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Bifunctional (Thio)urea–Phosphine Organocatalysts Derived from D-Glucose and α-Amino Acids and Their Application to the Enantioselective Morita–Baylis–Hillman Reaction

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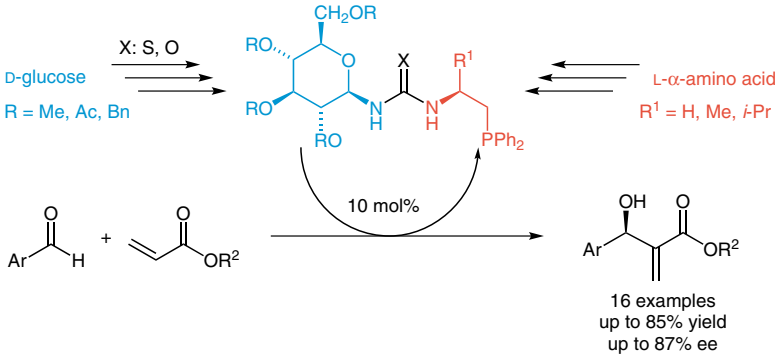

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Abstract Novel (thio)urea–tertiary phosphines were developed for use as bifunctional organocatalysts readily available from naturally occurring molecules: saccharides and amino acids. The efficiency of the organocatalysts was demonstrated in the asymmetric Morita–Baylis–Hillman (MBH) reaction of aromatic aldehydes with acrylates. The MBH products were obtained in good yields (up to 85%) and with high enantioselectivities (up to 87% ee).

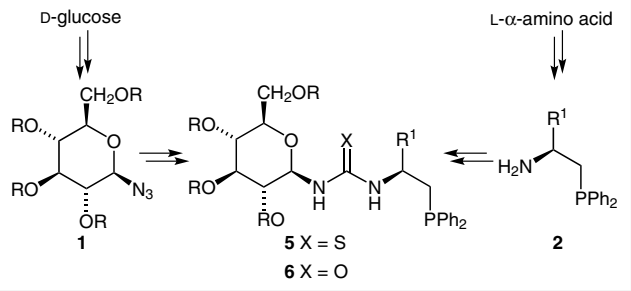
Key words organocatalysis, Morita–Baylis–Hillman reactions, phosphines, amino acids, asymmetric catalysis

Jan Veselý obtained his Ph.D. in 2005 under the supervision of Prof. Tomáš Trnka (Charles University in Prague) and Dr. Miroslav Ledvina (Institute of Organic Chemistry and Biochemistry IOCB, AS CR), working on the synthesis of linear and cyclic oligosaccharides. Then, he worked one year as a postdoc in the group of Stefan Oscarson, and one and a half years in the group of Armando Córdova (both at Arrhenius Laboratories, Stockholm University). After his return, he started an independent research career at the Charles University in Prague, where he currently holds the position of an associate professor. His research interests are the stereoselective preparation of sugar-derived building blocks, as well as the development of new asymmetric methodologies based on organocatalysis and their application in total synthesis.

Asymmetric catalysis with small organic molecules represents one of the fundamental pillars in asymmetric synthetic processes.[1,2] This rapidly evolving area has already shown a high synthetic potential in many chemical reactions, including enantioselective formation of single or multiple carbon–carbon or carbon–heteroatom bonds in single-step or cascade processes.[2a,3] Among the various concepts commonly used in asymmetric organocatalysis, hydrogen-bonding catalysis has emerged as a powerful approach. In particular, (thio)ureas,[4] squaramides,[5] and guanidinium ions[6] have proved to be highly promising organocatalysts. Since the pioneering work of Takemoto and co-workers,[7] which was inspired by the natural oxyanion hole of enzymes, a combination of a hydrogen-bond donor (thio)urea moiety and an amine as a Lewis base in a single chiral scaffold has become a popular motif in the development of organocatalysts. In contrast to well-developed bifunctional (thio)ureas derived from cinchona alkaloids, steroids, or peptides, little attention has been paid to the synthesis of bifunctional (thio)ureas derived from saccharides.[8] In 2007, Kunz and co-workers (inspired by Jacobsen's catalysts[9]) reported efficient bifunctional urea–aldimine organocatalysts derived from D-glucosamine for enantioselective Strecker reactions.[10] Other examples of bifunctional sugar-derived organocatalysts (thiourea–primary or tertiary amine) were reported by Ma and co-workers; in these organocatalysts, the carbohydrate unit serves as a bulky electron-withdrawing group to increase the acidity of the thiourea.[11] Later, Benaglia, Lay, and co-workers investigated a new family of (thio)urea–amine organocatalysts for the addition of acetylacetone to nitrostyrene.[12] Several other examples of bifunctional sugar-derived organocatalysts (thiourea–amine type) have been reported, and their catalytic activities have been investigated.[11,13] Compared with the extensive development carried out on bifunctional thiourea–amine organocatalysts, the development of

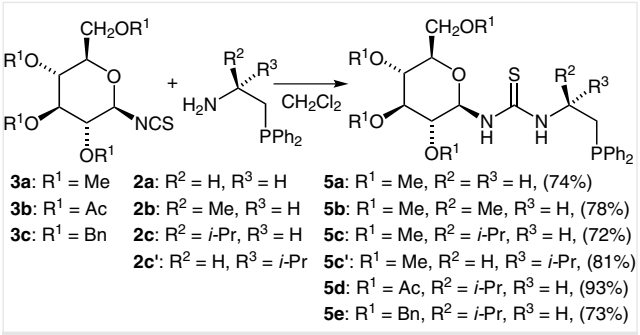
thiourea–trivalent phosphine organocatalysts remains a less-explored area, although phosphines belong to an important class of nucleophilic catalysts.[14] Recently, several bifunctional thiourea–phosphine organocatalysts derived from natural amino acids,[15] or synthetic compounds containing binaphthyl or cyclohexane motifs[16,17] have been developed and applied in a variety of enantioselective organic reactions. However, only one type of bifunctional thiourea–phosphine organocatalyst derived from saccharides and a cyclohexane skeleton has been reported.[18]

There are no previous reports of bifunctional thiourea–phosphine organocatalysts consisting of a saccharide unit and an amino acid derived chiral phosphine, although it is apparent that, like amino acids, carbohydrates are readily available chiral scaffolds. In view of these facts, we designed new types of bifunctional urea– and thiourea–phosphine organocatalysts **6** and **5** (Scheme 1), and we explored their efficiency in an enantioselective Morita–Baylis–Hillman (MBH) reaction.[19]



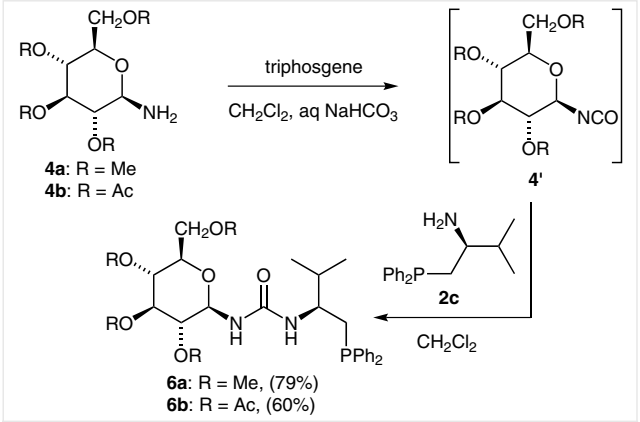
Scheme 1 Novel (thio)urea–phosphine organocatalysts **5** and **6**

In designing the bifunctional organocatalysts **5** and **6**, we chose D-glucose and a set of α-amino acids (glycine, L-alanine, and L-valine) as readily available starting materials (Scheme 1). As in previous reports,[11] the chosen glucopyranosyl unit serves as a bulky electron-withdrawing group, affording increased (thio)urea acidity, and the chosen phosphines display a remarkable combination of strong nucleophilicity and stability to air. The phosphines **2**, which display various steric effects from the neighboring alkyl moiety, were obtained from the corresponding α-amino acids by using *N*-*tert*-butoxycarbonyl or *N*-tosyl protective groups.[20,21] Isothiocyanates **3**, suitable for the construction of bifunctional thiourea–phosphine catalysts **5**, were prepared from D-glucose by using a reported procedure.[22] The thiourea–phosphine organocatalysts **5** were prepared by simple condensation of the key building blocks **3** and **2**, as shown in Scheme 2.[23]



Scheme 2 Preparation of thiourea–phosphine organocatalysts **5**

On the other hand, the synthesis of the urea–phosphine catalysts **6** did not required isolation of the intermediate isocyanates **4′**, and was therefore accomplished in two steps (formylation/condensation) from the corresponding glycosylamines **4** (Scheme 3).[24] Glycosylamines **4** were prepared by catalytic hydrogenation[22f] of the corresponding glycosyl azides **1**.[22c,d] All the prepared bifunctional catalysts were obtained in good to high yields (72–93%), and they exhibit good air and bench stability under standard conditions.



Scheme 3 Preparation of urea–phosphine organocatalysts **6**

The catalytic activity of the prepared organocatalysts **5** and **6** was initially evaluated in the MBH reaction of the model substrates 4-nitrobenzaldehyde (**10a**) and methyl acrylate (**11a**) in tetrahydrofuran at 25 °C. At the outset, we decided to compare the catalytic efficiency of **5** and **6** with that of other previously reported organocatalysts **7**–**9** (Figure 1).[7b,17,25]

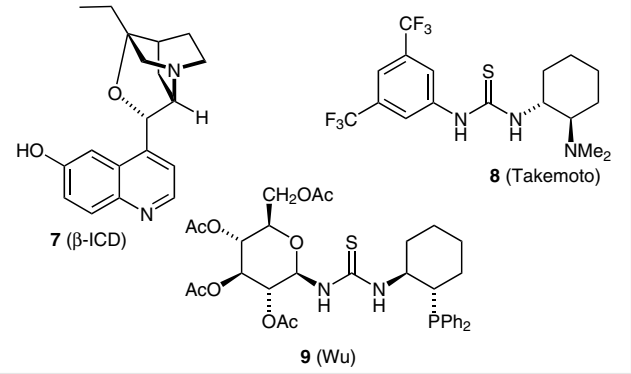
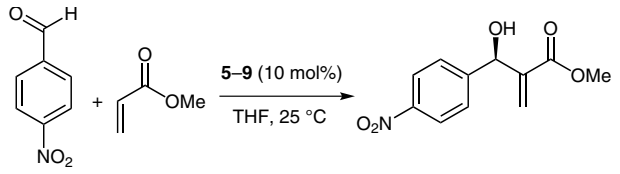


Figure 1 Other organocatalysts used in the MBH reaction

The thiourea catalysts **5** were more reactive than the urea catalysts **6** and they afforded product **12a** with greater enantioselectivity (Table 1, entries 1–7). Interestingly, the best enantiocontrol of the MBH reaction was observed with our thiourea–phosphine catalyst **5c**. The asymmetric reaction between 4-nitrobenzaldehyde (**10a**) and methyl acrylate (**11a**) in tetrahydrofuran catalyzed by **5c** afforded the corresponding allylic alcohol **12a** in 68% yield and 82% ee (entry 3).

Table 1 Screening of Catalysts for the MBH Reaction[a]



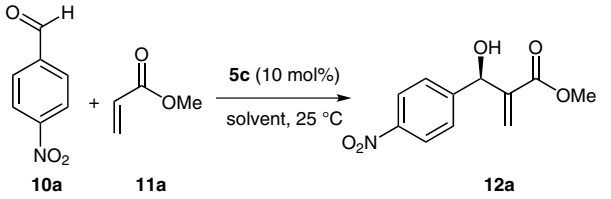
Entry	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5a**	24	83	12
2	**5b**	24	83	74
3	**5c**	24	68	82
4	**5d**	24	22	81
5	**5e**	24	65	80
6	**6a**	24	25	45
7	**6b**	24	12	5
8	**7**	72	13	6
9	**8**	24	0	–
10	**9**	24	80	80

[a] Reaction conditions: **5**–**9** (10 mol%), **10a** (0.1 mmol), **11a** (0.5 mmol), THF (1 mL), 25 °C.
[b] Isolated yield.
[c] Determined by HPLC using a chiral IC column.

When the diphenylphosphine moiety of the catalyst was modified, catalysts **5a** and **5b** showed a higher reactivity but a lower enantioselectivity (Table 1, entries 1 and 2). Interestingly, catalyst **5d** with an electron-withdrawing *O*-protecting group on the saccharide unit showed a lower reactivity, probably due to interference of the acetoxy group and the acidic thiourea group (entry 4). On the other hand, the presence of a bulkier noninterfering benzyl protecting group on the saccharide unit had only a limited effect on the reactivity of catalyst **5e** (entry 5). Note that changing the *O*-protecting group on the saccharide unit of the catalyst did not affect the stereochemical outcome of the reaction. Catalysts **5a**, **5b**, and **9** showed similar efficiencies after 24 hours, including full conversion of the starting materials (entries 1, 2, and 10). In addition, Wu's catalyst (**9**) gave **12a** with high enantioselectivity. Nevertheless, further modification of the phosphine scaffold of **9** to tune the stereocontrol of the reaction is more complicated than in the case of our catalysts **5**, in which a variety of natural or synthetic amino acid scaffolds can be used.

Encouraged with these results, we examined the effect of various solvents on the reaction catalyzed by **5c** (Table 2).[26] Screening of the reaction solvents revealed that the MBH reaction proceeded well in various ethers (Table 2, entries 2–4), and the best results with respect to efficiency and enantioselectivity were obtained in *tert*-butyl methyl ether (entry 2). In polar aprotic solvents, the model reaction gave the allylic alcohol **12a** in high yields but with lower enantiocontrol (entries 7 and 8). In protic solvents, low conversion and low yield of **12a**, and no enantiocontrol, were observed (entry 10).

Table 2 A Survey of Solvents for the MBH Reaction of 4-Nitrobenzaldehyde (**10a**) with Methyl Acrylate (**11a**)[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	toluene	45	82
2	TBME	78	86
3	*i*-Pr_2O	49	79
4	THF	68	82
5	CH_2Cl_2	52	70
6	$CHCl_3$	59	75
7	DMF	81	76
8	DMSO	86	72
9	MeCN	68	61
10	MeOH	22	1

[a] Reaction conditions: organocatalyst **5c** (10 mol%), **10a** (0.1 mmol), **11a** (0.5 mmol), solvent (1 mL), 25 °C, 24 h.
[b] Isolated yield.
[c] Determined by HPLC using a chiral IC column.

Further optimization studies showed that the temperature, the catalyst loading, and the **11**/**10** ratio had little effect on the stereocontrol of the reaction, whereas the yield of the reaction varied significantly with the temperature and catalyst loading (Supporting Information, Table SI1, entries 1–6). On the basis of these results, we found that the optimal conditions for the MBH reaction were room temperature, 10 mol% of catalyst **5c**, and a 5:1 ratio of **11** and **10** in *tert*-butyl methyl ether (Table 2, entry 2).

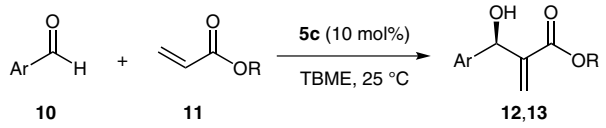
Having established the optimal reaction conditions, we examined the scope of the MBH reaction by employing a variety of aldehydes with various steric and electronic properties. As shown in Table 3, the reactions with aromatic aldehydes **10** gave the corresponding alcohols **12** in moderate to high yields and with good enantioselectivities. The electronic properties and location of the substituents on the aromatic moiety had obvious effects on the rate, efficiency, and selectivity of the MBH reaction. Substrates with electron-withdrawing groups, such as nitro, cyano, or trifluoromethyl groups, gave the corresponding alcohols **12a–e** in good yields and with high enantioselectivities (Table 3, entries 1–5). However, halogenated substrates (F, Cl, Br) reacted significantly more slowly, giving lower yields of allylic alcohols **12g–i** with moderate enantiomeric excesses (entries 7–9). In addition, aromatic aldehydes bearing heterocyclic rings were also found to be suitable substrates (entries 11 and 12). When aliphatic aldehydes were employed, the corresponding MBH alcohols were not obtained, even after a prolonged reaction time, and decomposition of the starting material was observed instead.

We also examined the MBH reaction of various acrylates **11**, catalyzed by **5c** (Table 3, entries 13–16). The alkyl group of the ester moiety had a significant effect on the reaction rate, but only a limited effect on the enantioselectivity of the reaction. With bulkier ester moieties, such as *tert*-butyl, the reaction rate decreased. The alcohol **13d** was obtained after a prolonged reaction time (2 days) in good yield (76%) and with high enantioselectivity (85% ee; entry 16).

To confirm the influence of the aminophosphine segment of the catalyst in controlling the enantioselectivity and efficiency of the reaction, we prepared catalyst **5c′**, derived from D-valine and D-glucose. The asymmetric reaction between 4-nitrobenzaldehyde (**10a**) and methyl acrylate (**11a**) in *tert*-butyl methyl ether catalyzed by **5c′** gave the corresponding allylic alcohol *ent*-**12a** in 85% yield and with –85% ee (Table 3, entry 17). This observation confirmed the key role of the aminophosphine portion of the catalyst in enantiocontrol of the reaction.

The absolute configuration of the MBH adducts was confirmed by chemical correlation with data reported previously.[25,27] The structure of the organocatalysts **5** and **6** was confirmed by a single-crystal X-ray diffraction analysis of **6a** (Figure 2).

Table 3 Substrate Scope of the MBH Reaction[a]



10 **11** **12,13**

Entry	Ar	R	Time (d)	Product	Yield[b] (%)	ee[c] (%)
1	4-$O_2NC_6H_4$	Me	1	**12a**	76	86
2	2-$O_2NC_6H_4$	Me	2	**12b**	69	62
3	3-$O_2NC_6H_4$	Me	1	**12c**	62	82
4	4-NCC_6H_4	Me	1	**12d**	77	84
5	4-$F_3CC_6H_4$	Me	4	**12e**	70	82
6	Ph	Me	7	**12f**	15	77
7	4-FC_6H_4	Me	4	**12g**	24	59
8	4-ClC_6H_4	Me	4	**12h**	24	69
9	4-BrC_6H_4	Me	4	**12i**	36	71
10	2-naphthyl	Me	4	**12j**	29	67
11	3-pyridyl	Me	4	**12k**	78	73
12	2-furyl	Me	4	**12l**	24	73
13	4-$O_2NC_6H_4$	Et	1	**13a**	70	85
14	4-$O_2NC_6H_4$	Bu	1	**13b**	75	87
15	4-$O_2NC_6H_4$	Bn	1	**13c**	83	80
16	4-$O_2NC_6H_4$	*t*-Bu	2	**13d**	76	85
17[d]	4-$O_2NC_6H_4$	Me	1	*ent*-**12a**	85	–85

[a] Reaction conditions: organocatalyst **5c** (10 mol%), **10** (0.1 mmol), **11** (0.5 mmol), *t*-BuOMe (1 mL), 25 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column.
[d] The reaction was performed with organocatalyst **5c′** (10 mol%).

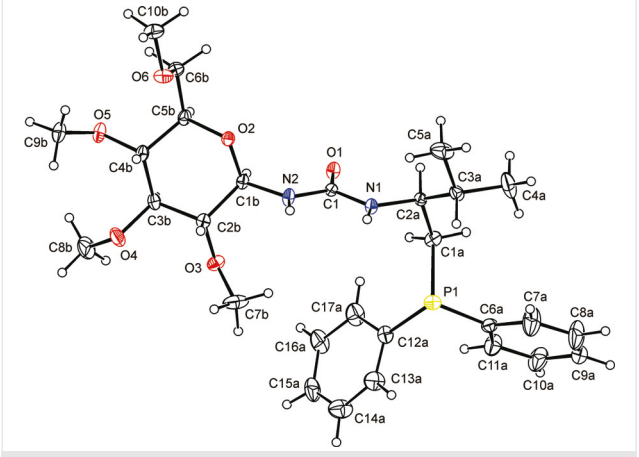


Figure 2 View of molecule **6a** with the atom-numbering scheme; displacement ellipsoids are drawn at a 30% probability level

In summary, we designed and prepared bifunctional (thio)urea–tertiary phosphine organocatalysts, which were readily available from naturally occurring biomolecules such as D-glucose, glycine, L-alanine, and L-valine. The efficiency of our organocatalysts in asymmetric MBH reactions was compared with that of other catalysts used previously. The L-valine-derived bifunctional thiourea–phosphine catalyst was found to be highly efficient in the MBH reaction, giving the MBH adducts with good to high yields (up to 85%) and high enantioselectivities (up to 87% ee).

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Supporting Information

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Primary Data

for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: 10.4125/pd0074th.

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(23) ***N*-[({(1*S*)-1-[(Diphenylphosphino)methyl]-2-methylpropyl}amino)carbonothioyl]-2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosylamine (5c); Typical Procedure for the Synthesis of the Thiourea Catalysts**

Isothiocyanate **3a** (1.16 g, 4.20 mmol) was dissolved in dry CH_2Cl_2 (10 mL) under argon in a dry Schlenk flask. A solution of aminophosphine **2c** (1.14 g, 4.20 mmol) in dry CH_2Cl_2 (10 mL) was slowly added from a syringe, and the mixture was stirred at r.t. for 5 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography [silica gel, hexane–EtOAc (4:1 to 1:1)] to give a colorless viscous oil that was freeze-dried to give a white solid; yield: 1.65 g (72%); $[\alpha]_D^{25}$ –26.1 (c 0.35, $CHCl_3$). IR (KBr): 507, 698, 740, 937, 985, 1030, 1096, 1165, 1186, 1251, 1308, 1347, 1368, 1389, 1431, 1455, 1479, 1541, 1550, 1616, 1739, 1814, 1885, 1960, 2833, 2902, 2929, 2953, 3052, 3072, 3306 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ_H = 7.55–7.49 (m, 2 H), 7.48–7.41 (m, 2 H), 7.37–7.27 (m, 6 H), 7.14 (br s, 1 H), 6.24 (br s, 1 H), 4.46 (br s, 1 H), 4.38 (br s, 1 H), 3.63 (s, 3 H), 3.60 (s, 3 H), 3.58 (dd, *J* = 14.3, 3.7 Hz, 1 H), 3.50 (s, 3 H), 3.48 (dd, *J* = 10.5, 5.5 Hz, 1 H), 3.33 (ddd, *J* = 9.7, 5.2, 1.9 Hz, 1 H), 3.26 (s, 3 H), 3.23–3.11 (m, 3 H), 2.39–2.26 (m, 2 H), 2.16 (dq, *J* = 13.3, 6.8 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ_C = 183.7 (s), 138.5 (d, J = 15.6 Hz), 138.3 (d, *J* = 12.0 Hz), 133.0 (s), 132.9 (s), 128.6 (s), 128.5–128.3 (m), 87.1 (s), 84.1 (s), 81.9 (s), 79.5 (s), 76.4 (s), 70.9 (s), 60.8 (s), 60.7 (s), 60.5 (s), 59.0 (s), 58.0 (d, *J* = 14.0 Hz), 31.4 (d, *J* = 6.5 Hz), 31.2 (d, *J* = 13.6 Hz), 18.6 (s), 17.5 (s). $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ_P –24.4. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}N_2O_5PS$: 549.2546; found: 549.2546.

(24) ***N*-[({(1*S*)-1-[(Diphenylphosphino)methyl]-2-methylpropyl}amino)carbonyl]-2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosylamine (6a); Typical Procedure for the Synthesis of the Urea Catalysts**

Amine **4a** (100.0 mg, 0.43 mmol) and triphosgene (126.2 mg, 0.43 mmol) were added to a mixture of CH_2Cl_2 (3 mL) and sat. aq $NaHCO_3$ (1 mL), and the mixture was stirred at r.t. for 2 h. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was dissolved in CH_2Cl_2 (1 mL). A solution of aminophosphine **2c** (86.8 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) was added dropwise, and the mixture was stirred at r.t. for 18 h. The resulting mixture was concentrated, and the residue was purified by flash column chromatography [silica gel, hexane–EtOAc (1:1)]. The product was crystallized ($CHCl_3$) to give a white glacial solid; yield: 124.0 mg (79%); mp 137–138 °C; $[\alpha]_D^{25}$ +22.6 (c 0.27, $CHCl_3$). IR (KBr, acetone): 510, 701, 740, 934, 952, 988, 1027, 1069, 1099, 1144, 1165, 1186, 1242, 1263, 1308, 1368, 1389, 1416, 1437, 1464, 1482, 1565, 1640, 1811, 1888, 1957, 2830, 2893, 2905, 2932, 2956, 3046, 3072, 3309 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ_H = 7.47 (tt, *J* = 5.1, 2.0 Hz, 2 H), 7.41 (tt, *J* = 6.0, 2.3 Hz, 2 H), 7.36–7.27 (m, 6 H), 4.98 (d, *J* = 6.9 Hz, 1 H), 4.82 (d, *J* = 7.0 Hz, 1 H), 4.61 (t, *J* = 8.0 Hz, 1 H), 3.75 (br s, 1 H), 3.64 (s, 3 H), 3.60 (dd, *J* = 10.4, 2.0 Hz, 1 H), 3.54 (s, 3 H), 3.53–3.50 (m, 1 H), 3.52 (s, 3 H), 3.31 (s, 3 H), 3.24 (t, *J* = 8.9 Hz, 1 H), 3.21–3.15 (m, 1 H), 2.98 (t, *J* = 8.9 Hz, 1 H), 2.23 (d, *J* = 7.2 Hz, 2 H), 2.02–1.94 (m, 1 H), 0.85 (d, *J* = 1.1 Hz, 3 H), 0.84 (d, *J* = 1.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ_C = 157.0 (s), 138.7 (d, *J* = 12.5 Hz), 132.9 (d, *J* = 19.3 Hz), 132.8 (d, *J* = 19.1 Hz), 128.7–128.4 (m), 87.1 (s), 82.7 (s), 82.0 (s), 79.4 (s), 75.8 (s), 70.9 (s), 60.7 (s), 60.4 (s), 60.2 (s), 59.1 (s), 52.9 (d, J = 14.2 Hz), 32.2 (s), 32.05 (d, *J* = 7.8 Hz), 18.9 (s), 17.3 (s). $^{31}P\{^1H\}$ NMR (121 MHz, $CDCl_3$): δ_P = –23.7. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{42}N_2O_6P$: 533.2775; found: 533.2776.

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(26) **Methyl 2-[(*R*)-Hydroxy(4-nitrophenyl)methyl]acrylate (12a); Typical Procedure for the Asymmetric MBH Reaction**

Acrylate **11a** (43.0 mg, 0.50 mmol) was added to a solution of organocatalyst **5c** (5.5 mg, 0.01 mmol) in *t*-BuOMe (1 mL) at r.t., and the solution was stirred for 15 min. Aldehyde **10a** (15.1 mg, 0.10 mmol) was added, and mixture was stirred at 25 °C for 1 d (Table 3). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography [silica gel, hexane–EtOAc (4:1)] to give a yellow solid; yield: 18.1 mg (76%); $[\alpha]_D^{25}$ –57.3 (*c* 0.52, MeOH, 86% ee). ^1H NMR

(600 MHz, $CDCl_3$): δ_H = 8.22 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 6.41 (s, 1 H), 5.89 (s, 1 H), 5.64 (d, *J* = 6.1 Hz, 1 H), 3.76 (s, 3 H), 3.34 (d, *J* = 6.3 Hz, 1 H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ_C = 166.4, 148.5, 147.5, 140.9, 127.3, 123.6, 72.8, 52.2. MS (EI-TOF): *m*/*z* = 237.1 $[M]^{+\bullet}$. HPLC (ChiralPak IC column, heptane–*i*-PrOH (80:20), flow rate: 1.0 mL/min, λ = 220 nm): t_R = 6.69 min (minor), 8.04 min (major).

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