J|A|C|S
COMMUNICATIONS

Published on Web 05/22/2004

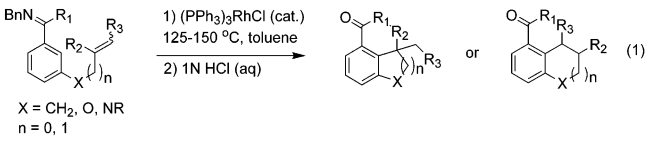
Highly Efficient and Enantioselective Cyclization of Aromatic Imines via Directed C−H Bond Activation

Reema K. Thalji, Jonathan A. Ellman,* and Robert G. Bergman*

Center for New Directions in Organic Synthesis,† Department of Chemistry, University of California−Berkeley, and Chemical Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California 94720

Received November 8, 2003; E-mail: jellman@uclink.berkeley.edu, bergman@cchem.berkeley.edu

Despite substantial recent research activity in the C−H activation area,[1,2] to our knowledge there is only one report on the catalytic enantioselective coupling of aromatic C−H bonds with alkenes.[3] In that case, only very modest ees were observed. Recently, we reported on the intramolecular alkylation of aromatic imines in which the alkene is tethered meta to the imine (eq 1).[4] This reaction exhibits a much broader alkene scope than that obtained in related systems[2] and provides an efficient route to functionalized bicyclic ring systems that would be difficult to access by other methods. By allowing the coupling of highly substituted alkenes, this reaction enables the preparation of branched products bearing stereocenters. Herein, we communicate our development of an asymmetric variant of these reactions, leading to the first highly enantioselective catalytic reaction involving aromatic C−H bond activation. Moreover, the identified catalyst system enables the intramolecular alkylation reaction to be performed at temperatures 75 °C lower than our previously reported conditions. Indeed, the reaction can even be carried out at room temperature for one of the optimal substrates. This reaction should prove to be especially valuable in view of the fact that there are no known general methods for preparing these compounds enantioselectively.



(1)

We focused our efforts on the chiral monodentate phosphorus ligands displayed in Chart 1 because chelating phosphines provide inefficient catalysts for this reaction. Our investigation began by testing the cyclization of ketimine **17** with rhodium complexes of each of these ligands (Table 1). Of the phosphines tested (**1**−**6**), the P−N ligands (**1**, **2**, and **4**) gave poor conversions; these results are consistent with the previous observation that chelating ligands retard the reaction rate. The P−O ligands **3**, **5**, and **6** gave much higher conversions, probably due to the fact that oxygen coordinates more weakly than nitrogen to late transition metal centers. Notably, rhodium complexes of **5** and **6** both proved to be much more efficient catalysts than the previously reported achiral Wilkinson's catalyst (125 °C, 4 h) but gave only modest ees.

Phosphite and phosphoramidite ligands are appealing due to the ease and modularity of their syntheses.[5] The (−)-TADDOL-based phosphites **7**−**9**, the (−)-TADDOL-based phosphonite **10**, the (*S*)-binol-derived phosphite **11**, and phosphoramidites that incorporate unhindered secondary amines **12**−**14** all proved to be ineffective catalysts, giving either poor conversions, poor ees, or both. In contrast, impressive enantioselectivities and conversions were

Chart 1

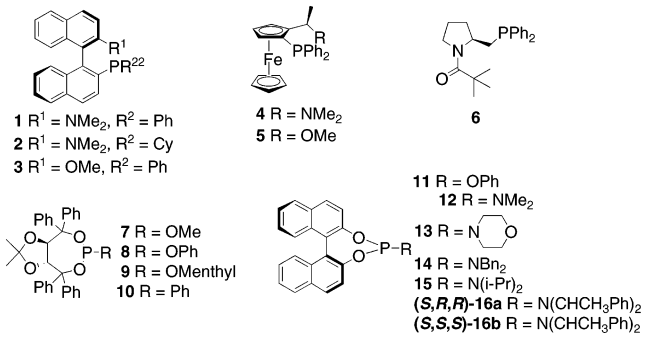
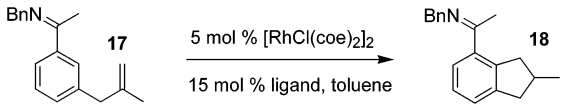


Table 1. Asymmetric Cyclization of Ketimine **17** Using Various Chiral Monophosphine Ligands



ligand	temp (°C)	time (h)	% yield **18**[a]	% ee[b]
1	125	20	5[c]	nd
2	125	20	trace[c]	nd
3	125	20	48[c]	8 (*S*)
4	125	20	9[c]	nd
5	75	6	99	35 (*R*)
6	100	6	56	23 (*S*)
7	75	20	93[c]	17 (*R*)
8	75	20	94[c]	9 (*R*)
9	75	20	91[c]	38 (*R*)
10	125	20	34[c]	0
11	125	20	6[c]	nd
12	125	2.5	15[c]	19 (*S*)
13	125	2.5	14[c]	0
14	125	2.5	52[c]	58 (*S*)
15	125	<2	100	83 (*S*)
16a	125	<2	100	88 (*S*)
16b	125	<2	99	87 (*S*)

[a] Yields based on ^{1}H NMR integration relative to 2,6-dimethoxytoluene internal standard. [b] Ees determined after hydrolysis of **18** with 1 N HCl (aq) using chiral GC or HPLC. Sense of induction is indicated in parentheses. [c] Remainder of mass balance is unreacted starting material.

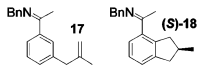
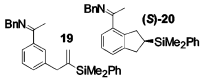
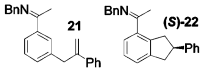
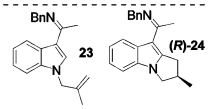
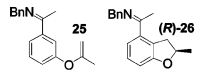
obtained with the (*S*)-binol-derived phosphoramidites **15**, **16a**, and **16b**.

Ketimine **17** cyclized quantitatively in the presence of 5 mol % $[RhCl(coe)_2]_2$ and 15 mol % **16a** to give **18** in 88% ee within 2 h at 125 °C. The sense of stereochemical induction is predominantly determined by the binol backbone of the phosphoramidite ligands; comparing diastereomers **16a** (88% ee, 125 °C) and **16b** (87% ee, 125 °C) shows that the stereochemistry of the amino group is insignificant. The phosphoramidite/Rh ratio in the cyclization of **17** was found to be optimal at 1.5 or 1; higher ratios significantly slow the reaction rate without affecting enantioselectivity.[6] This

† The Center for New Directions in Organic Synthesis is supported by Bristol-Meyers Squibb as a Sponsoring Member.

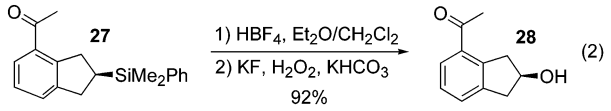
10.1021/ja0394986 CCC: $27.50

Table 2. Asymmetric Cyclization of Aromatic Imines[a,b]

Substrate	Product	Entry	Ligand	Temp (°C)	Time (h)	%yield[c]	%ee[d]
		1	**15**	125	2	100	83
		2[e]	**15**	50	48	65	93
		3	**16a**	125	2	100	88
		4	**16a**	**50**	**9**	**94**	**95**
		5	**16b**	125	2	99	87
		6[e]	**16b**	50	48	92	95
		**7**	**15**	**125**	**0.3**	**91**	**70**
		8	**16a**	125	0.25	98	22
		9	**16a**	50	20	75	25
		10	**16b**	125	0.25	100	27
		11	**16b**	50	20	96	42
		12	**15**	125	0.5	94	76
		13	**15**	75	4	100	83
		14	**16a**	125	1	99	80
		15	**16a**	**75**	**3**	**96**	**90**
		16	**16b**	125	0.5	95	79
		17	**16b**	75	3.5	98	90
		18[e]	**15**	125	12	78	63
		19[e]	**16a**	**125**	**1**	**90**	**70**
		20[e]	**16b**	125	1	99	68
		21	**15**	125	0.25	99	86
		22	**15**	50	>200	69	89
		23	**16a**	125	0.25	99	90
		24	**16a**	50	1.5	99	93
		25	**16a**	**rt**	**23**	**95**	**96**
		26	**16b**	125	0.25	99	91
		27	**16b**	50	1.5	99	95
		28	**16b**	rt	100	99	96

[a] Reactions performed using 5 mol % $[RhCl(coe)_2]_2$ and 15 mol % ligand in toluene-d_8. [b] Absolute configurations of **(*S*)-22** and **(*R*)-26** were assigned by chemical derivatization and X-ray structure determination (see Supporting Information). The absolute configurations of **(*S*)-18**, **(*S*)-20**, and **(*R*)-24** were assigned by analogy. [c] Yields based on ^{1}H NMR integration relative to 2,6-dimethoxytoluene internal standard. [d] Ees determined after hydrolysis of the imine product using chiral GC or HPLC. [e] Performed using 10 mol % ligand.

result suggests that only one ligand is bound to the metal in the active catalyst.



(2)

Due to the efficiency of the reaction with ligands **15**, **16a**, and **16b** at 125 °C, we lowered the temperature in hopes of further enhancing the enantioselectivity (Table 2). Indeed, at 50 °C, the cyclization of **17** using ligand **16a** proceeded with 95% ee and 94% yield in 9 h (Table 2, entry 4). It is noteworthy that the temperature is 75 °C lower than that required in our previously optimized study using Wilkinson's catalyst.[4a] Similar increases in ee were obtained using ligands **15** and **16b**, although reaction rates were not as high (Table 2, entries 2 and 6).

To explore the scope of this enantioselective cyclization reaction, substrates **19**, **21**, **23**, and **25** were evaluated using the optimal ligands (Table 2). At 125 °C, complete conversion was observed within 1 h for each ligand. Upon lowering the temperature to 50 or 75 °C, ligands **16a** and **16b** consistently provided more efficient reaction rates than ligand **15**, and **16a** was slightly more efficient than **16b**. Ligands **16a** and **16b** also provided higher enantioselectivities for all but the sterically encumbered silyl substrate **19** where the least hindered ligand **15** gave the optimal result (entry 7). Importantly, ketimine **19** is a versatile substrate, as the $SiMe_2Ph$ functionality can be stereospecifically converted into an OH group using conditions developed by Fleming[7] and Tamao[8] (eq 2). Styrenyl substrate **21** and indole **23** both cyclized rapidly, and ligand **16a** gave the best conversion and enantioselectivity (entries 15 and 19, respectively).

Vinyl ether **25** provides the most efficient reaction. At room temperature, the reaction proceeded cleanly with ligand **16a**, giving the desired product **26** in high yield and with 96% ee (entry 25). Here again, ligand **16b** is a less efficient catalyst but provides an ee as high as that obtained with diastereomer **16a** (entry 28).

The exceptional rates and enantioselectivities observed using the phosphoramidite ligands[6] may be due to their unique binding properties, which include reduced σ donation to rhodium and enhanced π acceptor ability compared to phosphines. The enantioselectivities are presumably due to highly diastereoselective migratory insertion of the olefin into the Rh−H bond after C−H activation.[9]

In summary, we have developed a highly enantioselective and efficient method for the intramolecular imine-directed C−H/olefin coupling reaction using chiral phosphoramidite ligands. Application of this methodology to other substrates and to the preparation of biologically relevant compounds is currently underway.

Acknowledgment. This work was supported by the NIH GM069559 (to J.A.E.) and the Director and Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy, under Contract DE-AC03-76SF00098 (to R.G.B.).

Supporting Information Available: Complete experimental details and spectral data for all compounds described (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For C−H activation reviews, see: (a) Kakiuchi, F.; Murai, S. *Top. Organomet. Chem.* **1999**, *3*, 47−79. (b) Guari, Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047−1055. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1699−1712. (d) Shilov, A. E.; Shul'pin G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (e) Arndtsen, B. A.; Bergman, R. G.; Mobley, A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154−162. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (g) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34* (8), 633−639.

(2) (a) Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatini, A.; Sonoda, M.; Chatani, N.; Murai, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62−83. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616−6623. (c) Lim, Y. G.; Kang, J. B.; Kim, Y. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2201−2206. (d) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371−5372. (e) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778−779. (f) Jun, C. H.; Hong, J. B.; Kim, Y. H.; Chung, K. Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 3440−3441.

(3) (a) For enantioselective aromatic C−H coupling to olefins, see: Mikami, K.; Hatano, M.; Terada, M. *Chem. Lett.* **1999**, *1*, 55−56. (b) For enantioselective alkene C−H coupling to olefins, see: Fujii, N.; Kakiuchi, F.; Yamada, A.; Chatani, N.; Murai, S. *Chem. Lett.* **1997**, 425−426. (c) For atropselective alkene coupling to biaryl compounds, see: Kakiuchi, F.; Le Gendre, P.; Yamada, A.; Ohtaki, H.; Murai, S. *Tetrahedron: Asymmetry* **2000**, *11* (13), 2647−2651. (d) For leading references on enantioselective hydroacylation, see: Taura, Y.; Tanaka, M.; Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron* **1991**, *47* (27), 4879−4888. Barnhart, R. W.; Wang, X.; Noheda, P.; Bergens, S. H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1994**, *116*, 1821−1830. (e) For a review of enantioselective C−H activation via metal-carbenoids, see: Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103* (8), 2861−2903. (f) For diastereoselective olefin insertion into chiral Zr complexes, see: Rodewald, S.; Jordan, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 4491−4492.

(4) (a) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123* (39), 9692−9693. (b) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5* (8), 1301−1303.

(5) (a) For TADDOL-derived ligands, see: Alexakis, A.; Burton, J.; Vastra, J.; Benhaim, C.; Fournioux, X.; van den Heuvel, A.; Levêque, J.-M.; Mazé, F.; Rosset, S. *Eur. J. Org. Chem.* **2000**, 4011−4027. (b) For binol-derived ligands, see: Feringa, B. L. *Acc. Chem. Res.* **2000**, *33* (6), 346−353.

(6) Similar results were observed in Rh-catalyzed hydrogenation using phosphoramidite ligands: van den Berg, M.; Minnaard, A. J.; Haak, R. M.; Leeman, M.; Schudde, E. P.; Meetsma, A.; Feringa, B. L.; de Vries, A. H. M.; Malijaars, C. E. P.; Willans, C. E.; Hyett, D.; Boogers, J. A. F.; Henderickx, H. J. W.; de Vries, J. G. *Adv. Synth. Catal.* **2003**, *345* (1&2), 308−323.

(7) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, *4*, 317. (b) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1.

(8) Tamao, K. *Adv. Silicon Chem.* **1996**, *3*, 1.

(9) This is assuming a mechanism analogous to that proposed by Jun et al. for the corresponding intermolecular reaction. See ref 2f.

JA0394986