Bicyclic O,P Ligands for Catalytic Asymmetric 1,4-Addition to α,β-Unsaturated Ketones

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Abstract: A new class of bicyclic O,P ligands has been prepared and evaluated in the 1,4-addition to α,β-unsaturated ketones. The best results with the bicyclic ligand were obtained using a lower catalyst loading than what has been reported with similar ligands when adding a Grignard reagent to 2-cyclohexenone.

Keywords: asymmetric catalysis; cuprates; heterocycles; Michael addition; O,P ligands

Introduction

Enantioselective conjugate addition of carbon nucleophiles to α,β-unsaturated ketones has been a challenge to organic chemists for a long time. One way to achieve this is to use a stoichiometric amount of copper together with a chiral ligand, which results in a stereoselective addition (Figure 1).

Much attention has been focused on the possibility to obtain a catalytic system for the reaction.[1–10] In previous work by Tomioka,[11] promising results have been obtained using the proline-derived ligand **1**, see Figure 2.

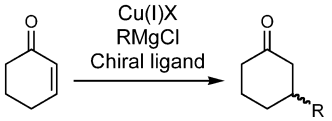
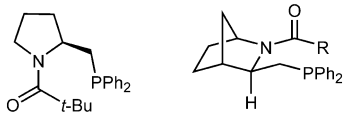


Figure 1. Typical Michael addition.



1 **2a**: R = *t*-Bu **2b**: R = Me

Figure 2. Pyrrolidine and azanorbornyl derivatives used as chiral ligands in asymmetric 1,4-addition.

We now report on the synthesis of the new bicyclic ligands **2a** and **b** and their application in the copper-catalysed addition of a Grignard reagent to α,β-unsaturated ketones.

Results and Discussion

Ligands **2a** and **b** are readily available from amino alcohol **3** which, in turn, is conveniently prepared in three steps from (*S*)-(−)-1-phenylethylamine, ethyl glyoxylate and cyclopentadiene by a diastereoselective aza-Diels–Alder reaction.[12] The rigid 2-azanorbornyl derivatives formed therefrom can be formed in both enantiomers and on a large scale[13] and have proven to be very successful as ligands in a number of catalytic asymmetric reactions.[14–18] Boc protection of the amine and tosylation of the alcohol gave **5**. The introduction of the diphenylphosphinoyl group proved to be difficult, since neither the use of $NaPPh_2$, derived from chlorodiphenylphosphine and sodium, nor $LiPPh_2 \cdot BH_3$ resulted in acceptable yields of the desired product. However, reaction of tosylate **5** with $LiPPh_2$, prepared from PPh_3 and lithium metal in THF,[19] gave **6** in 77% isolated yield. *N*-Deprotection and subsequent acylation then afforded ligands **2a** and **b** in high yields, Scheme 1.

The ligands were evaluated in the enantioselective 1,4-addition to **7** as outlined in Table 1.

As can be seen in Table 1 the bicyclic ligand **2a** shows a different reaction behaviour compared with the proline-derived ligand **1**. Using the conditions that have been reported to give the best results with ligand **1** led to almost no product at all when **2a** was used as the chiral ligand. However, it was found that the counter ion of the copper salt had a profound effect on both yield and selectivity of the catalyst. The use of CuCl resulted in 54% yield and 41% ee. The selectivity was further improved when CuBr was used (entry 6), while $CuBr \cdot Me_2S$ resulted in decreased enantioselectivity (25% ee, entry 7) but gave exclusively 1,4 addition.[20] One difference between

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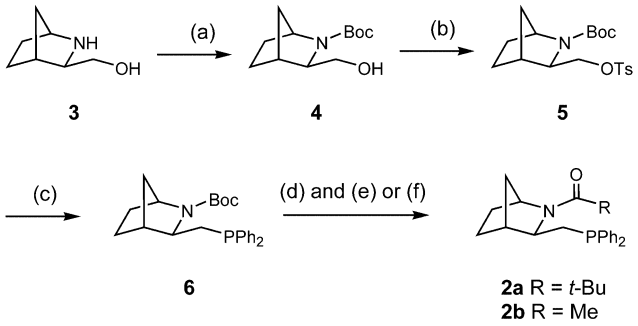

Scheme 1. (a) Et_3N, Boc_2O THF, rt, 88%; (b) TsCl, pyridine, CH_2Cl_2, 0 °C to rt, 97%; (c) $LiPPh_2$, THF 0 °C to rt, 77%; (d) HCl, THF, reflux; (e) Et_3N, *t*-BuCOCl, CH_2Cl_2, 0 °C to rt, > 98% (two steps): (f) Et_3N, AcCl, CH_2Cl_2, 0 °C to rt, 83% (two steps).

the two different catalysts is their behaviour when decreasing the ligand loading. Going down from 34 mol % to 17 mol % of ligand **1** gave both lower yield and ee while ligand **2b** gave higher yield and ee. The reason for this behaviour is not known to us. Best results were obtained with CuI that gave the product in 71% ee and 73% yield (entry 5). It should be noted that these results were obtained using only 4.7 mol % of the chiral ligand. Attempts to further decrease catalyst loading did not give satisfactory results. The use of ligand **2b** resulted in similar enantioselectivities as **2a** but gave a higher degree of 1,2 addition.

Ligands **1** and **2a** were also evaluated in a reaction using chalcone as substrate. However, as can be seen in Table 2, it is evident that these ligands are unsuitable for chalcones as they give a racemic product.

Conclusion

Two new chiral bicyclic O,P ligands have been prepared and evaluated in the enantioselective 1,4-addition to α,β-unsaturated systems. It was found that, at lower catalyst loadings, these new bicyclic ligands performed better than the earlier reported proline-de-

Table 1. Addition of BuMgCl to 2-cyclohexenone promoted by ligands **1, 2a** and **2b**.

Entry	Ligand	Mol % Ligand	Copper(I) Salt	Yield [%][a]	ee [%][b]	Config.[b]	Selectivity 1,4 : 1,2[c]
1	**1**	34	CuI	55[d]	79	S	4.0 : 1
2	**1**	17	CuI	35	45	*S*	4.8 : 1
3	**2**°	34	CuI	8.3	–[e]	–	1.6 : 1
4	**2**°	17	CuI	44	72	*R*	1.9 : 1
5	**2a**	4.7	CuI	73	71	*R*	> 10 : 1
6	**2a**	17	CuBr	28	55	*R*	1.2 : 1
7	**2a**	17	$CuBr \cdot Me_2S$	74	25	*R*	–[f]
8	**2a**	17	CuCl	54	41	*R*	4.9 : 1
9	**1**	17	CuCN	43	12	*S*	2.8 : 1
10	**2a**	34	CuCN	28	50	*R*	1.4 : 1
11	**2a**	17	CuCN	41	59	*R*	2.0 : 1
12	**2a**	17	CuCN[g]	55	56	*R*	2.3 : 1
13	**2a**	9.5	CuCN	26	28	*R*	2.3 : 1
14	**2b**	17	CuCN	25	52	R	0.8 : 1

[a] Isolated yield after flash chromatography (deactivated silica gel, pentane/EtOAc).
[b] Determined by specific optical rotation (see Experimental Section).
[c] Determined by ^{1}H NMR [1,4]/[1,2].
[d] No quantitative separation.
[e] Yield too low to be able to determine ee.
[f] No [1,2] addition could be detected.
[g] 17 mol % TMSCl added before adding Grignard reagent.

Table 2. Addition of BuMgCl to chalcone promoted by ligands **1** or **2a**.

Entry	Ligand	Mol % Ligand	Copper(I) Salt	Yield [%][a]	ee [%][b]	Selectivity[c]
1	**2a**	17	CuCN	12	rac	–
2	**1**	17	CuCN	71	rac	17.6

[a] Isolated yield after flash chromatography (deactivated silica gel, pentane/EtOAc).
[b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H).
[c] Determined by ^{1}H NMR [1,4]/[1,2].

rived ligand **1**. Further studies on this class of ligands are in progress.

Experimental Section

General Remarks

Liquid chromatography was carried out on a chiral column (Daicel ChiralCel OD-H), using a 254 nm UV detector and a flow rate of 0.5 mL/min (*i*-PrOH/hexane: 1/99). Flash chromatography was performed on silica gel (Matrex 60A, 37–70 μm). When mentioned, deactivated silica gel means that it was treated with 5% Et_3N in pentane and the column was eluted with the same solvent mixture until the exiting eluent was basic to pH paper. Analytical TLC was carried out on precoated plates, SIL G-60 UV_{254}, purchased from Macherey-Nagel. Slow addition was made using a syringe pump. Polarimetry was performed on a Perkin Elmer 241 polarimeter. Infrared spectra were obtained from a Perkin-Elmer 1760 FTIR. ^1H and ^{13}C NMR were obtained either on a Varian Gemini 200, a Varian XL 300 or a Varian Unity 400 using the residual peak from $CHCl_3$ δ = 7.26 for ^1H or $CDCl_3$ δ = 77.0 for ^{13}C as reference. Unless otherwise noted, materials were obtained from commercial suppliers and used without any further purification. THF and diethyl ether were distilled from a sodium-benzophenone solution. Dichloromethane was distilled from CaH_2. 2-Cyclohexenone was dried with MS 4 Å, distilled under vacuum and stored over MS 4 Å.

(1*S*,3*R*,4*R*)-3-Hydroxymethyl-2-azabicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (4)

In a 250-mL round-bottomed flask, a solution of Boc_2O (3.5 g, 16.2 mmol) in THF (20 mL) was prepared under argon. To this solution triethylamine (4.0 ml, 28.4 mmol) was added. Then **3**[12] was added dropwise as a solution in THF (20 mL). The reaction mixture was stirred at rt for 5 h. The reaction mixture was then diluted with diethyl ether (10 mL), washed with brine (2 × 10 mL), water (10 mL), dried with $MgSO_4$, filtered and evaporated to give crude **4**. Flash chromatography [silica, pentane/EtOAc (95/5 to 40/60)] gave **4** as pale yellow oil; yield: 4 g (88%); R_f = 0.57 (EtOAc/pentane: 60/40); $[\alpha]_D^{20}$: +71.6 (*c* 0.87, $CHCl_3$); IR (neat): ν = 3420, 1697, 1670, 1397, 1165 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.24 (m, 2H), 1.45 [s, 9H, $C(CH_3)_3$], 1.65 (m, 4H), 2.28 (s, 1H), 3.45 (m, 1H), 3.56 (m, 2H), 4.08 (s, 1H), 4.46 (m, 1H); ^{13}C NMR: δ = 27.9, 28.4, 29.7, 35.7, 39.7, 57.9, 66.6, 67.3, 80.2, 157.4; MS (EI): *m/z* (rel. intensity) = 227 (M^+, 1%), 68 (42), 96 (15), 112 (18), 140 (100), 196 (26); anal. calcd. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16; found: C 62.94, H 9.74, N 6.20.

(1*S*,3*R*,4*R*)-3-(Toluene-4-sulfonyloxymethyl)-2-azabicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (5)

In a 250-mL round-bottomed flask, a solution of **4** (2.4 g, 10.5 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C. To this solution, pyridine (2.0 mL, 24.8 mmol) was added followed by addition of tosyl chloride (2.4 g, 12.6 mmol) as a solution in CH_2Cl_2 (20 mL). The mixture was allowed to stir overnight at rt. The reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with brine (2 × 10 mL) and water (10 mL), dried with $MgSO_4$, filtered and evaporated to give crude **5**. Flash chromatography [silica, pentane/EtOAc (100/0 to 80/20)] gave **5** as a colourless oil; yield: 3.88 g (97%); R_f = 0.82 (EtOAc/pentane: 60/40); $[\alpha]_D^{20}$: +65.5 (*c* 1.11, $CHCl_3$); IR (neat): ν = 1698, 1366, 1177 cm^{-1}; ^1H NMR ($CDCl_3$; mixture of rotamers): δ = 1.22 (m, 2H), 1.32 [s, 9H, $C(CH_3)_3$], 1.39 [s, 9H, $C(CH_3)_3$], 1.65 (m, 8H), 2.43 (s, 6H), 2.51 (m, 2H), 3.30 (m, 1H), 3.44 (m, 1H), 3.64 (t, 1H), 3.77 (t, 1H), 4.10 (m, 6H), 7.33 (m, 4H, tosyl), 7.77 (m, 4H, tosyl); ^{13}C NMR (mixture of rotamers): δ = 21.6, 27.2, 28.3, 28.4, 29.6, 30.1, 33.8, 34.6, 38.6, 39.2, 56.7, 57.6, 61.5, 61.7, 68.4, 68.6, 79.8, 127.9, 129.8, 133.0 and 145.2; MS (EI): *m/z* (rel. intensity) = 281 (M^+ – Boc, < 1%), 53 (17), 54 (30), 65 (28), 66 (32), 67 (100), 68 (74), 77 (11), 78 (10), 79 (14), 80 (68), 81 (17), 82 (12), 94 (72), 108 (54), 112 (29), 138 (17), 153 (66); anal. calcd. for $C_{19}H_{27}NO_5S$: C 59.82, H 7.13, N 3.67; found: C 59.05, H 7.19, N 3.61.

(1*S*,3*R*,4*R*)-3-[(Diphenylphosphanyl)-methyl]-2-azabicyclo[2.2.1]heptane-2-carboxylic Acid *tert*-Butyl Ester (6)

In a two-necked round-bottomed flask equipped with a condenser, a solution of triphenylphosphine (2750 mg, 10.48 mmol) in THF (6 mL) was prepared under argon. Lithium metal (146 mg, 20.96 mmol) was added under a flow of argon and the mixture was stirred at rt until the metal was dissolved and the solution turned deep red. Then *tert*-butyl chloride (1.1 mL, 10.48 mmol) was added dropwise to quench the phenyllithium. This solution was then added dropwise *via* a syringe to a solution of **5** (1.00 g, 2.62 mmol) in THF (5 mL) under argon at 0 °C. The reaction mixture was then stirred for 2 h at rt and quenched with methanol (6 mL) and the solvents were evaporated. Flash chromatography [silica, pentane/EtOAc (100/0 to 90/10)] gave **6** as a white solid; yield: 800 mg (77%); R_f = 0.75 (EtOAc/pentane: 20/80); mp 113–115 °C; $[\alpha]_D^{20}$: +92.8 (*c* 1.08, $CHCl_3$); IR (neat): ν = 2224, 1591, 1484 cm^{-1}; ^1H NMR ($CDCl_3$; mixture of rotamers): δ = 1.30 (m, 4H), 1.43 [s, 9H, $C(CH_3)_3$], 1.50 [s, 9H, $C(CH_3)_3$], 1.60 (m, 6H), 1.90 (m, 4H), 2.6 (s, 1H), 2.7 (s, 1H), 2.73 (m, 1H, CHP), 2.95 (m, 1H, CHP), 3.28 (m, 1H, CHP), 3.46 (m, 1H, CHP), 4.10 (s, 3H), 4.23 (s, 3H), 7.25–7.55 (m, 16H), 7.64 (m, 4H); ^{13}C NMR (mixture of rotamers): δ = 27.6, 28.5, 29.6, 30.2, 32.1, 32.2, 32.7, 32.9, 33.9, 34.6, 40.4, 40.8, 40.9, 56.9, 57.7, 61.9, 62.2, 78.8, 79.4, 128.2, 128.4, 128.4, 128.6, 132.4, 132.6 132.7, 132.9, 133.0, 154.5; ^{31}P NMR: δ = −21.86, −21.32; MS (EI): *m/z* (rel. intensity) = 295 (M^+ – Boc, 5%), 68 (18), 183 (26), 185 (11), 199 (30), 200 (100), 201 (17); anal. calcd. for $C_{24}H_{30}NO_2P$: C 72.89, H 7.65, N 3.54; found: C 72.86, H 7.79, N 3.46.

(1*S*,3*R*,4*R*)-1-{3-[(Diphenylphosphanyl)-methyl]-2-azabicyclo[2.2.1]hept-2-yl}-2,2-dimethylpropan-1-one (2a)

In a 100-mL round-bottomed flask, a solution of **6** (1.7 g, 4.3 mmol) under nitrogen and conc. HCl (2.5 mL, 30.1 mmol)

in THF (40 mL) was allowed to reflux over night. The reaction mixture was cooled to 0 °C and 20% NaOH (aqueous) was added until pH 10. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, filtered and evaporated. The crude was dissolved in CH_2Cl_2 under argon and cooled to 0 °C. Triethylamine (1.5 mL, 10.8 mmol) followed by pivaloyl chloride (0.90 mL, 7.31 mmol) were added. The reaction mixture was allowed to stir overnight at rt. The solvent was evaporated and flash chromatography [silica, pentane/EtOAc (100/0 to 90/10)] gave **2a** as a white solid; yield: 1.6 g (99%); R_f = 0.75 (EtOAc/pentane: 20/80); $[\alpha]_D^{20}$: +54.5 (*c* 1.03, $CHCl_3$); mp 105–106 °C; IR (neat): ν = 2973, 1617, 1407 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.24 (m, 9H), 1.33 (m, 2H), 1.5–1.7 (m, 4H), 1.92 (m, 1H), 2.74 (s, 1H), 3.18 (m, 1H), 3.66 (m, 1H), 4.47 (s, 1H), 7.24–7.42 (m, 8H), 7.69 (m, 2H); ^{13}C NMR: δ = 27.0, 27.4, 27.9, 30.1, 32.2, 35.5, 39.3, 58.9, 63.0, 128.2, 128.3, 128.4, 128.5, 132.6, 132.7, 132.9, 133.0, 176.0; ^{31}P NMR: δ = −20.67; MS (EI): *m/z* (rel. intensity) = 379 (M^+, 1%), 67 (10), 95 (39), 96 (14), 155 (11), 177 (14), 178 (100), 179 (16), 183 (44), 185 (13), 201 (40), 202 (46), 203(10), 215 (18); anal. calcd. for $C_{24}H_{30}NOP$: C 75.96, H 7.97, N 3.69; found: C 74.53, H 7.30, N 4.11.

(1*S*,3*R*,4*R*)-1-{3-[(Diphenylphosphanyl)-methyl]-2-azabicyclo[2.2.1]hept-2-yl}-ethanone (2b)

In a 25-mL round-bottomed flask, a solution of **6** (201.7 mg, 0.510 mmol) and conc. HCl (0.30 mL, 3.6 mmol) in THF (10 mL) was allowed to reflux overnight under nitrogen. The reaction mixture was cooled to 0 °C and quenched with 20% NaOH (aqueous) until pH 10. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with brine (20 mL), dried with $MgSO_4$, filtered and solvent evaporated. The crude residue was dissolved in CH_2Cl_2 (8 mL) under argon and cooled to 0 °C. Triethylamine (0.5 mL, 3.59 mmol) and acetyl chloride (0.166 mL, 2.33 mmol) were added in this order. The reaction mixture was allowed to stir overnight at rt. The solvent was evaporated and flash chromatography (deactivated silica, EtOAc/pentane: 75/25) gave **2b** as a white solid; yield: 142.43 mg (83%); R_f = 0.30 (EtOAc/pentane: 75/25); mp 143–145 °C; $[\alpha]_D^{20}$: +99.3 (*c* 1.02, $CHCl_3$); IR (neat): n = 2969, 1636, 1434, 1417 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 1.2–1.37 (m, 2H), 1.46–1.80 (m, 4H), 1.95 (m, 1H), 2.03 (s, 3H), 2.72 (s, 1H), 3.12 (m, 1H), 3.59 (m, 1H), 4.06 (s, 1H), 7.25–7.49 (m, 8H), 7.71 (m, 2H); ^{13}C NMR: δ = 22.8, 27.4, 31.0, 33.8, 35.4, 40.5, 59.1, 62.1, 128.3, 128.4, 128.5, 128.6, 128.7, 132.5, 132.7, 132.9, 133.1, 169.0; MS (EI): *m/z* (rel. intensity) = 337 (M^+, 19%), 67 (14), 69 (38), 95 (33), 96 (32), 108 (17), 109 (11), 121 (19), 122 (11), 136 (100), 137 (45), 152 (15), 155 (30), 156 (14), 183 (72), 184 (36), 185 (18), 198 (17), 199 (21), 201 (83), 202 (94), 203 (23), 212 (69), 213 (31), 215 (30), 242 (20), 260 (15), 270 (19); anal. calcd. for $C_{21}H_{24}NOP$: C 74.76, H 7.17, N 4.15; found: C 75.76, H 8.05, N 3.57.

Catalytic Conjugate Addition of Butylmagnesium Chloride to 2-Cyclohexenone (Table 1, Entry 11)

In a 50-mL round-bottomed flask, a solution of **2a** (45.45 mg, 0.120 mmol) and CuCN (5.58 mg, 0.0623 mmol) in diethyl ether (8 mL) was stirred under nitrogen at rt for 20 min. The mixture was then cooled to −78 °C and butylmagnesium chloride (420 μL, 0.840 mmol) was added. After stirring for 20 min 2-cyclohexenone (70 μL, 0.700 mmol), in diethyl ether (2 mL) was added during 15 min. The reaction mixture was stirred until completion according to TLC (EtOAc/pentane: 10/90) and then quenched with saturated aqueous NH_4Cl (10 mL) and 22% NH_4OH (aqueous) (10 mL). The blue solution was stirred for 30 min and the layers were separated. The aqueous phase was extracted with ether (3 × 20 mL). The organic phases were combined and washed with 10% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL). The organic phase was dried with $MgSO_4$, filtered and evaporated to give the crude product. Flash chromatography [deactivated silica, pentane/EtOAc (100/0 to 90/10)] gave **8** as a colourless oil;[21] yield: 44 mg (41%). The ee was determined from the optical rotation as specified previously.[3]

Acknowledgements

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