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Highly active and enantioselective copper-catalyzed conjugate addition of diethylzinc to cyclohexenone using sugar derivative diphosphites

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Abstract

High enantioselectivity combined with unprecedented high catalytic activity (81% ee and TOF $\approx$1200 h^{-1}) are achieved in the copper-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone with new C_1-chiral diphosphites derived from the readily available D-(+)-xylose.

1. Introduction

Nowadays, catalytic asymmetric synthesis using organometallic reagents is one of the most active areas of research in organic synthesis.[1] The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates,[2] and in particular, the addition of organocuprates to enones, is an attractive method to form a C–C bond and simultaneously introduce a new stereogenic center.[3] A number of successful methods for enantioselective 1,4-addition based on chiral auxiliaries or stoichiometric organometallic reagents have been widely studied, but few highly enantioselective catalytic processes have been reported.[3c] Copper (I) catalysts have given better results than their Ni^{II} and Co^{II} counterparts, which usually provide only moderate enantioselectivities for acyclic substrates.[4] Moreover, the use of dialkylzinc seems to be a better approach[5] than the Grignard reagents, which usually need the presence of additives such as HMPA or DBU to achieve good enantioselectivies.[6] Recently, excellent enantioselectivies have been obtained using several chiral phosphorus amidites,[5d–f] amido-phosphine,[5g] phosphite-oxazolines[5b] and phosphite[5c,5h–j] ligands.

Despite the high enantioselectivities obtained with different catalytic systems,[5] further investigations are required in order to enhance the activity for practical purposes. In this context, the

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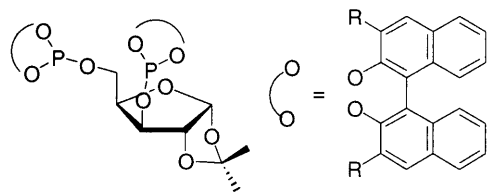
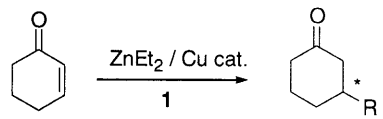
design and synthesis of new readily available ligands is still a highly significant research subject in asymmetric catalysis. Despite the accessibility and low cost of carbohydrate synthons, the full potential of the carbohydrate chiral pool for providing chiral ligands has hardly been exploited.[7] Following our promising results with diphosphite[8] and thioether-hydroxyl[9] ligands with a xylofuranose backbone and the success of various sugar ligands in catalysis,[10] we designed a new set of diphosphite ligands derived from readily available D-(+)-xylose. Here we also report their use in the Michael addition of diethylzinc to 2-cyclohexenone, widely used as a substrate model (Scheme 1).



1a (S^{ax}), R = H

b (R^{ax}), R = H

c (R^{ax}), R = $SiMe_3$



2 (*R*)-**3**/(*S*)-**3**

Scheme 1.

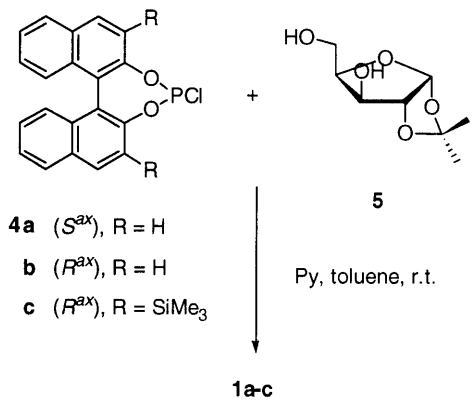
2. Results and discussion

2.1. Ligand synthesis

Bulky diphosphites **1a–c** were easily prepared by reacting two equiv. of the corresponding phosphorochloridites **4a–c** with 1,2-*O*-isopropylidene-α-xylofuranose **5** (Scheme 2). Diol **5** was easily synthesized from D-(+)-xylose on a large scale by previously described highly effective methods.[11] Phosphorochloridites **4a–c** were prepared from the appropriate diols and PCl_3 in the presence of pyridine using standard procedures.[12] Diphosphites **1a–c** were stable during purification on neutral silica gel under argon and were isolated in good yields as white solids stable in air. The VT-^{31}P NMR spectra of the ligands exhibit two sharp singlets which indicates that pure diastereoisomers have been obtained.

2.2. Conjugate addition of 2-cyclohexenone

Ligands **1a–c** were used in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone. The catalytic system was generated in situ by adding one equiv. of the corresponding diphosphite to a dichloromethane solution of $Cu(OTf)_2$. The effect of different reaction



Scheme 2.

parameters (such as temperature, solvent, catalyst concentration, etc.) were investigated and the results are summarized in Table 1. In general, unprecedented turnover frequencies and almost total regioselectivities were obtained. No 1,2-addition product was detected by GC analysis.

Table 1
Catalytic conjugate addition of $ZnEt_2$ to **2**[a]

Entry	Ligand	Solvent	T (°C)	TOF[b]	% Conv.[c]	% **3**[d]	% Ee[e]
1	1a	CH_2Cl_2	0	1200	100	99	43 (S)
2	1a	Toluene	0	1200	100	93	45 (S)
3	1a	THF	0	1116	93	87	41 (S)
4	1a	CH_2Cl_2	25	1200	100	99	38 (S)
5	1a	CH_2Cl_2	−20	744	100[f]	91	32 (S)
6	1a	CH_2Cl_2	−40	456	89[f]	86	19 (S)
7	1b	CH_2Cl_2	0	780	100[f]	98	35 (R)
8	1c	CH_2Cl_2	0	1200	100	99	81 (R)
9	1c	CH_2Cl_2	25	1200	100	99	78 (R)
10	1c	CH_2Cl_2	−20	786	100[f]	89	77 (R)
11[g]	1c	CH_2Cl_2	0	1354	99[f]	97	79 (R)
12[h]	1c	CH_2Cl_2	0	300	100	98	80 (R)
13[i]	6	Toluene	0	33	100	–[j]	83.2 (S)

[a] Reaction conditions: $Cu(OTf)_2$ (0.025 mmol), ligand (0.025 mmol), $ZnEt_2$ (3.5 mmol), **2** (2.5 mmol), solvent (6 ml).

[b] TOF in mol **2** × mol $Cu^{-1} \times h^{-1}$ determined after 5 minutes reaction time by GC.

[c] % Conversion determined by GC using undecane as internal standard after 5 minutes.

[d] Regioselectivity in **3** determined by GC using undecane as internal standard.

[e] Enantiomeric excess measured by GC using Lipodex A column.

[f] Conversion measured after 15 minutes.

[g] $Cu(OTf)_2$ (0.0125 mmol), [**2**]/[Cu] = 200.

[h] $Cu(OTf)_2$ (0.05 mmol), **2** (1.25 mmol), [**2**]/[Cu] = 25.

[i] Data from Ref. 5h, TOF and conversion measured at 3 hours.

[j] Not reported.

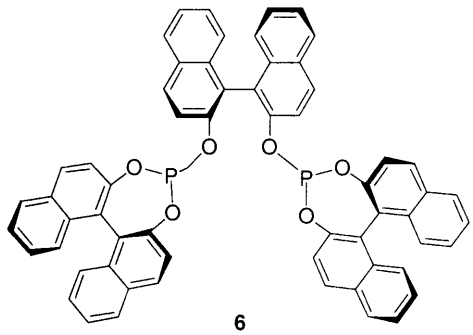
The addition of diethylzinc proceeded with similar enantioselectivities in solvents with both low and high polarities (entries 1–3). However, regioselectivities in favor of the 1,4-product were lower when toluene and specially THF were used.

The effect of the temperature was also studied. The best enantioselectivity (up to 81%, entry 8) combined with excellent regioselectivity (99%) and activity (TOF $\approx$1200 h^{-1}) were found at 0°C. Lowering the temperature had a negative effect on conversion, regio- and enantioselectivity. The enantiomeric excess decreased considerably when the reaction temperature was lowered for ligands **1a** and **1b**, but only slightly for ligand **1c**. These results are in line with those reported for related Cu–diphosphite catalytic systems containing bisphenol moieties.[8]

Varying the catalyst concentration had an influence on activity, but not on 1,4-regio- and enantioselectivity (entries 8, 11 and 12).

The results obtained with ligand **1a** and **1b** show that the different configuration in the binaphthyl moieties had an influence on both conversion and enantioselectivity. Thus, the (R^{ax})-**1b** ligand gave the (*R*)-product with 65% conversion and 35% ee after 5 minutes, whereas the diastereoisomeric (S^{ax})-**1a** ligand gave the opposite enantiomer with 100% conversion and 43% ee. If the results with **1b** and **1c** are compared it can also be concluded that the presence of $SiMe_3$ in the *ortho* positions had a positive influence on both conversion and enantioselectivity.

It should be noted that under similar reaction conditions, ligand **1c** showed much higher turnover frequencies (1200 vs 33 h^{-1}) and similar enantioselectivity (81% vs 83.2%) than those reported for the most successfully tested diphosphite ligand **6**.[5h]



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In conclusion, we have presented the synthesis of new diphosphite ligands derived from readily available D-(+)-xylose. The combination of unprecedented catalytic performances and high enantioselectivities in simple unoptimized reactions makes these kinds of ligands very attractive for practical purposes in the enantioselective 1,4-addition of cyclic enones. The scope and limitations of these ligands is now being evaluated.

3. Experimental

3.1. General comments

All experiments were carried out under argon. All solvents were dried using standard published methods and distilled before use. Phosphorochloridites **4a**–**c**[12] and 1,2-*O*-isopropylidene-α-D-xylofuranose **5**[11] were prepared by previously reported methods. Elemental analyses

were performed on a Carlo Erba EA-1108 instrument. ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ (^{1}H and ^{13}C) as internal standard or H_3PO_4 (^{31}P) as external standard. All assignments in NMR spectra were determined by COSY and HETCOR spectra. Gas chromatographic analyses were run on a Hewlett–Packard HP 5890A instrument equipped with a Hewlett–Packard HP 3396 series II integrator.

3.2. 3,5-Bis[((S)-1,1′-binaphthyl-2,2′-diyl)phosphite]-1,2-O-isopropylidene-D-(+)-xylofuranose ***1a***

In situ formed **4a** (5 mmol) was dissolved in toluene (15 ml) to which pyridine (1 ml, 12.5 mmol) was added. The solution of azeotropically dried **5** (0.38 g, 2 mmol) in pyridine (1 ml, 12.5 mmol) and toluene (15 ml) was added in 30 minutes to the solution of **4a** at rt. The reaction mixture was stirred overnight at rt and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam which was purified by flash chromatography under argon (eluent: toluene, Rf. 0.18). Yield: 0.98 g (54%). Elemental analysis: found (%): C, 70.22; H, 4.56; calculated (%) for $C_{48}H_{36}O_9P_2$: C, 70.42; H, 4.43. ^{31}P NMR ($CDCl_3$), δ(ppm): 145.9 (s), 114.6 (s). ^{1}H NMR ($CDCl_3$), δ(ppm): 1.12 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.42 (m, 2H, H-5′, H-5), 3.52 (m, 1H, H-4), 3.61 (m, 1H, H-3), 3.78 (d, 1H, H-2, $^{3}J_{2-1}=3.6$ Hz), 5.73 (d, 1H, H-1, $^{3}J_{1-2}=3.6$ Hz), 6.39 (d, 1H, $J=8.5$ Hz, arom), 7.1–7.4 (m, 9H, arom), 7.5–7.7 (m, 6H, arom), 7.8–8.1 (m, 8H, arom). ^{13}C NMR ($CDCl_3$), δ(ppm): 25.9 (CH_3), 26.4 (CH_3), 57.0 (d, C-5, $J_{P-C}=1.9$ Hz), 70.3 (d, C-3, $J_{P-C}=2.3$ Hz), 73.6 (d, C-4, $J_{P-C}=6.3$ Hz), 84.1 (d, C-2, $J_{P-C}=2.9$ Hz), 104.5 (C-1), 111.6 (CMe_2), 118.9, 119.1, 120.7, 120.8, 121.7, 124.8, 125.1, 125.2, 125.8, 125.9, 126.1, 126.3, 126.9, 127.0, 127.1, 128.1, 128.2, 128.3, 129.5, 130.1, 130.3 (CH=).

3.3. 3,5-Bis[((R)-1,1′-binaphthyl-2,2′-diyl)phosphite]-1,2-O-isopropylidene-D-(+)-xylofuranose ***1b***

Treatment of in situ formed **4b** (2.2 mmol) and **5** (1 mmol, 0.19 g) as described for **1a** afforded diphosphite **1b**, which was purified by flash column chromatography (eluent: toluene, Rf. 0.20). Yield: 0.67 g (41%) of a white powder. Elemental analysis: found (%): C, 70.87; H, 4.54; calculated (%) for $C_{48}H_{36}O_9P_2$: C, 70.42; H, 4.43. ^{31}P NMR ($CDCl_3$), δ(ppm): 146.8 (s), 115.0 (s). ^{1}H NMR ($CDCl_3$), δ(ppm): 1.21 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.12 (m, 1H, H-5′), 3.47 (m, 3H, H-5, H-4, H-3), 4.03 (d, 1H, H-2, $^{3}J_{2-1}=3.3$ Hz), 5.74 (d, 1H, H-1, $^{3}J_{1-2}=3.3$ Hz), 6.22 (d, 1H, $J=8.7$ Hz, arom), 7.1–7.4 (m, 9H, arom), 7.5–7.7 (m, 6H, arom), 7.8–8.1 (m, 8H, arom). ^{13}C NMR ($CDCl_3$), δ(ppm): 26.0 (CH_3), 26.5 (CH_3), 56.8 (d, C-5, $J_{P-C}=2.5$ Hz), 70.2 (d, C-3, $J_{P-C}=2.3$ Hz), 73.6 (d, C-4, $J_{P-C}=5.7$ Hz), 84.1 (d, C-2, $J_{P-C}=2.9$ Hz), 104.5 (C-1), 111.7 (CMe_2), 117.8, 118.8, 119.0, 120.3, 120.4, 124.1, 124.2, 124.8, 125.0, 125.2, 125.8, 126.1, 126.2, 126.4, 126.8, 127.0, 127.1, 127.6, 128.2, 128.4, 128.5, 129.7, 130.2, 130.4, (CH=).

3.4. 3,5-Bis[((R)-3,3′-bis(trimethylsilyl)-1,1′-binaphthyl-2,2′-diyl)phosphite]-1,2-O-isopropylidene-D-(+)-xylofuranose ***1c***

Treatment of in situ formed **4c** (2.2 mmol) and **5** (1 mmol, 0.19 g) as described for **1a** afforded diphosphite **1c**, which was purified by flash column chromatography (eluent: toluene:NEt_3 (100:1), Rf. 0.85). Yield: 525 mg (49%) of a white powder. Elemental analysis: found (%): C, 64.89; H, 6.33; calculated (%) for $C_{60}H_{68}O_9P_2Si_4$: C, 65.08; H, 6.19. ^{31}P NMR ($CDCl_3$), δ(ppm): 136.6 (s), 144.4 (s). ^{1}H NMR ($CDCl_3$), δ(ppm): 0.15 (s, 9H, CH_3Si), 0.35 (s, 9H, CH_3Si), 0.37

(s, 9H, CH_3Si), 0.46 (s, 9H, CH_3Si), 0.98 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 3.47 (m, 1H, H-5′), 3.77 (ddd, 1H, H-5, $^2J'_{5-5}=10.4$ Hz, $^3J_{5-4}=5.8$ Hz, $^3J_{5-P}=9.0$ Hz), 4.16 (m, 1H, H-4), 4.44 (dd, 1H, H-3, $^3J_{3-4}=3.0$ Hz, $^3J_{3-P}=9.6$ Hz), 4.54 (d, 1H, H-2, $^3J_{2-1}=3.6$ Hz), 5.76 (d, 1H, H-1, $^3J_{1-2}=3.6$ Hz), 7.0–7.5 (m, 10H, arom), 7.8–8.1 (m, 10H, arom). ^{13}C NMR ($CDCl_3$), δ(ppm): −0.6 (CH_3Si), −0.1 (CH_3Si), 0.1 (CH_3Si), 0.3 (CH_3Si), 25.7 (CH_3), 26.3 (CH_3), 61.5 (d, C-5, $J_{P-C}=2.4$ Hz), 78.3 (d, C-3, $J_{P-C}=4.1$ Hz), 78.9 (t, C-4, $J_{P-C}=3.0$ Hz), 84.1 (d, C-2, $J_{P-C}=4.0$ Hz), 104.6 (C-1), 111.8 (CMe_2), 124.7, 124.9, 126.4, 126.6, 126.8, 127.0, 127.7, 128.2, 128.4, 136.9, 137.2 (CH=).

3.5. Typical procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexenone

In a typical procedure a solution of $Cu(OTf)_2$ (9 mg, 0.025 mmol) and diphosphite (0.025 mmol) in dichloromethane (3 ml) was stirred for 30 minutes at rt. After cooling to 273 K, diethylzinc (1 M sol. in hexanes, 3.5 ml, 3.5 mmol) was added. A solution of 2-cyclohexenone (0.24 ml, 2.5 mmol) and undecane as GC internal standard (0.25 ml) in dichloromethane (3 ml) was then added. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through flash silica. The conversion and enantiomeric excesses were obtained by GC using a Lipodex-A column.[13]

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