Rh-Catalyzed 1,4-Additions

Asymmetric Addition of Aryl Boron Reagents to Enones with Rhodium Dicyclophane Imidazolium Carbene Catalysis**

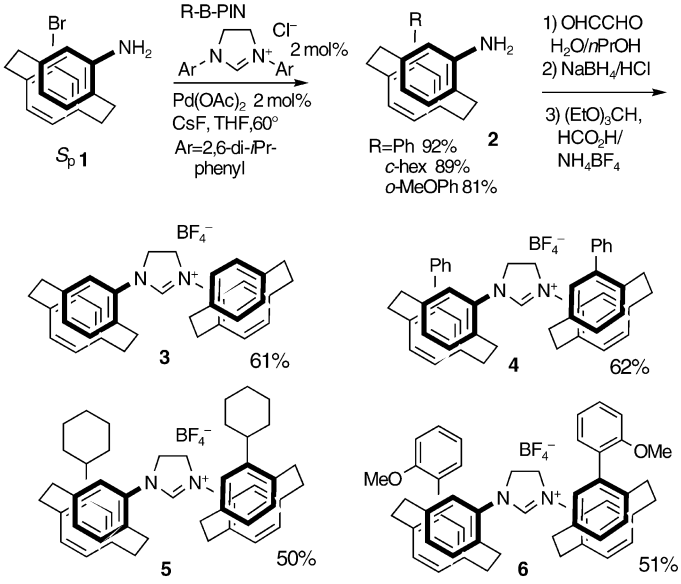
*Yudao Ma, Chun Song, Changqing Ma, Zhijun Sun, Qiang Chai, and Merritt B. Andrus**

Rhodium–binap catalysts have been used with great success for asymmetric conjugate additions of aryl boron compounds to enones and other electron-deficient alkenes.[1] The approach, pioneered by Miyaura, Hayashi, and co-workers offers particular advantages over copper-based methods,[2] including high selectivities, ligand availability, water tolerance, and moderate temperatures. Limitations remain to be addressed, including expanding the scope to alkyl reagents, lowering the amount of borane needed for high reactivity, and identifying new ligands that can be modified readily to accommodate new substrates.[3] As a first step to address these issues and as part of an effort to identify new asymmetric catalysts, we report herein the synthesis and use of a novel class of chiral dicyclophane imidazolium, N-heterocyclic carbene (NHC) ligands. Conditions are reported for the highly selective conjugate addition of aryl borane reagents (1.5 equiv) to cyclic and acyclic enones at moderate temperature. These new C_2-symmetric dicyclophane imidazolium ligands can be readily modified to allow substrate–ligand matching with this process and in applications to other asymmetric transformations.

Complexes of N-heterocyclic carbenes (NHC) with transition metals[4] have been developed to catalyze Heck,[5] Suzuki–Miyaura,[6] Stille, and Kumada coupling reactions,[4] hydrogenation reactions,[7] and ruthenium metathesis reactions.[8] We recently reported base-free conditions with NHC–palladium catalysts for Heck and Suzuki coupling reactions and the use of novel, bulky NHC ligands for Sonogashira reactions.[9] Imidazolium carbene ligands provide higher stability and reactivity than phosphanes through strong σ-bond donation to the metal, together with attenuated back-bonding through donation of the nitrogen lone pair of electrons.[10] This combination of electronic effects renders the metal more electron-rich, allowing a more favorable oxidative insertion step. Typical NHC complexes, formed by treatment of an imidazolium salt with base and a metal, are air-stable and can be purified by chromatography in some cases. Alternatively, the NHC–Pd complex can be formed in situ from the imidazolium precursor without added base. Although numerous recent reports of NHC ligands can be found, the area of asymmetric catalysis with chiral imidazolium ligands remains in its infancy.[11]

Planar chiral [2.2]paracyclophane ligands previously have included diphosphanes,[12] oxazoline-phosphanes,[13] oxazoline-imidazolium,[7c] oxazoline-selenides,[14] oxazoline-alcohols,[15] and Schiff base phenols. These have been used for hydrogenation, allylic substitution, and organozinc addition reactions.[16] Dimeric chiral [2.2]paracyclophanes are rare and their use as catalysts has not been reported previously.[17]

The synthesis of the new ligands began with the known compound S_p-pseudo-*ortho*-bromoamino[2.2]paracyclophane (**1**; Scheme 1). This material can be readily accessed either from the resolved S_p-dibromo[2.2]paracyclophane or from the



Scheme 1. Synthesis of chiral [2.2]paracyclophane imidazolium carbene precursor ligands. R-B-PIN = *B*-aryl pinnacolatoborane

amino[2.2]paracyclophane.[18] The S_p-pseudo-*ortho*-dibromide was treated with ammonia under palladium-coupling conditions to give **1**. Alternatively, Boc-protected S_p-amino[2.2]paracyclophane[19] can be brominated with NBS (*N*-bromosuccinimide) to give **1**. Suzuki–Miyaura coupling with aryl and cyclohexyl pinacolatoboron compounds under palladium–NHC catalysis gave the amino[2.2]cyclophanes **2** in high yields.[9a,20] A one-pot three-step procedure[21] was then used to generate the S_p C_2-symmetric dicyclophane imidazolium ligands **3**–**6**. Ligand **3** was obtained directly from the known S_p-amino[2.2]paracyclophane.[19] Treatment with aqueous glyoxal gave the corresponding diimine, which was reduced to the diamine with sodium borohydride. Triethyl orthoformate with catalytic formic acid followed by anion exchange with ammonium tetrafluoroborate gave the dicyclophane imidazolium target **3** in 61% yield. Ligands **4**–**6**

[*] Prof. M. B. Andrus, C. Song
Department of Chemistry and Biochemistry, Brigham Young University
Provo, UT 84602-5700 (USA)
Fax: (+1) 801-422-0153
E-mail: mbandrus@chem.byu.edu
Prof. Y. Ma, C. Ma, Z. Sun, Q. Chai
Chemistry College of Shandong University
Shanda South Road No. 27, Jinan, Shandong, 250100 (P. R. China)

[**] This work was funded by the National Institutes of Health (GM57275, M.B.A.), Brigham Young University, and The Chemistry College of Shandong University (Y.M.).

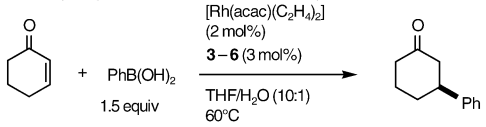
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200352679

were made by following the same sequence from the S_p-amino[2.2]cyclophanes **2** (R = phenyl, cyclohexyl, and *o*-anisyl, respectively).

These new ligands **3**–**6** were screened in the reaction of phenyl boronic acid (1.5 equiv) and 2-cyclohexenone under standard conditions in THF/water (Table 1). TLC was used to

Table 1: Rh–dicyclophane imidazolium catalysis.



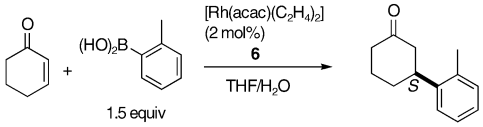
Entry	Ligand	*t* [h]	Yield [%][a]	*ee* [%][b]
1	**3**	4	69	61
2	**4**	8	86	91
3	**5**	6.5	89	97
4	**6**	3	96	98
5	**6**	3	75	95[c]

[a] Yield of product isolated after silica-gel chromatography. [b] Determined by chiral HPLC (OD-H column, heptane/*i*-propyl alcohol 98:2). [c] Catalyst loading changed: Rh (0.2 mol%), ligand (0.3 mol%).

establish when the reaction had gone to completion. The yields shown are for isolated, purified (silica-gel chromatography) (*S*)-3-phenylcyclohexanone product based on 2-cyclohexenone. In the presence of $[Rh(acac)(C_2H_4)_2]$ (2 mol%) and imidazolium ligand (3 mol%), high yields were obtained at 60 °C for all ligands investigated. In contrast, when the reaction was carried out with the same rhodium source but with binap ligand, only adequate reactivity was found at 100 °C.[1] Only when 0.2 mol% of the rhodium catalyst was used did the yield of the isolated product decrease to 75% in this case. The unsubstituted dicyclophane NHC ligand **3** gave product with only moderate enantioselectivity (61% *ee*). Ligand **4**, the diphenyl variant, reacted at a slower rate, but gave product with improved enantioselectivity (91% *ee*). The dicyclohexyl ligand **5** showed further improvement (97% *ee*). Dianisyl derivative **6** proved to be superior (98% *ee*), and the product was isolated in an excellent yield of 96% after only 3 h.

Numerous variations of the reactions conditions were explored for the addition of *o*-tolylboronic acid to cyclohexanone in the presence of the rhodium–**6** complex (Table 2). With the amount of rhodium held constant at 2 mol%, the amount of imidazolium **6** was varied from 0 to 4 mol%. Without added ligand, no product was obtained after 3 h (Table 2, entry 1). The yield was very low, 27% when 1 mol% of **6** was used (Table 2, entry 2), but the selectivity remained high at 89% *ee*. The optimal amount of **6** was found to be 3 mol%, 2:1 ligand/Rh, which resulted in 91% yield, 95% *ee* at 60 °C after 3 h (Table 2, entry 4). When the reaction was stopped after 2 h, the product was obtained in 56% yield (96% *ee*) (Table 2, entry 5). At 35 °C (Table 2, entry 6) a lower yield was obtained with no improvement in selectivity. At 80 °C, the selectivity dropped to 66% *ee* (Table 2, entry 7). When THF alone was used without water, the reaction was much slower and gave a lower yield and selectivity (Table 2,

Table 2: Variations on the conditions.



Entry	**6** [mol%]	THF/H_2O	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	0	10:1	60	3	0	-
2	1	10:1	60	3	27	89
3	2	10:1	60	3	82	93
4	3	10:1	60	3	91	95
5	4	10:1	60	3	90	95
6	3	10:1	35	3	83	94
7	3	10:1	80	2	95	66
8	3	10:0	60	6	80	81
9	3	5:1	60	2	85	68
10	3	3:1	60	2	43	-
11	3	10:1	60	1	97	36[a]
12	3	10:1	60	3	82	95[b]
13	3	10:1	60	5	82	93[c]

[a] Reaction performed with added Na_2CO_3 (1 equiv). [b] Aryl boronic acid: 1.2 equiv. [c] The chloride salt of ligand **6** was used instead of BF_4^-.

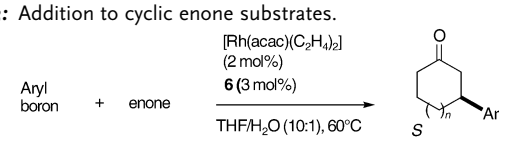
entry 8). The rate was faster when a greater proportion of water was used, however the selectivities were much lower (Table 2, entries 9 and 10). The use of a dioxane/water (10:1) solvent mixture, typical conditions for Rh–binap-catalyzed reactions, gave the product in 89% yield with 95% *ee* after 5 h. Methanol and methanol/water combinations gave good reaction rates, but with lower selectivities. Added bases investigated (Na_2CO_3, $NaHCO_3$, Cs_2CO_3, CsF, and K_2CO_3); all increased the rate of the reaction but gave poor selectivity. When the amount of boronic acid was lowered to 1.2 equivalents, the high selectivity was maintained, but the yield decreased (82%; Table 2, entry 12). A similar effect was noted when the counteranion on the imidazolium salt **6** was changed from tetrafluoroborate to chloride (Table 2, entry 13).

The optimal reaction conditions with ligand **6** were applied in the addition of various aryl boronic acids and potassium trifluoroborates[1f] to several cyclic enones (Table 3). Phenylboronic acid added to all three enones in high yield and with good selectivity. The *p*-methoxyphenyl- and *o*-tolylboron reagents gave similar results. The electron-deficient reagents *p*-acetyl- and trifluoromethylboronic acid also gave excellent yields and selectivities. Under these conditions, the potassium trifluoroborate reagents reacted at a faster rate, but with lower selectivity.

The reactions of acyclic enones with the phenylboron reagents were also explored (Table 4). In general, the yields were again excellent; however, the selectivities were significantly lower. The highest selectivity in this case was found with isopropylvinyl methyl ketone (91% *ee*). The trifluoroborate reagent again reacted at a faster rate, but with lower selectivity.

The origin of the selectivity appears to be related to the binap-catalyzed process proposed by Miyaura, Hayashi, and co-workers.[1] These new C_2-symmetric biscyclophane carbene ligands also present four asymmetric quadrants for substrate binding and nucleophile delivery (Scheme 2). In the absence

Table 3: Addition to cyclic enone substrates.



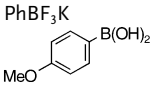
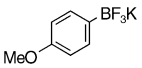
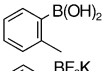
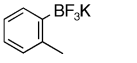
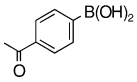
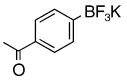
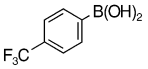
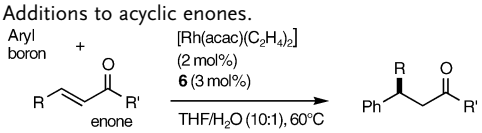
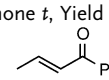
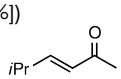
Aryl boron	Enone *t*, Yield [%] (*ee* [%])		
$PhB(OH)_2$	3 h,96 (98)	3.5 h, 94 (93)	3.5 h, 97 (92)
$PhBF_3K$	1 h, 96 (91)	1 h, 93 (85)	1 h, 95 (90)
	3 h, 90 (93)	3.5 h, 90 (85)	
	1 h, 89 (96)	1 h, 89 (85)	
	3 h, 91 (95)	4 h, 92 (90)	
	1 h, 95 (90)	45 min, 94 (87)	
	4 h, 92 (95)	4 h, 89 (92)	
	30 min, 93 (94)	45 min, 92 (83)	
	3.5 h, 96 (97)	4 h, 93 (92)	

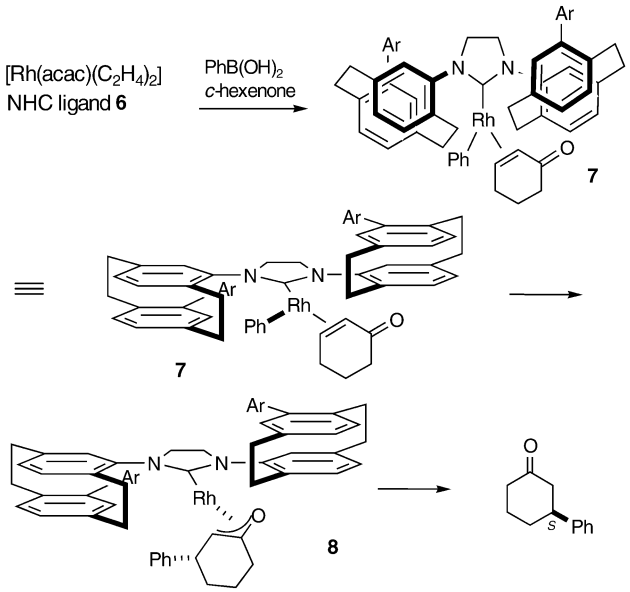
Table 4: Additions to acyclic enones.



Aryl boron	Enone *t*, Yield [%] (*ee* [%])		
			
$PhB(OH)_2$	2.5 h, 95 (81%)	2.5 h, 92 (78%)	2.5 h, 83 (91%)
$PhBF_3K$	45 min, 96 (80%)	45 min, 95 (73%)	45 min, 94 (81%)

of base, the anion of acetylacetone may function as base to produce the rhodium carbene. Palladium–NHC complexes can form in the absence of base. In this case, the aryl boron transmetallates with the NHC–rhodium complex. Complexation with the enone gives **7**. From a 3D view, preferred placement of the enone in an unobstructed quadrant can be assumed. The cyclophane groups, with the aryl substituent rotated back, away from the metal, sterically obstruct the upper right- and lower left-hand quandrants, flanking the central metal carbene. Transfer of the aryl group to the *Si* face of the enone then generates oxallyl–rhodium intermediate **8**. Hydrolysis with water liberates the *S* product and regenerates the catalyst (Scheme 2).

In summary, a new class of asymmetric biscyclophane carbene ligands has been developed. For the first time, very high selectivities are obtained in the presence of a chiral imidazolium ligand for carbon–carbon bond formation in an addition process. The route to these ligands is flexible and



Scheme 2. Origin of asymmetric induction.

allows the synthesis of numerous variations with different electronic and steric properties. This opens up opportunities for other rhodium-based processes and asymmetric, transition-metal-catalyzed reactions with these ligands for which high reactivity at lower temperatures can be found. Efforts to this end are now underway in our laboratories.

Received: August 19, 2003 [Z52679]

Keywords: addition · boron · cyclophanes · homogeneous catalysis · rhodium

[1] a) T. Hayashi, M. Takahashi, Y. Takaya, M. Ogasawara, *J. Am. Chem. Soc.* **2002**, *124*, 5052; b) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N, Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579; c) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4230; for a review, see: d) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829; for a recent report with aryl siloxanes, see: e) S. Oi, A. Taira, Y. Honma, Y. Inoue, *Org. Lett.* **2003**, *5*, 97; for a recent approach with a Rh phosphoramidite, see: J.-G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 681; for the use of potassium trifluoroborates, see: f) M. Pucheault, S. Darses, J.-P. Genêt, *Tetrahedron Lett.* **2002**, *43*, 6157; g) M. Pucheault, S. Darses, J.-P. Genêt, *Eur. J. Org. Chem.* **2002**, 3552.

[2] a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346; b) A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J.-M. Levesque, F. Maze, *Eur. J. Org. Chem.* **2000**, 4011; c) L. Liang, T. T. L. Au-Yeung, A. S. C. Chan, *Org. Lett.* **2002**, *4*, 3799; d) H. Mizutani, S. J. Degrado, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 779.

[3] For a recent report of the use of an achiral cationic palladium catalyst at lower temperatures, see: T. Nishikata, Y. Yamamoto, N. Miyaura, *Angew. Chem.* **2003**, *115*, 2874; *Angew. Chem. Int. Ed.* **2003**, *42*, 2768.

[4] W. A. Herrmann, *Angew. Chem.* **2002**, *114*, 1342; *Angew. Chem. Int. Ed.* **2002**, *41*, 1290.

[5] C. Yang, H. M. Lee, S. P. Nolan, *Org. Lett.* **2001**, *3*, 1511.

[6] a) A. Fürstner, A. Leitner, *Syn. Lett.* **2001**, 290; b) G. A. Grasa, A. C. Hillier, S. P. Nolan, *Org. Lett.* **2001**, *3*, 1077.
[7] For asymmetric hydrogenation, see: a) M. C. Perry, X. Cui, M. T. Powell, D. R. Hou, J. H. Reibenspiess, K. Burgess, *J. Am. Chem. Soc.* **2003**, *125*, 113; b) H. Seo, H. J. Park, B. Y. Kim, J. H. Lee, S. U. Son, Y. K. Chung, *Organometallics* **2003**, *22*, 618; c) C. Bolm, T. Focken, G. Raabe, *Tetrahedron: Asymmetry* **2003**, *14*, 1733.
[8] a) T. J. Seiders, D. W. Ward, R. H. Grubbs, *Org. Lett.* **2001**, *3*, 3225; b) J. J. Van Veldhuizen, S. B. Garber, J. S. Kingsbury, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 4954.
[9] a) M. B. Andrus, C. Song, *Org. Lett.* **2001**, *3*, 3761; b) M. B. Andrus, C. Song, J. Zhang, *Org. Lett.* **2002**, *4*, 2079; c) Y. Ma, C. Song, W. Jiang, Q. Wu, X. Liu, M. B. Andrus, *Org. Lett.* **2003**, *5*, 3317.
[10] W. A. Herrmann, C. Kocher, *Angew. Chem.* **1997**, *109*, 2256; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2162.
[11] For hydrosilylations, see: a) W. A. Herrmann, L. J. Gooßen, C. Köcher, G. R. J. Artus, *Angew. Chem.* **1996**, *108*, 2980; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2805; b) D. Enders, H. Gielen, K. Breuer, *Tetrahedron: Asymmetry* **1997**, *8*, 3571; for the addition of organozinc reagents, see: c) F. Guillen, C. L. Winn, A. Alexakis, *Tetrahedron: Asymmetry* **2001**, *12*, 2083; d) J. Pytkowicz, S. Roland, P. Mangeneney, *Tetrahedron: Asymmetry* **2001**, *12*, 2087; For the Stetter reaction, see: e) D. Enders, U. Kallfass, *Angew. Chem.* **2002**, *114*, 1822; *Angew. Chem. Int. Ed.* **2002**, *41*, 1743; see references [7] and [8] for additional examples.
[12] For use in hydrogenation reactions, see: a) P. J. Pye, K. Rossen, R. A. Reamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, *119*, 6207; b) P. J. Pye, K. Rossen, R. A. Reamer, R. P. Volante, P. J. Reider, *Tetrahedron Lett.* **1998**, *39*, 4441.
[13] For use in allylic substitution reactions, see: X.-W. Wu, X. K. Yuan, W. Sun, M.-J. Zhang, X.-L. Hou, *Tetrahedron: Asymmetry* **2003**, *14*, 107.
[14] X.-L. Hou, X.-W. Wu, L.-X. Dai, B.-X. Cao, J. Sun, *Chem. Commun.* **2000**, 1195.
[15] For use in addition of organizinc reagents, see: X.-W. Wu, X.-L. Hou, L.-X. Dai, J. Tao, B.-X. Cao, B. J. Sun, *Tetrahedron: Asymmetry* **2001**, *12*, 529.
[16] a) T. I. Danilova, V. I. Rozenberg, E. V. Sergeeva, E. Z. A. Starikova, S. Bräse, *Tetrahedron: Asymmetry* **2003**, *14*, 2013; b) S. Dahmen, S. Bräse, *Chem. Commun.* **2002**, 26; c) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, *Angew. Chem.* **2002**, 114, 3844; *Angew. Chem. Int. Ed.* **2002**, *41*, 3692.
[17] E. Ludger, L. Wittkowski, *Eur. J. Org. Chem.* **1999**, *7*, 1653.
[18] a) K. Rossen, P. J. Pye, A. Maliakal, R. P. Volante, *J. Org. Chem.* **1997**, *62*, 6462; b) P. Pye, K. Rossen, R. P. Volante, U.S. Patent A-5874629.
[19] H. Falk, P. Reich-Rohrwig, K. Schlögl, *Tetrahedron* **1970**, *26*, 511.
[20] Y. Ma, C. Song, M. B. Andrus, unpublished results for aryl halides.
[21] This is a modification of a known procedure: A. J. Arduengo III, *Acc. Chem. Res.* **1999**, *32*, 913.

