol-functionalized reagents **1b** and **2b**.

These results represent a new design paradigm for polystyrene-supported reagents and demonstrate that the polymer backbone can be functionalized in such a way as to simultaneously incorporate multiple different catalytic or reagent groups. Owing to the facile synthesis of many styrene derivatives, it is anticipated that this strategy will be applicable to the generation of many other polyfunctional polystyrene-supported reagents and catalysts, and will simplify product isolation from reactions that require numerous different reagents and catalysts. Efforts to determine the limits of this strategy are currently underway.[35]

Experimental Section

General methods: All reactions were carried out under a nitrogen or an argon atmosphere in oven- or flame-dried glassware. Tetrahydrofuran was purified by using a Solv-Tek purification system that employs activated Al_2O_3. Dichloromethane (DCM) and 1,2-dichloroethane (DCE) were distilled from CaH_2 under an argon atmosphere. Commercially available reagents were used as received. All reactions were monitored by TLC analysis by using GF254 silica gel coated plates. Column chromatography was carried out by using silica gel (300–400 mesh) at increased pressure. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO by using either a Bruker DRX-300 or 400 spectrometer operating at 300 or 400 MHz for ^1H analysis and 75 or 100 MHz for ^{13}C analysis. ^{31}P NMR spectra were recorded in $CDCl_3$ by using a Bruker DRX-400 spectrometer operating at 162 MHz for ^{31}P analysis. Chemical shift data is expressed in ppm with reference to TMS and the residual solvent peak(s). HRMS (EI) data was recorded by using a Finnigan MAT 96 mass spectrometer.

4-Vinylbenzyl alcohol (3b):[31] A solution of 4-vinylbenzyl chloride (32.0 g, 213 mmol), sodium acetate (23.0 g, 280 mmol), and Bu_4NI (7.9 g, 21.3 mmol) in dry THF (300 mL) was heated to reflux for 48 h. After cooling to room temperature, the resulting mixture was diluted with water (200 mL), and extracted with $CHCl_3$ (3×300 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 4-vinylbenzyl acetate as an orange oil (37.1 g, 99%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.10$ (s, 3H), 5.09 (s, 2H), 5.26 (d, $J=10.9$ Hz, 1H), 5.76 (d, $J=17.6$ Hz, 1H), 6.71 (dd, $J=17.6$, 10.9 Hz, 1H), 7.32 (d, $J=8.1$ Hz, 2H), 7.40 ppm (d, $J=8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=20.9$, 66.0, 114.3, 126.3, 128.5, 135.4, 136.3, 137.6, 170.8 ppm; HRMS (EI): m/z calcd for $C_{11}H_{12}O_2$: 176.0837; found: 176.0833.

An aqueous 6 N NaOH (50 mL) solution was added to a solution of 4-vinylbenzyl acetate (37.1 g, 211 mmol) in EtOH (150 mL). The reaction mixture was left at reflux for 3 h. After cooling to room temperature, the resulting mixture was diluted with water (200 mL) and extracted with $CHCl_3$ (3×300 mL). The dried and concentrated organic layers were purified by means of distillation (100 °C, 20 mm Hg) to afford **3b** as a colorless liquid (17.0 g, 60%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.64$ (s, 2H), 5.24 (d, $J=10.9$ Hz, 1H), 5.75 (d, $J=17.6$ Hz, 1H), 6.71 (dd, $J=17.6$, 10.9 Hz, 1H), 7.29 (d, $J=8.1$ Hz, 2H), 7.39 ppm (d, $J=8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=65.0$, 113.9, 126.4, 127.2, 136.5, 137.0, 140.4 ppm; HRMS (EI): m/z calcd for $C_9H_{10}O$: 134.0732; found: 134.0728.

4-*tert*-Butyldimethylsilyloxybenzaldehyde:[33] A solution of *tert*-butyldimethylsilylchloride (6.8 g. 45.0 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise to a solution of 4-hydroxybenzaldehyde (3.7 g, 30.0 mmol) and triethylamine (6.3 mL, 45.0 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with water (100 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by means of flash column chromatography by using 10% EtOAc/hexane as the eluent to afford 4-*tert*-butyldimethylsilyloxybenzaldehyde as a yellow oil (6.9 g, 98%). ^1H NMR (400 MHz, $CDCl_3$): $\delta=0.15$ (s, 6H), 0.89 (s, 9H), 6.84 (d, $J=8.5$ Hz, 2H), 7.69 (d, $J=8.5$ Hz, 2H), 9.79 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=-4.4$, 18.2, 25.7, 120.5, 130.4, 131.9, 161.5, 190.9 ppm; HRMS (EI): m/z calcd for $C_{13}H_{20}O_2Si$: 236.1233; found: 236.1230.

4-*tert*-Butyldimethylsilyloxystyrene (3f):[33] *n*BuLi (2.5 M solution in hexane, 18 mL, 45.0 mmol) was added dropwise to a solution of methyltriphenylphosphonium bromide (16.1 g, 45.0 mmol) in dry THF (50 mL) at 0 °C. After stirring for 15 min, a solution of 4-*tert*-butyldimethylsilyloxybenzaldehyde (6.9 g, 30.0 mmol) in dry THF (50 mL) was added by using a dropping funnel. Upon complete addition, the reaction mixture

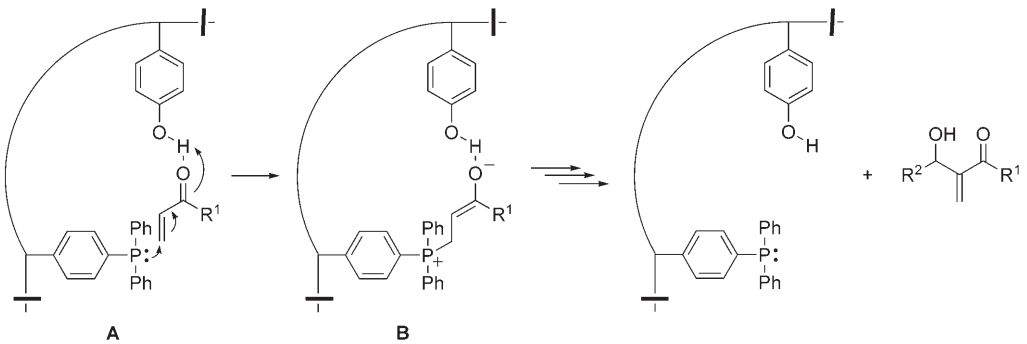


Figure 2. Catalysis of MBH reactions by bifunctional polymer-supported PPh_3 reagent **1c**.

was allowed to warm to room temperature. The yellow suspension was stirred for 4 h and then quenched with an aqueous saturated NH_4Cl solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (3×100 mL). The combined organic layers were washed with water (3×150 mL) and brine (3×150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by means of flash column chromatography by using hexane as the eluent to afford **3f** as a colorless oil (5.3 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.19 (s, 6H), 0.98 (s, 9H), 5.12 (d, J=10.9 Hz, 1H), 5.60 (d, J=17.6 Hz, 1H), 6.65 (dd, J=17.6, 10.9 Hz, 1H), 6.79 (d, J=8.5 Hz, 2H), 7.28 ppm (d, J=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=−4.4, 18.3, 25.7, 111.7, 120.2, 127.4, 131.0, 136.4, 155.6 ppm; HRMS (EI): m/z calcd for $C_{14}H_{22}OSi$: 234.1440; found: 234.1441.

4-(*N*-Methyl-*N*-vinylbenzylamino)pyridine (5):[32] NaH (60% in mineral oil, 1.2 g, 52.0 mmol) was added to a solution of 4-(*N*-methylamino)pyridine (4.2 g, 39.0 mmol) in dry THF (30 mL) at 0°C. The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 30 min. The reaction mixture was then cooled to 0°C again before 4-vinylbenzyl chloride (4 mL, 26.0 mmol) was added dropwise. Upon complete addition, the reaction was stirred at room temperature for 18 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The resulting oil was dissolved in CH_2Cl_2 (150 mL), washed with water (3× 150 mL) and brine (3×150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by means of flash column chromatography by using 1% MeOH/CH_2Cl_2 as the eluent to afford **5** as a viscous brown oil (4.8 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.06 (s, 3H), 4.56 (s, 2H), 5.23 (d, J=10.9 Hz, 1H), 5.73 (d, J= 17.6 Hz, 1H), 6.54 (d, J=6.0 Hz, 2H), 6.69 (dd, J=17.6, 10.9 Hz, 1H), 7.12 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H), 8.21 ppm (d, J=5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=37.7, 54.7, 106.7, 113.9, 126.6, 129.2, 136.3, 136.7, 136.78, 149.9, 153.8 ppm; HRMS (EI): m/z calcd for $C_{15}H_{16}N_2$: 224.1313; found: 224.1309.

General procedure for non-cross-linked polystyrene-supported PPh_3 reagent synthesis (procedure A): AIBN was added to a solution of styrene, polar styrene monomer **3b** or **3d**–**e** and **4** in toluene. The mixture was purged with N_2 for 30 min and the solution was then stirred at 85°C for 24 h. The solution was concentrated in vacuo and then the residue was redissolved in THF. This solution was added slowly to vigorously stirred MeOH at 0°C. The white precipitate was filtered and dried in vacuo. EA was used to determine the phosphorous content, and thus the PPh_3 loading level.

Poly[styrene-*co*-(4-styryldiphenylphosphane)] (1a): Procedure A was followed by using styrene (3.6 g, 34.6 mmol), **4** (1.7 g, 5.8 mmol), and AIBN (0.1 g, 0.4 mmol) in toluene (26 mL). The residue was redissolved in THF (5 mL) and cold MeOH (300 mL) was used for precipitation to afford **1a** as a white powder (3.2 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88–1.85 (br m, 18H), 6.45–7.38 ppm (br m, 44H); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−6.18 ppm. The ratio of monomer incorporation into **1a** was determined by means of ^{1}H NMR spectroscopy to be 5.5:1.0 (styrene/**4**). This ratio corresponds to a PPh_3 loading level of 1.1 mmol g^{-1} for **1a**. EA indicated that **1a** contained 3.9% P, which corresponds to a PPh_3 loading level of 1.3 mmol g^{-1} for **1a**.

Poly[styrene-*co*-(4-vinylbenzyl alcohol)-*co*-(4-styryldiphenylphosphane)] (1b): Procedure A was followed by using styrene (2.2 g, 20.8 mmol), **3b** (1.4 g, 10.4 mmol), **4** (1.4 g, 5.2 mmol), and AIBN (0.1 g, 0.4 mmol) in toluene (28 mL). The residue was redissolved in THF (5 mL) and cold MeOH (300 mL) was used for precipitation to afford **1b** as a white powder (2.6 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92–2.17 (br m, 19H), 4.52 (br s, 4H), 6.54–7.60 ppm (br m, 42H); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−16.64 ppm. The ratio of monomer incorporation into **1b** was determined by means of ^{1}H NMR spectroscopy to be 3.7:2.0:1.0 (styrene/**3b**/**4**). This ratio corresponds to a PPh_3 loading level of 1.1 mmol g^{-1} for **1b**. EA indicated that **1b** contained 3.8% P, which corresponds to a PPh_3 loading level of 1.2 mmol g^{-1} for **1b**.

Poly[styrene-*co*-(4-hydroxystyrene-)*co*-(4-styryldiphenylphosphane)] (1c): Compound **1d** (5.0 g, 10.5 mmol) was added to a solution of NaOH (4.2 g, 105.8 mmol) in 1:1:3 MeOH/H_2O/THF (50 mL). The reaction mixture was stirred at room temperature for 24 h and then quenched with water (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was taken up in THF (5 mL) and the solution was added slowly to vigorously stirred cold MeOH (200 mL) at 0°C. The white precipitate was filtered and dried in vacuo to afford **1c** as a white powder (3.5 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.88–1.83 (br m, 16H), 6.19–7.84 ppm (br m, 41H); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−6.33 ppm. The ratio of monomer incorporation into **1c** was determined by means of ^{1}H NMR spectroscopy to be 3.2:1.9:1.0 (styrene/4-hydroxystyrene/**4**). This ratio corresponds to a PPh_3 loading level of 1.2 mmol g^{-1} for **1c**. EA indicated that **1c** contained 3.7% P, which corresponds to a PPh_3 loading level of 1.2 mmol g^{-1} for **1c**.

Poly[styrene-*co*-(4-acetoxystyrene)-*co*-(4-styryldiphenylphosphane)] (1d): Procedure A was followed by using styrene (3.2 g, 30.5 mmol), **3d** (2.5 g, 15.3 mmol), **4** (2.2 g, 7.6 mmol), and AIBN (0.1 g, 0.5 mmol) in toluene (40 mL). The residue was redissolved in THF (8 mL) and cold MeOH (500 mL) was used for precipitation to afford **1d** as a white powder (5.5 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94–1.78 (br m, 19H), 2.24 (br s, 6H), 6.53–7.39 ppm (br m, 36H); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−6.26 ppm; after oxidation: ^{31}P NMR (162 MHz, $CDCl_3$, TMS): δ=29.98 ppm. The ratio of monomer incorporation into **1d** was determined by means of ^{1}H NMR spectroscopy of oxidized **1d** to be 3.3:1.9:1.0 (styrene/**3d**/**4**). This ratio corresponds to a PPh_3 loading level of 1.1 mmol g^{-1} for **1d**. EA indicated that **1d** contained 4.1% P, which corresponds to a PPh_3 loading level of 1.3 mmol g^{-1} for **1d**.

Poly[styrene-*co*-(4-methoxystyrene)-*co*-(4-styryldiphenylphosphane)] (1e): Procedure A was followed by using styrene (2.9 g, 27.8 mmol), **3e** (1.9 g, 13.9 mmol), **4** (4.0 g, 7.0 mmol), and AIBN (0.1 g, 0.5 mmol) in toluene (34 mL). The residue was redissolved in THF (10 mL) and cold MeOH (600 mL) was used for precipitation to afford **1e** as a white powder (4.7 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.39–1.78 (br m, 20H), 3.70 (br s, 6H), 6.55–7.33 ppm (br m, 49H); ^{31}P NMR (162 MHz, $CDCl_3$): δ=−6.26 ppm; after oxidation: ^{31}P NMR (162 MHz, $CDCl_3$): δ=30.10 ppm. The ratio of monomer incorporation into **1e** was determined by means of ^{1}H NMR spectroscopy of oxidized **1e** to be 2.5:1.2:1.0 (styrene/**3e**/**4**). This ratio corresponds to a PPh_3 loading level of 1.3 mmol g^{-1} for **c**. EA indicated that **1e** contained 5.1% P, which corresponds to a PPh_3 loading level of 1.7 mmol g^{-1} for **1e**.

General procedure for non-cross-linked polystyrene-supported DMAP reagent synthesis (procedure B): AIBN was added to a solution of styrene, polar styrene monomer **3b** or **3d**–**f** and **5** in toluene. The mixture was purged with N_2 for 30 min and the solution was stirred at 85°C for 24 h. The solution was concentrated in vacuo and then the residue was redissolved in THF. This solution was added slowly to vigorously stirred cold MeOH at 0°C. The precipitate was filtered and dried in vacuo. EA was used to determine nitrogen content, and thus the DMAP loading level.

Poly{styrene-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2a): Procedure B was followed by using styrene (6.9 g, 99.8 mmol), **5** (3.7 g, 16.6 mmol), and AIBN (0.2 g, 1.2 mmol) in toluene (70 mL). The residue was redissolved in THF (10 mL) and cold MeOH (600 mL) was used for precipitation to afford **2a** as a yellow powder (4.8 g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.88–2.18 (br m, 16H), 3.00 (br s, 3H), 4.41 (br s, 2H), 6.49–7.26 (br m, 25H), 8.21 ppm (br s, 2H). The ratio of monomer incorporation into **2a** was determined by means of ^{1}H NMR spectroscopy to be 4.0:1.0 (styrene/**5**). This ratio corresponds to a DMAP loading level of 1.6 mmol g^{-1} for **2a**. EA indicated that **2a** contained 4.5% N, which corresponds to a DMAP loading level of 1.6 mmol g^{-1} for **2a**.

Poly{styrene-*co*-(4-vinylbenzyl alcohol)-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2b): Procedure B was followed by using styrene (5.6 g, 53.5 mmol), **3b** (1.4 g, 10.7 mmol), **5** (1.2 g, 5.4 mmol), and AIBN (0.1 g, 0.7 mmol) in toluene (35 mL). The residue was redissolved in THF (10 mL) and cold MeOH (400 mL) was used for precipitation to afford **2b** as a white powder (3.5 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.88–1.65 (br m, 27H), 2.98 (br s, 3H), 4.11–4.58 (br m, 5H), 6.49–7.06 (br m, 37H), 8.16 ppm (br s, 2H). The ratio of monomer incorporation into **2b** was determined by means of ^{1}H NMR spectroscopy to be

5.7:1.8:1.0 (styrene/**3b**/**5**). This ratio corresponds to a DMAP loading level of 1.0 mmol g^{-1} for **2b**. EA indicated that **2b** contained 2.7% N, which corresponds to a DMAP loading level of 1.1 mmol g^{-1} for **2b**.

Poly{styrene-*co*-(4-hydroxystyrene)-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2c): Compound **2f** (2.7 g, 4.9 mmol) was added to a solution of 1 M TBAF (24.3 mL, 24.3 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was redissolved in THF (4 mL) and the solution was added slowly to vigorously stirred cold MeOH (200 mL) at 0 °C. The white precipitate was filtered and dried in vacuo to afford **2c** as a white powder (1.7 g, 80%). ^{1}H NMR (300 MHz, DMSO): δ = 1.23–2.15 (br m, 19H), 3.09 (br s, 4H), 4.57 (br s, 2H), 6.67–7.14 (br m, 29H), 8.18 ppm (br s, 2H). The ratio of monomer incorporation into **2c** was determined by means of ^{1}H NMR spectroscopy to be 3.2:2.0:1.0 (styrene/4-hydroxystyrene/**5**). This ratio corresponds to a DMAP loading level of 1.2 mmol g^{-1} for **2c**. EA indicated that **2c** contained 2.8% N, which corresponds to a DMAP loading level of 1.0 mmol g^{-1} for **2c**.

Poly{styrene-*co*-(4-acetoxystyrene)-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2d): Procedure B was followed by using styrene (2.7 g, 25.9 mmol), **3d** (2.1 g, 12.9 mmol), **5** (1.5 g, 6.5 mmol), and AIBN (0.1 g, 0.5 mmol) in toluene (30 mL). The residue was redissolved in THF (5 mL) and cold MeOH (300 mL) was used for precipitation to afford **2d** as a yellow powder (1.9 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93–1.78 (br m, 20H), 2.16 (br s, 6H), 3.01 (br s, 2H), 4.42 (br s, 2H), 6.51–7.26 (br m, 31H), 8.21 ppm (br s, 2H). The ratio of monomer incorporation into **2d** was determined by means of ^{1}H NMR spectroscopy to be 3.5:2.0:1.0 (styrene/**3d**/**5**). This ratio corresponds to a DMAP loading level of 1.1 mmol g^{-1} for **2d**. EA indicated that **2d** contained 2.6% N, which corresponds to a DMAP loading level of 0.9 mmol g^{-1} for **2d**.

Poly{styrene-*co*-(4-methoxystyrene)-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2e): Procedure B was followed by using styrene (3.7 g, 35.7 mmol), **3e** (2.4 g, 17.8 mmol), **5** (2.0 g, 8.9 mmol), and AIBN (0.1 g, 0.6 mmol) in toluene (30 mL). The residue was redissolved in THF (7 mL) and cold MeOH (600 mL) was used for precipitation to afford **2e** as a yellow powder (3.3 g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93–2.17 (br m, 23H), 2.95 (br s, 3H), 3.73 (br s, 7H), 4.41 (br s, 2H), 6.50–7.26 (br m, 37H), 8.20 ppm (br s, 2H). The ratio of monomer incorporation into **2e** was determined by means of ^{1}H NMR spectroscopy to be 4.4:2.2:1.0 (styrene/**3e**/**5**). This ratio corresponds to a DMAP loading level of 1.0 mmol g^{-1} for **2e**. EA indicated that **2e** contained 3.0% N, which corresponds to a DMAP loading level of 1.1 mmol g^{-1} for **2e**.

Poly{styrene-*co*-(4-*tert*-butyldimethylsilyloxystyrene)-*co*-[4-(*N*-methyl-*N*-vinylbenzylamino)pyridine]} (2f): Procedure B was followed by using styrene (3.7 g, 35.7 mmol), **3f** (4.2 g, 17.8 mmol), **5** (2.0 g, 8.9 mmol), and AIBN (0.1 g, 0.6 mmol) in toluene (50 mL). The residue was redissolved in THF (8 mL) and cold MeOH (600 mL) was used for precipitation to afford **2f** as a yellow powder (3.3 g, 33%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (br s, 12H), 0.97 (br s, 18H), 1.39–1.77 (br m, 22H), 2.93 (br s, 3H), 4.40 (br s, 2H), 6.50–7.24 (br m, 35H), 8.20 ppm (br s, 2H). The ratio of monomer incorporation into **2f** was determined by means of ^{1}H NMR spectroscopy to be 4.2:2.0:1.0 (styrene/**3f**/**5**). This ratio corresponds to a DMAP loading level of 0.9 mmol g^{-1} for **2f**.

General procedure for intramolecular MBH reactions catalyzed by reagents 1a–e: Compounds **1a–e** (0.125 mmol) were added to a solution of **6a–f** (0.5 mmol) in DCE (3 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature until TLC indicated that the starting material had almost completely disappeared in one reaction by using **1a–e**. The reaction mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by means of flash column chromatography to afford the desired product **7a–f**.

General procedure for intermolecular MBH reactions between aldehydes 8a–h and methyl vinyl ketone (9) catalyzed by reagents 2a–e: Aldehydes **8a–h** (0.5 mmol) and **9** (126 μL, 1.5 mmol) were added to solutions of **2a–e** (0.05 mmol) in THF (2 mL) under an argon atmosphere. The reaction mixture was stirred at 60 °C for 3 d and then concentrated in vacuo. The crude product was purified by means of flash column chromatography to afford the desired product **10a–h**.

General procedure for intermolecular MBH reactions between aldehydes 8f–g and 8i–k and 2-cyclopenten-1-one (11): Compound **11** (42 μL, 0.5 mmol) was added to a solution of aldehydes **8f–g** or **8i–k** (0.5 mmol) and **2a–e** (0.5 mmol) in CH_2Cl_2 (0.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 d and then concentrated in vacuo. The crude product was purified by means of flash column chromatography to afford the desired product **12a–e**.

General procedure for intermolecular MBH reactions between aldehydes 8f–g and 8i–k and 2-cyclohexen-1-one (13): 2-Cyclohexen-1-one (**13**) (48 μL, 0.5 mmol) was added to a solution of aldehydes **8f–g** or **8i–k** (0.5 mmol) and **2a–e** (0.5 mmol) in CH_2Cl_2 (0.5 mL) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 5 d and then concentrated in vacuo. The crude product was purified by means of flash column chromatography to afford the desired product **14a–e**.

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