Available online at www.sciencedirect.com
SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 3241–3244

Tetrahedron Letters

Bis-paracyclophane *N*-heterocyclic carbene–ruthenium catalyzed asymmetric ketone hydrosilylation

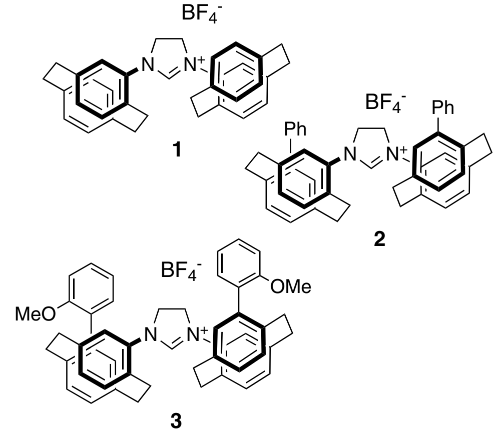
Chun Song,[b] Changqin Ma,[a] Yudao Ma,[a,*] Wenhua Feng,[a] Shutao Ma,[a] Qiang Chai[a] and Merritt B. Andrus[b,*]

[a] *Chemistry College of Shandong University, Shanda South Road #27, Jinan, Shandong 250100, PR China*
[b] *Brigham Young University, C100 BNSN, Department of Chemistry and Biochemistry, Provo, UT 84602-5700, USA*

Received 15 February 2005; accepted 4 March 2005

Abstract—New chiral bis-paracyclophane *N*-heterocyclic carbene (NHC) ligands **1**–**3** have been explored for ruthenium catalyzed asymmetric hydrosilylation of ketones using diphenylsilane to give enantioenriched alcohols. These ligands provide for efficient asymmetric reduction in the presence of silver(I) triflate (1 mol %) at room temperature with high reactivity and selectivity. Acetophenone **4** was reduced with 1 mol % catalyst in 96% isolated yield, 97% ee. Following removal of the silyl ether, various alcohols **5** were obtained from aromatic ketones in high yield and selectivity.

Asymmetric ketone reduction under nonhydrogenation conditions provides a useful route to secondary alcohols under mild, chemo-selective conditions. Meerwien–Ponndorf–Verley and oxazaborolidine based methods have been developed that demonstrate great success with this important synthetic transformation.[1] Hydrosilylation using transition metal catalysts, primarily based on rhodium and ruthenium, has also been reported to access enantioenriched alcohols from ketones.[2] Following previous success with rhodium catalyzed arylboronic acid additions,[3] the use of novel, chiral paracyclophane *N*-heterocyclic carbene ligands (Scheme 1) for highly selective ruthenium catalyzed hydrosilylation is now reported.



Scheme 1.

Nishiyama established the standard for asymmetric hydrosilylation reporting pyridylbisoxazoline–rhodium catalysts (4 mol %) and diphenylsilane to reduce acetophenone in 91% yield and 94% ee.[4] *P*,*N*-Phosphine–oxazoline and ferrocene based catalysts have also been reported with promising results.[5] More recently Fu has reported the use of a planar chiral *P*,*N*-ferrocene based catalyst that shows very high selectivity (98% ee) at room temperature using mesitylphenylsilane[6] and Lipshutz and co-workers have reported the use of biphenyl-bis-dixylylphosphine ligands under copper catalysts with polymethylsilyl hydride at low temperature.[7] Imidazolium *N*-hetrocyclic carbene (NHC) based ligands have also been reported for hydrosilylation reactions. Monodentate rhodium bis-naphthyl and aminoalcohol derived catalysts showed moderate selectivity.[8] Shi reported the development of a highly selective binaphthyl-bisbenzoimidazole ligand and Gade and co-workers have demonstrated the success of NHC–oxazoline ligands.[9]

We recently reported a new class of bis-paracyclophane–NHC ligands **1**–**3** and demonstrated their use as

---

Keywords: Hydrosilylation; Paracyclophane; Asymmetric catalysis.

* Corresponding authors. Tel.: +1 8014228171; fax: +1 8014220153; e-mail: mbandrus@chem.byu.edu

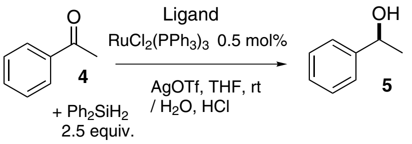
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.03.026

ruthenium complexes for arylboronic acid additions to enones.[3] Planar chiral [2.2]paracyclophane ligands include diphosphines,[10] oxazoline-phosphines,[11] oxazoline-imidazolium,[12] oxazoline-selenides,[13] oxazoline-alcohols,[14] and Schiff base-phenols for hydrogenation, allylic substitution, and organozinc addition reactions.[15] Dimeric chiral [2.2]paracyclophanes are rare and their use as catalysts has not been reported previously.[16]

The synthesis of the bis-paracyclophane ligands **1**–**3** begins with the known compound S_p-pseudo-*ortho*-bromoamino [2.2]paracyclophane[17] as previously reported.[3] The ligands were used under the conditions of Uemura using conveniently available ruthenium dichloride tris(triphenylphosphine) (0.5 mol %) with added silver triflate (1 mol %) in THF at room temperature (Table 1). With ligand **1**, acetophenone was reduced, following work-up with HCl and purification by chromatography, in 98% yield and 90% ee (chiral HPLC).[18] Ligands **2** and **3** both gave *S*-phenylethanol in excellent selectivity, 98% ee. Use of $[RuCl_2(PhH)]_2$ with **3** also gave a high yield (97%, 24 h) but with reduced selectivity, 92% ee. The other test substrate at this time was 3-methylpropylphenylketone, which was reduced using **3** in 97% ee (not shown). Ligand **2** was less selective, 90% ee in this case. Ligand **3** was selected for further investigation to optimize the conditions and reduce other substrates. Various solvents were explored with **3** and THF proved to be superior. Use of chloroform lowered the selectivity to 77% ee. Toluene and benzene gave low yields (36% and 20%) and the selectivity was very low. Dioxane was also low yielding, 58%, however the selectivity was not greatly reduced, 92% ee. The ratio of the metal to the ligand was also explored. At 1:1 ratio, the reactivity was high, 96% in 16 h, and the selectivity was compromised, 83% ee. At 1:2 ratio, the yield (97%, 20 h) and the selectivity improved, 96% ee. The optimal ratio at 1:2.4 (98%, 97% ee) is superior to 1:3 where both the yield (67%) and the selectivity (91% ee) begin to be lowered.

Various additives were also explored along with catalyst and silane loadings for the process. Use of copper(II) triflate, in place of silver(I) triflate, gave high reactivity, 97% (20 h) with lowered selectivity, 92% ee. Use of 18-c-6 with potassium carbonate gave very low selectivity (11% ee) and tetrabutylammonium bromide (TBAB) gave no reaction. Use of 0.1 mol % ruthenium, with 0.24 mol % **3**, the reaction rate was very slow, 98 h, and the yields and selectivities were reduced, 86%, 93% ee. Use of greater amounts of the catalyst, for example, 1 mol % ruthenium with 2.4 mol % **3**, showed no significant improvement, 97%, 98% ee. Use of 1 equiv of diphenylsilane gave a low yield, 56% (24 h) and the selectivity was reduced, 90% ee. With 2 equiv, the yield was reduced, 89% (18 h) and the selectivity was the same, 97% ee. Use of 3 equiv gave no improvement over the optimal 2.5 equiv shown.

Table 1. Hydrosilylation with cyclophane ligands



Ligand	Ru/lig. ratio	Time (h)	% Yield	% ee
1	1:2.4	16	98	90
2	1:2.4	16	98	97
3	1:2.4	16	98	97
3	1:2.4	24	86	77[a]
3	1:1	16	96	83
3	1:2	20	97	96
3	1:3	24	67	91

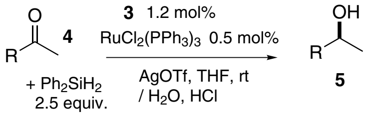
[a] $CHCl_3$ used as solvent.

Other methyl ketones were used under the optimized conditions using the Ru·**3** complex as catalyst (Table 2). Cyclohexylmethyl ketone was one the of few substrates that did not show high selectivity, 58% ee. All other arylmethyl ketones, including *ortho*-substituted substrates gave excellent yields and selectivities. More electron rich, methyl and methoxy aryl ketones reacted with high rates. *p*-Trifluoromethyl acetophenone required 24 h and gave an 81% yield with only 77% ee.

This ligand **3**–ruthenium combination also gave excellent yields and selectivities for more hindered aryl ketone substrates (Table 3). Ethyl, isopropyl, and *sec*-butyl phenyl ketones were highly selective, 90–93% ee. Even cyclohexylphenyl ketone reacted in 90% yield with 88% ee. Cyclic aryl ketones, indanone and benzocyclohexanone also reacted with high selectivity, 93% and 92% ee.

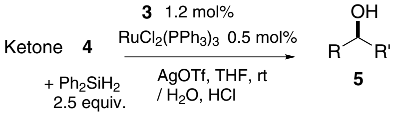
While the origin of the stereoinduction remains difficult to elucidate at this time, the nature of the Ru–ligand formation and the step responsible for the selectivity may be compared to mechanistic findings reported by Prock and Giering for the related rhodium based process (Scheme 2). Key findings in this and previous studies determined that the reaction is first order in silane and rhodium and there is a saturation effect with acetophenone only when ketone is present at high concentration.[19] In the case of ruthenium with **3**, excess ligand may be needed to favor formation of mono-NHC complex **A**. Silane then adds to the 14 e complex to give the

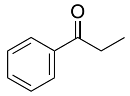
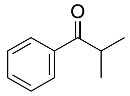
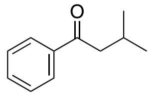
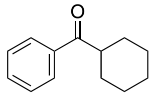
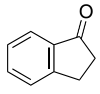
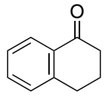
Table 2. Reduction of methyl ketones

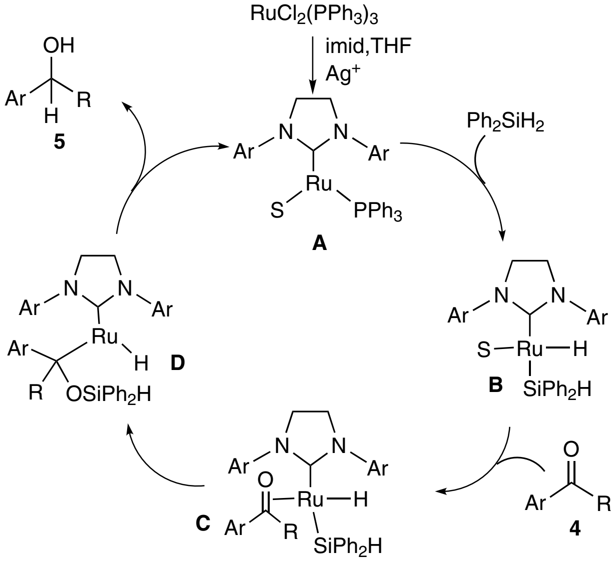


R =	Time (h)	% Yield	% ee
Ph	16	98	97
c-Hexyl	36	93	58
2-PhEt	15	95	93
2-Naphthyl	20	98	96
o-MeOPh	15	92	96
o-Tolyl	16	96	94
o-BrPh	36	91	93
o-ClPh	20	90	97
p-Tolyl	12	98	96
p-MeOPh	12	91	93
p-F_3CPh	48	81	77

Table 3. Ketone hydrosilylation



Ketone	Time (h)	% Yield	% ee
	16	96	92
	18	95	93
	36	89	90
	30	90	88
	18	80	93
	30	90	92



Scheme 2.

metal hydride **B**. This step may be considered as the turnover-limiting step. Dissociation of a solvent ligand then allows for ketone coordination to give intermediate **C**. Rapid transfer of silane to the carbonyl oxygen then gives the inserted silyl ether **D** and reductive elimination generates product and the complex **A**. The influence of the chiral paracyclophanes would be expressed with the reversible formation of the distorted square planar η^2-carbonyl complex **C**.

In summary, asymmetric hydrosilylation of ketones was performed with new paracyclophane NHC ligands complexed to ruthenium to give secondary alcohols in high yield and selectivity under mild conditions. These results expand the scope of these ligands and point the way toward their use in other transition metal catalyzed applications.

Acknowledgments

We are grateful to Brigham Young U. (M.B.A.), and The Chemistry College of Shandong U. (Y.M.) for funding this work.

Supplementary data

^{1}H NMR and optical rotation data for all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.026.

References and notes

1. (a) Noyori, R.; Yamakawa, M.; Hashiguchi, S. *J. Org. Chem.* **2001**, *66*, 7931; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
2. (a) Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, 2000; Chapter 2; (b) Riant, O.; Mostefai, N.; Courmarcel, J. *Synthesis* **2004**, 2943.
3. Ma, Y.; Song, C.; We, J.; Andrus, M. B. *Angew. Chem., Int. Ed.* **2003**, *42*, 5871.
4. Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846.
5. (a) Sudo, A.; Yoshida, H.; Saigo, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3205; (b) Nishibayashi, Y.; Takai, I.; Uemura, S.; Hidai, M. *Organometallics* **1998**, *17*, 3420; For more recent P,S-ligands see: (c) Evans, D. A.; Michael, F. E.; Tedrow, J. S.; Campos, K. R. *J. Am. Chem. Soc.* **2003**, *125*, 3534.
6. Tao, B.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 3892.
7. (a) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779; (b) Lee, D.; Yun, J. *Tetrahedron Lett.* **2004**, *45*, 5415; Titanium based catalysts have also been developed: (c) Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640.
8. (a) Herrmann, W. A.; Goossen, L. J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed.* **1996**, *35*, 2805; (b) Enders, D.; Gielen, H.; Runsink, J.; Breuer, K.; Brode, S.; Boehn, K. *Eur. J. Inorg. Chem.* **1998**, 913.
9. (a) Duan, W.-L.; Shi, M.; Rong, G.-B. *Chem. Commun.* **2003**, 2916; (b) Gade, L. H.; Cesar, V.; Bellemin-Laponnaz, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1014.
10. (a) Pye, P. J.; Rosen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207; (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441.
11. Wu, X.-W.; Yuan, X. K.; Sun, W.; Zhang, M.-J.; Hou, X.-L. *Tetrahedron: Asymmetry* **2003**, *14*, 107.
12. Bölm, C.; Focken, T.; Raabe, G. *Tetrahedron: Asymmetry* **2003**, *14*, 1733.
13. Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *J. Chem. Soc., Chem. Commun.* **2000**, 1195.

14. Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Tao, J.; Cao, B.-X.; Sun, B. J. *Tetrahedron: Asymmetry* **2001**, *12*, 529.
15. (a) Danilova, T. I.; Rozenberg, V. I.; Sergeeva, E. V.; Starikova, E. Z. A.; Bräse, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2013; (b) Dahmen, S.; Bräse, S. *J. Chem. Soc., Chem. Commun.* **2002**, 26; (c) Hermanns, N.; Dahmen, S.; Bölm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692.
16. Ludger, E.; Wittkowski, L. *Eur. J. Org. Chem.* **1999**, *7*, 1653.
17. (a) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462; (b) Pye, P.; Rossen, K.; Volante, R. P. U.S. Patent A-5,874,629.
18. Representative procedure: A dry flask was charged with [$RuCl_2(PPh_3)_3$] (4.8 mg, 0.005 mmol), ligand **3** (9.4 mg, 0.012 mmol) and AgOTf (2.4 mg, 0.01 mmol, 1.0 mol %) in THF (5.0 mL) under argon. The mixture was stirred in rt for 30 min and ketone (1.0 mmol) was added, followed by diphenylsilane (0.46 mL, 2.5 mmol) in THF (3.0 mL) added slowly by syringe. The reaction was kept in 0 °C and the progress of the reaction was monitored by TLC. After the reaction was judged to be complete, methanol (2.0 mL) was added slowly and the mixture was poured into a solution of hydrochloride acid (1 N, 6 mL). The mixture was stirred for 30 min and extracted by CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The solvent was concentrated by rotary evaporation and the crude material was purified by silica gel chromatography using ethyl acetate/hexanes (10–25%). The known product compounds, with the isolated yields indicated in the tables were characterized by the individual data as shown in the Supplementary data. % Ee was measured by chiral HPLC (Chiracel, OD column) or GC (β-Dex column).
19. Reyes, C.; Prock, A.; Giering, W. P. *Organometallics* **2002**, *21*, 546.