J|A|C|S
COMMUNICATIONS

Published on Web 04/11/2006

All-Carbon Quaternary Centers via Catalytic Asymmetric Hydrovinylation. New Approaches to the Exocyclic Side Chain Stereochemistry Problem

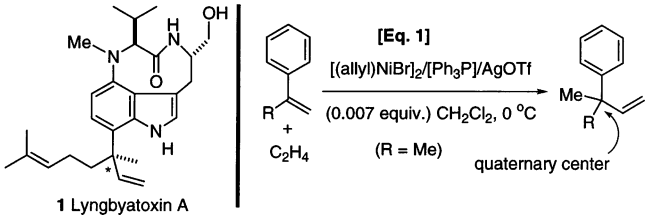
Aibin Zhang and T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

Received February 10, 2006; E-mail: rajanbabu.1@osu.edu

The search for new methods for stereoselective generation of all-carbon quaternary centers[1] is a subject of considerable topical interest, and several recent publications report catalytic procedures to accomplish this challenging goal.[2] While planning an enantioselective synthesis of Lyngbya toxin A,[3] which contains an all-carbon quaternary center at the benzylic position, we decided to investigate asymmetric hydrovinylation of substituted vinylarenes as a general way of constructing this asymmetric center. Since hydrovinylation[4] introduces a highly versatile latent functionality in the form of a vinyl group, the resulting intermediates could be quite valuable for further synthetic elaboration. Viability of such a reaction had indeed been demonstrated earlier in the hydrovinylation of 1-methylstyrene,[5a] using a protocol (eq 1)[5b] that was originally developed for the reaction between ethylene and vinylarenes. Subsequent work from our laboratories has expanded the scope and selectivity of the hydrovinylation reaction, and several new ligands[6] have been found useful for this exacting reaction. Recently, we also reported successful asymmetric hydrovinylation of strained olefins[6d] and of 1,3-dienes.[6h] In this paper, we report that highly enantioselective hydrovinylation[6b−e,h,8] of 1-alkylvinylarenes can be accomplished using phosphoramidite ligands[7] under highly tolerant conditions similar to what was developed for other reactions.

Generation of a Quaternary Center via Asymmetric Hydrovinylation



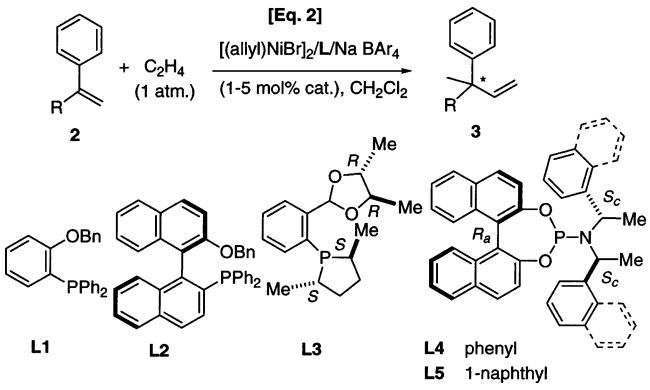
We began our studies with an examination of hydrovinylation of 1-ethylstyrene (**2**, R = Et) using ligands **L1**−**L5** (eq 2). The results of the scouting experiments are listed in Table 1. A sample of the racemic product was prepared in a reaction of ethylene with 1-ethylstyrene in the presence of catalytic amounts of [(allyl)NiBr]$_2$, [*o*-(benzyloxy)phenyl]diphenylphosphine, and Na B(3,5-bistrifluoromethylphenyl)$_4$ [Na BARF] (Table 1, entry 1). We have previously employed this ligand for the hydrovinylation of dienes.[6h]

Catalysts derived from the MOP ligand (**L2**)[5a] showed no reactivity, while those derived from phospholane ligand **L3**[6g,9] which gave high enantiomeric excesses and turnover numbers in the hydrovinylation of a number of styrene derivatives, showed only moderate reactivity under similar conditions (entries 2−4). Among the chiral ligands we examined, the phosphoramidite **L4** was found to provide the best results. Ligand **L4**, a phosphoramidite with an *N*-1-phenylethyl substituent, when treated with [(allyl)NiBr]$_2$ followed by Na BARF gave a very active precatalyst that effects the hydrovinylation of 1-ethylstyrene at −70 °C (4 h), with as little as 1 mol % of catalyst to give a quantitative reaction (entry10).[10] Under these conditions, no isomerization [to (*Z*)- and (*E*)-1,2-dimethylstyrenes] or oligomerization products were detected, as judged by careful GC analysis and ^{1}H NMR spectroscopy. The yields and selectivities are highly reproducible, and as expected, best selectivity is observed at low temperatures. They are independent of the catalyst loading (entries 8−10), indicating the total absence of background reactions. Use of a bulkier phosphoramidite ligand carrying an *N*-1-naphthylethyl substituent leads to lower activities and selectivities (entries 11 and 12).

Table 1. Asymmetric Hydrovinylation of 1-Ethylstyrene[a]

entry	ligand (mol %)	temp (°C)	time (h)	conv. (%)	ee (%, conf.)[b,c]
1	**L1**/5	25	48	<74[d]	−
2	**L3**/5	−10	16	<67[d]	27 (*R*)
3	**L3**/5	0	19	<76[d]	27 (*R*)
4	**L3**/5	25	22	<72[d]	25 (*R*)
5	**L4**/5	−10	21	>99	79 (*R*)
6	**L4**/5	−30	17	>99	77 (*R*)
7	**L4**/5	−55	19	>99	88 (*R*)
8	**L4**/5	−70	17	>99	93 (*R*)
9	**L4**/5	−70	4	>99	96 (*R*)
10	**L4**/1	−70	4	>99	95 (*R*)
11	**L5**/1	−70	4	<5	−
12	**L5**/1	−10	4	<15	37 (*R*)

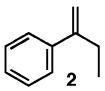
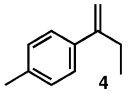
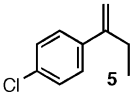
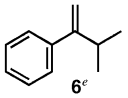
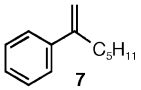
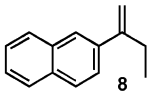
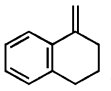
[a] See Supporting Information for experimental details. [b] Determined by GC analysis on a cyclodex-B column. [c] Configuration assigned by comparison of GC retention times with those of a known compound.[2g] [d] Uncertainty results from the volatility of the starting material.



Hydrovinylation of several 1-alkylstyrene derivatives was attempted under the optimal conditions, and the results are tabulated in Table 2. While the 4-methyl substrate **4** gave excellent selectivity for the formation of the expected product, the 4-chloro derivative **5** gave up to 5% isomerization of the starting olefin (entry 3). A similar minor side reaction was also observed for the substrates **7** and **9**. An isopropyl group at the 1-position of the styrene (**6**) retards the reaction (entry 4), and it is best accomplished at 24 °C with 10 mol % catalyst. Even though the yield of the reaction is only

10.1021/ja060999b CCC: $33.50

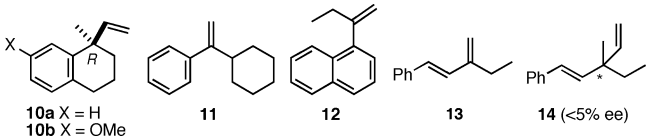
Table 2. Asymmetric Hydrovinylation of 1-Alkylvinylarenes[a]

no.	vinylarene	*T* (°C)/ *t* (h)	conv./ yield	sel.[b]	ee (%)[c]
1.	 **2**	–70/4	>99/>95	>99	>95
2.	 **4**	–60/12	>99/>90	>99	90
3.	 **5**	–70/11	>94/>90	>95[d]	90
4.	 **6**[e]	24/20	61[f]/60	>97	>95
5.	 **7**	–70/8	>98/93	>96[d]	>50[g]
6.	 **8**	–70/14	>99/>98	>99	93
7.	 **9**	–70/4	>98/70	71[d]	>95

[a] See eq 2 for details. [b] Selectivity for HV product. [c] Determined by GC, *R* isomer of **3**; all others assigned by analogy to **3**. Product from **9** (entry 7) assigned by comparison of $[\alpha]^{25}_{D}$ with that of a related compound.[11b] See Supporting Information for details. [d] Rest isomerized product from starting material. [e] 10 mol % catalyst used. [f] Rest starting material. [g] Enantiomeric excess determined via Mosher esters of hydroboration product.[10]

moderate, very high enantiomeric excess (~97%) was observed for the isolated product. The 2-naphthyl derivative **8** gave excellent yield (>98%) and selectivity (>99%) for the expected product. The tetralin derivative **9** represents a different class of substrates that underwent the hydrovinylation reaction giving >95% ee. Significant isomerization (~30%) of the starting material to an endocyclic olefin is a major distraction of this otherwise useful reaction. Compounds (e.g., **10b**) structurally related to the HV product **10a** from **9** have been synthesized previously via intramolecular asymmetric Heck reactions (~93% ee),[11a] stoichiometric oxazoline directed alkylation (~99% ee),[11b] and enzyme-catalyzed desymmetrization of a chiral malonate (97% ee).[11c] By comparison, the asymmetric hydrovinylation route is significantly shorter (2 steps from 1-tetralone vs >10 steps), and operationally simpler.

Among the other olefins **11**−**13**, only the acyclic diene **13** undergoes hydrovinylation at low temperatures, and the product **14** is formed in nearly racemic form, contaminated with product of ethylene addition at the benzylic position.



10a X = H **10b** X = OMe **11** **12** **13** **14** (<5% ee)

In summary, we have demonstrated the feasibility of a new catalytic method for the generation of quaternary centers. Expansion of the scope of this reaction to heteroaromatic compounds, cyclic and acyclic dienes, and bicyclic molecules will be reported in due course.

Acknowledgment. Financial assistance for this research by U.S. National Science Foundation (CHE-0308378) and the Petroleum Research Fund of the American Chemical Society (36617-AC1) is gratefully acknowledged.

Supporting Information Available: Full experimental details of typical hydrovinylation reaction, spectroscopic and chromatographic data for characterization of compounds listed. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews and history of the problem, see: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363 and references therein. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (c) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (d) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (e) Martin, S. F. *Tetrahedron* **1980**, 36, 419.

(2) For some recent notable accomplishments in this area that rely on diverse strategies, see: (a) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925. (b) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168. (c) Augustin, M. D.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (d) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (e) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. (f) Mermerian, A. H.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 5604. (g) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877. (h) Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988. (i) Xu, K.; Lalic, G.; Sheehan, S. M.; Shair, M. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2259. (j) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11943. (k) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533.

(3) (a) Edwards, D. J.; Gerwick, W. H. *J. Am. Chem. Soc.* **2004**, *126*, 11432. For synthesis, see: (b) Muratake, H.; Natsume, M. *Tetrahedron* **1991**, *4*, 8535. (c) Kozikowski, A. P.; Shum, P. W.; Basu, A.; Lazo, S. *J. Med. Chem.* **1991**, *34*, 2420. (d) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1987**, *28*, 2265.

(4) (a) For recent reviews, see: (a) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845. (b) Jolly, P. W.; Wilke, G. Hydrovinylation. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: New York, 1996; Vol. 2, p 1024.

(5) (a) RajanBabu, T. V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* **2003**, *68*, 8431. (b) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459.

(6) Phosphinites: (a) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734. Phosphoramidites: (b) Franció, G.; Faraone, F.; Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736. (c) Hölscher, M.; Franciò, G.; Leitner, W. *Organometallics* **2004**, *23*, 5606. (d) Kumareswaran, R.; Nandi, N.; RajanBabu, T. V. *Org. Lett.* **2003**, *5*, 4345. (e) Park, H.; Kumareswaran, R.; RajanBabu, T. V. *Tetrahedron* **2005**, *61*, 6352. Phospholanes: (f) Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899. (g) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515. Phosphoramidites and phospholanes have also been used for highly enantioselective hydrovinylation of 1,3-dienes: (h) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 54.

(7) Arnold, L, A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.

(8) While this manuscript was being readied for publication, a closely related paper appeared on the Internet, which has since appeared in press: Shi, W.-J.; Zhang, Q.; Xie, J.-H.; Zhu, S.-F.; Hou, G.-H.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2006**, *128*, 2780. Advantages of our method include the use of a readily available ligand (Strem Chemicals), low catalyst loading (1% vs 10%), higher yields, and higher overall selectivities for a number of substrates.

(9) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 3159.

(10) See Supporting Information for details.

(11) (a) Takemoto, T.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 8477 (corrections: ibid *J. Am. Chem. Soc.* **1994**, *116*, 11207). (b) Hulme, A, N.; Henry, S. S.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 1265. (c) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 371.

JA060999B