A New and Practical Procedure for Asymmetric 1,4-Addition of Boronic Acids to α,β-Unsaturated Ketones Catalyzed by Rh-(R)-*Digm*-BINAP System

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Abstract: Rh-catalyzed C-C bond asymmetric formation under basic conditions in organoaqueous or alcoholic solvents has been described using the atropoisomeric water-soluble ligand (R)-*Digm*-BINAP. The addition of phenylboronic acid to cyclohexenone has been efficiently optimized leading to quantitative yield and enantiomeric excesses up to 98% using 1–3 mol% catalyst. Easy product-catalyst separation has been found using ethylene glycol as the reaction solvent. Other α,β-unsaturated ketones and boronic acids could be engaged in the 1,4-addition. The mole fraction of the catalyst could be decreased to 0.005% with still acceptable ee. A TON of 13200 was obtained.

Key words: chiral cationic water-soluble ligand, boronic acids, α,β-unsaturated ketones, asymmetric C-C bond formation, rhodium

The transition metal catalyzed reactions and specifically homogeneous catalysis have brought a considerable impact for a wide variety of chemical processes ranging from large-scale industrial area to fine organic synthesis.[1] Among them, the metal-catalyzed reactions using atropoisomeric diphosphines of the BINAP type have found a widespread development, due to the spectacular ability of those ligands to induce asymmetry in C-C and C-H bonds.[2] In the meantime, the expansion of efficient environmentally safe systems has given the ability to combine the high activity and selectivity of the catalyst with the easier product separation and possible catalyst recycling.[3] The synthesis of water-soluble ligands has positively responded to the key challenge of green chemistry in terms of safety, selectivity and separation of the product from the catalyst.[4] We have been engaged for a long time in the application of atropoisomeric ligands for asymmetric C-H bonds,[5] and in the use of water-soluble achiral ligands in C-C bonds formation[6,7]. Our group has recently described the synthesis of a new achiral water-soluble ligand *m*-TPPTC,[8] a chiral cationic ligand (R)-*Digm*-BINAP **1**[9] and the application in palladium, ruthenium and rhodium chemistry.[8–10]

Pioneered by Miyaura and Hayashi,[11] a particular attention recently lightens rhodium-catalyzed asymmetric C-C bond reactions that combine organoboron reagents and diverse electron-deficient olefins.[12] Highly stable potassium organotrifluoroborates have also been recently found to achieve efficiently rhodium(I)-catalyzed asymmetric 1,4-additions to enones.[13] The atropoisomeric (R)-BINAP **2** was once again an outstanding ligand for these couplings (Scheme 1).[11–15] To our knowledge, only two other ligand families, the phosphite[16] and proline derivatives[17] have been found to induce similar results. The general conditions imply a Rh(I) catalyst, a chiral ligand, in a 10:1 dioxane/water mixture at temperature ranging 60–100 °C. The mechanism has been recently disclosed and proceeds through a phenylrhodium, an oxa-π-allylrhodium and an hydroxorhodium species.[18] These conditions have several unique advantages over other asymmetric 1,4-addition reactions, but preclude an easy separation of product from catalyst and catalyst recycling. An achiral version of this reaction has been recently developed in neat water under basic conditions using the water-soluble ligand *m*-TPPTC.[10] Having in hand a unique cationic atropoisomeric ligand **1**, we envisaged to test its efficiency in asymmetric C-C bond formation. We wish therefore to describe herein our preliminary results concerning the Rh-catalyzed asymmetric 1,4-addition of boron derivatives.
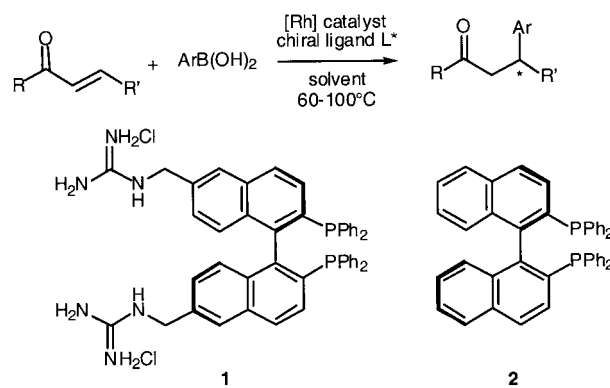
Scheme 1

The addition of phenylboronic acid to cyclohexenone was chosen as a standard reaction and our results are summarized in Table 1. The use of [Rh(cod)Cl]$_2$ in neat water[10] and the chiral cationic ligand **1** led to a very disappointing result (entry 1). The coupling adduct was isolated with 83% yield and 9% ee. Switching to the well-known Rh(acac)(C$_2$H$_4$)$_2$[11] gave a better result (entry 2), as the yield reached 100% in shorter time and the enantiomeric excess increased to 53%. The addition of a co-solvent such as dioxane, which is usually employed with (R)-BINAP **2**, slowed the reaction when it was used as a 10:1

mixture with water (entry 3). The arylated ketone was isolated with a fair enantiomeric excess of 84%. Without any base (entry 4), the reaction was very sluggish even if the enantiomeric excess was still good. Increasing the amount of water afforded a substantial decrease of the enantiomeric excess (entry 5). The use of other rhodium catalysts such as $Rh(cod)_2PF_6$ (entries 6, 7) was also investigated. This cationic precursor did not give better results. Once again, we observed a very fast reaction in the presence of Na_2CO_3 but the enantiomeric excesses were very much dependent on the quantity of water. The enantiomeric excess dropped to 4% by switching from a 10:1 dioxane/water to a 1:10 mixture (entry 6 compared to entry 7). Being confronted with a conflicting effect of water (acceleration of the water and decrease of the ee) we decided to test another polar solvent such as ethylene glycol, which has already been a good alternative solvent for palladium-catalyzed couplings[19] and ruthenium C–H bond formation.[9]

We were grateful to observe that the reaction occurred as fast as in the dioxane/water system and that the enantiomeric excess reached 91% (entry 8). The optimized conditions using 3 mol% rhodium, 6 mol% ligand afforded the desired adduct within a very short time and with an excellent ee (entry 9). The absolute configuration of the coupling adduct was confirmed to be R, and the reaction with (R)-$Digm$-BINAP **1** followed the same facial discrimination as with (R)-BINAP **2**. Considering the proposed mechanism,[18] ethylene glycol or water[20] may participate in the protonolysis of the same intermediate. One key challenge in the development of homogeneous catalysis was also addressed. The separation of product from the catalyst was very easy and no further purification was necessary.[21]

The generality of our new catalytic system was then expanded using only 1 mol% of rhodium 1.2 mol% of chiral ligand **1** and 2.5 equivalents of boronic acids (Table 2). The addition of phenylboronic acid to cyclohexenone afforded the corresponding functionalized cyclohexanone with 100% yield and 98% ee (entry 1). Other α,β-unsaturated ketones could be efficiently reacted in ethylene glycol under basic conditions. The cycloheptenone (entry 2) and the linear nonenone (entry 3) afforded the phenyl derivatives in 44% and 78% isolated yields, respectively. The enantiofacial discrimination also produced good enantiomeric excesses, 89% and 81% respectively. Other boronic acids could also be good partners for the asymmetric coupling. Indeed, the use of the electrodonating methoxyboronic acid afforded the functionalized cyclohexanone with 57% yield and an excellent ee of 97% (entry 4). A good chemoselectivity was also observed with the 4-bromoboronic acid. Quantitative yield of the brominated adduct susceptible to react via further organometallic coupling was obtained with 92% ee (entry 5).

In catalytic asymmetric catalysis, reducing the catalyst loading is also a main challenge for economical and industrial view point. In these reactions, two examples have been described so far, using respectively 0.3 mol% and 0.1 mol% of rhodium catalyst and phosphite chiral ligand or (S)-BINAP.[16,14c]

In our case, as shown in Table 3, attempts to reduce the catalyst/substrate ratio still afforded high yield and enantiomeric excess using 0.5 mol% catalyst within 5 hours (entry 2) compared to our standard conditions (entry 1). The mole fraction of rhodium could then be decreased to 0.005 mol% (S/C = 20000, entry 3). The lower yield and ee could be improved by using 2 equivalents of ligand

Table 1 Asymmetric Addition of Phenylboronic Acid to Cyclohexenone
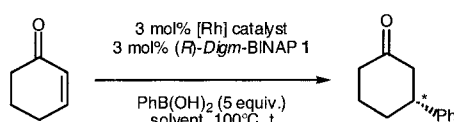
Entry	[Rh] Catalyst	Solvent	Additive (2 equiv)	t (h)	Yield (%)[a]	ee (%)[b]
1	$[Rh(cod)Cl]_2$	H_2O	Na_2CO_3	6	83	9
2	$Rh(acac)(C_2H_4)_2$	H_2O	Na_2CO_3	1	100	53
3	$Rh(acac)(C_2H_4)_2$	dioxane/H_2O 10:1	Na_2CO_3	2	100	84
4	$Rh(acac)(C_2H_4)_2$	dioxane/H_2O 10:1	/	7	8	90
5	$Rh(acac)(C_2H_4)_2$	dioxane/H_2O 1:10	Na_2CO_3	1	100	61
6	$Rh(cod)_2PF_6$	dioxane/H_2O 10:1	Na_2CO_3	1	100	66
7	$Rh(cod)_2PF_6$	dioxane/H_2O 1:10	Na_2CO_3	1	100	4
8	$Rh(acac)(C_2H_4)_2$	ethylene glycol	Na_2CO_3	1	100	91
9[c]	$Rh(acac)(C_2H_4)_2$	ethylene glycol	Na_2CO_3	1	100	98

[a] Isolated yield.
[b] Measured by HPLC OD-H, (R)-isomer.
[c] 6 mol% ligand.

Table 2 Asymmetric Addition of ArB(OH)$_2$ to α,β Unsaturated Ketones

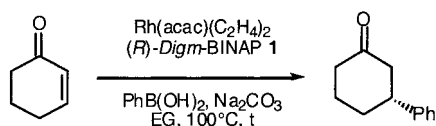| Entry	α,β-Unsaturated Ketone	Ar	Functionalized Ketone	Yield (%)[a]	ee (%)[b]
1		Ph		100	98
2		Ph		44	89
3		Ph		78	81
4		4-MeO-C$_6$H$_4$		57	97
5		4-Br-C$_6$H$_4$		99	92[c]

[a] Isolated yield.
[b] Measured by HPLC OJ or OD-H.
[c] Measured after debromination reaction.

per rhodium atom, which probably stabilized the corresponding catalyst (entry 4).

In conclusion, Rh-catalyzed C-C bond formation has been efficiently performed under basic conditions in ethylene glycol using a cationic BINAP type ligand. We also ob-

Table 3 Asymmetric Addition of Phenylboronic Acid to Cyclohexenone

Entry	Substrate:Catalyst	Time (h)	Yield (%)[a]	ee (%)[b]	TON
1	33	1	100	91	33
2	200	5	98	91	196
2	20000	72	36	81	7200
3[c]	20000	48	66	88	13200

[a] Isolated yield.
[b] Measured by HPLC OD-H.
[c] Rh/L = 1:2.

served that the use of a larger amount of water induced a decrease of the enantiomeric excess. The conditions were optimized on cyclohexenone and led to quantitative yield and high enantiofacial discrimination with enantiomeric excesses up to 98%. The major advantage of this procedure lies in the very easy separation of the product from the catalyst, with no purification step. This new catalyst system is also compatible to various α,β-unsaturated ketones and boronic acids. Low mole fraction of catalyst and ligand could be employed with still acceptable yield and ee. Further applications are currently under investigation including the recycling of the Rh/(*R*)-*Digm*-BINAP system.

Acknowledgement

References

(1) Cornils, B.; Herrmann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compound*; VCH: New York, **1996**.

(2) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809.

(3) Cornils, B.; Herrmann, W. A. In *Aqueous-Phase Organometallic Catalysis*; Wiley-VCH: New York, **1998**.

(4) (a) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Li, C. J.; Chan, T. K. *Organic Reactions in Aqueous Media*; JohnWiley & Son: New York, **1997**. (d) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, **1998**.

(5) (a) Genêt, J.-P. *Reductions in Organic Synthesis, A.C.S. Symposium Series 641*; ACS: New York, **1996**, 31–51. (b) Ratovelomanana–Vidal, V.; Genêt, J.-P. *J. Organomet. Chem.* **1998**, *567*, 163. (c) Ratovelomanana-Vidal, V.; Genêt, J.-P. *Can. J. Chem.* **2000**, *78*, 846.

(6) For recent reviews on Pd-catalyzed reactions, see: (a) Genêt, J.-P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305. (b) Genêt, J.-P.; Savignac, M.; Lemaire-Audoire, S. In *IUPAC Monographs: Chemistry for the 21st Century, Transition Metal Catalysed Reactions*; Murahashi, S.-I.; Davies, S. G., Eds.; Blackwell: London, **1999**, 55.

(7) (a) Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* **2001**, *3*, 2065. (b) Dupuis, C.; Adiey, K.; Charruault, L.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* **2001**, *42*, 6523.

(8) Amengual, R.; Genin, E.; Michelet, V.; Savignac, M.; Genêt, J.-P. *Adv. Synth. Catal.* **2002**, *344*, 393.

(9) (a) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Dellis, P. *Tetrahedron Lett.* **2001**, *42*, 3423. (b) Guerreiro, P.; Genêt, J.-P.; Dellis, P. French patent, 99 15217, **1999**. (c) For the synthesis of (*R*)-*Diam*-BINAP, see: Lemaire, M.; ter Halle, R.; Samson, E.; Colasson, B.; Spagnol, M. French Patent 99 02510, **1999**. (d) See also: ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **2000**, *41*, 643.

(10) Amengual, R.; Michelet, V.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5905.

(11) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579.

(12) (a) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. (b) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. (c) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 8944. (d) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

(13) (a) Pucheault, M.; Darses, S.; Genêt, J.-P. *Tetrahedron Lett.* **2002**, *43*, 6155. (b) Pucheault, M.; Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2002**, *in press*.

(14) (a) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479. (b) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047. (c) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (d) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Chirality* **2000**, *12*, 469. (e) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *66*, 6852.

(15) For recent reviews on asymmetric 1,4-addition, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033.

(16) Reetz, M.; Moulin, D.; Gosberg, A. *Org. Lett.* **2001**, *3*, 4083.

(17) Kuriyama, M.; Tomioka, K. *Tetrahedron Lett.* **2001**, *42*, 921.

(18) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(19) Unpublished results (E. Genin, D.E.A. Multinational de Chimie Moléculaire de l'Ecole Polytechnique).

(20) Ethylene glycol, purchased from Acros, contains 0.05% water and was used without further treatment.

(21) Typical procedure : A solution of Rh(acac)(C$_2$H$_4$)$_2$ (1.3 mg, 0.006 mmol) and (*R*)-*Digm*-BINAP (5.0 mg, 0.006 mmol) in degassed ethyleneglycol (1.0 mL) was stirred under argon for 15 minutes at room temperature, then phenylboronic acid (122 mg, 1 mmol), sodium carbonate (43 mg, 0.4 mmol) and cyclohexenone (20 μL, 0.2 mmol) were successively added. The heterogeneous mixture was stirred at 100 °C until completion of the reaction (gas chromatography). After cooling at room temperature the solution was extracted two times with ethyl acetate. The combined organic layers were filtered on a short pad of silica gel and evaporated under reduced pressure. A slight yellow oil (34 mg, 100%) was obtained. The purity of the compound was checked by gas chromatography and ^{1}H NMR. The enantiomeric excess was determined by HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98:2, 1 mL/min).