ORGANIC
LETTERS

2006
Vol. 8, No. 17
3801−3804

# Platinum-Catalyzed Intramolecular Asymmetric Hydroarylation of Unactivated Alkenes with Indoles

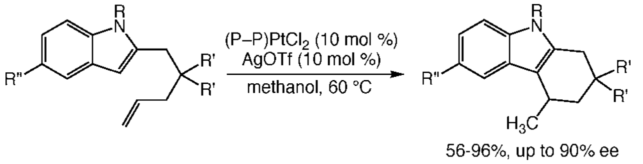
**Xiaoqing Han and Ross A. Widenhoefer***

*Duke University, P. M. Gross Chemical Laboratory,*
*Durham, North Carolina 27708-0346*

*rwidenho@chem.duke.edu*

**Received June 12, 2006**

## ABSTRACT



**A 1:1 mixture of the platinum bis(phosphine) complex [(*S*)-4]$PtCl_2$ [(*S*)-4 = (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP] catalyzes the intramolecular asymmetric hydroarylation of 2-(4-pentenyl)indoles in moderate to good yield with up to 90% ee.**

The transition metal-catalyzed addition of an aromatic C−H bond across the C═C bond of an unactivated alkene (hydroarylation) is an area of current interest relevant to both organic synthesis and industrial-scale functionalization of hydrocarbon feedstocks.[1−6] A number of different catalysts have been developed for the hydroarylation of unactivated alkenes including Rh(I),[1] Ru(II),[2] Ru(III),[3] Ir(III),[4] and Zr(IV)[5] complexes. Lacking, however, are general and efficient methods for the asymmetric hydroarylation of unactivated alkenes. Examples of effective asymmetric hydroarylation are exceedingly rare and have been restricted to arenes that possess an imine directing group.[6]

Polycyclic indole derivatives such as carbazoles and their partially saturated counterparts constitute an important class of naturally occurring, biologically active molecules.[7] For this reason, the development of new and efficient methods for the synthesis of polycyclic indole derivatives continues to attract considerable attention. As part of a program directed toward the development of new catalytic methods for the hydrofunctionalization of unactivated alkenes with carbon,[8,9] nitrogen,[10] and oxygen[11] nucleophiles, we have recently reported the platinum-catalyzed intramolecular hydroarylation of unactivated alkenes.[9] As an example, reaction of 1-methyl-

---

(1) (a) Tan, K. L.; Park, S.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2004**, *69*, 7329. (b) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2005**, *70*, 6775. (c) Wiedemann, S. H.; Ellman, J. A.; Bergman, R. G. *J. Org. Chem.* **2006**, *71*, 1969. (d) Wiedemann, S. H.; Lewis, J. C.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2006**, *128*, 2452. (e) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692. (f) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301. (g) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964. (h) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685. (i) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616.

(2) (a) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826 and references therein. (b) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506.

(3) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581.

(4) (a) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414. (b) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Mol. Catal. A: Chem* **2002**, *180*, 1.

(5) Jordan, R. F.; Taylor, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 778.

(6) (a) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496. (b) Thalji, R. K.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2004**, *126*, 7192. (c) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2006**, *8*, 1745.

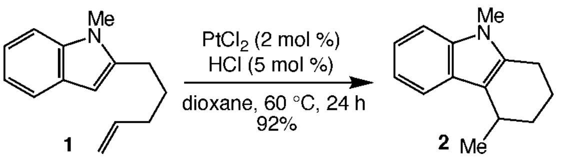
(7) (a) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (c) Saxton, J. E. *Nat. Prod. Rep.* **1997**, 559.

(8) (a) Widenhoefer, R. A. *Pure Appl. Chem.* **2004**, *76*, 671 and references therein. (c) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem.*−*Eur. J.* **2004**, *10*, 6333. (d) Qian, H.; Pei, T.; Widenhoefer, R. A. *Organometallics* **2005**, *24*, 287. (e) Liu, C.; Widenhoefer, R. A. *Tetrahedron Lett.* **2005**, *46*, 285.

(9) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700.

10.1021/ol061441b CCC: $33.50

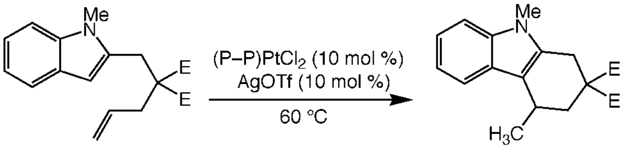
2-(4-pentenyl)indole (**1**) with a catalytic amount of $PtCl_2$ (2 mol %) in dioxane that contained a trace of HCl (5 mol %) at 60 °C for 24 h led to isolation of tetrahydrocarbazole **2** in 92% yield (eq 1). The efficiency and stereoselectivity of Pt(II)-catalyzed hydroarylation pointed to the potential development of an analogous asymmetric hydroarylation protocol. Indeed, here we report the platinum-catalyzed asymmetric intramolecular hydroarylation of unactivated alkenes with indoles.[12]



We initially targeted the known dicationic platinum dimer $[(BINAP)Pt(\mu\text{-}Cl)]_2(OTf)_2$[13] as a catalyst for asymmetric hydroarylation on account of the diverse range of catalytic asymmetric transformations that employ BINAP as a supporting ligand.[14] Although a 1:1 mixture of [(*S*)-BINAP]$PtCl_2$ and AgOTf was an active catalyst for the intramolecular hydroarylation of alkenyl indole **3**, no significant asymmetric induction was observed (Table 1, entry 1). However, subsequent experimentation identified (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP [(*S*)-**4**] as an effective ligand for Pt-catalyzed asymmetric hydroarylation (Table 1). In an optimized protocol,[15] treatment of **3** with a catalytic 1:1 mixture of [(*S*)-**4**]$PtCl_2$ and AgOTf (10 mol %) at 60 °C in methanol for 20 h led to isolation of tetrahydrocarbazole **5** in 93% yield with 90% ee (Table 1, entry 10).[16]

Several points regarding the optimization of the conversion of **3** to **5** are worth noting. First, no effort was made to exclude air or moisture in these experiments. Second, the enantioselectivity of intramolecular hydroarylation increased with the increasing steric bulk of the P-bound aryl groups, in particular, the meta substituents of these aryl groups (Table 1, entries 1−6). This behavior has been observed previously in the context of asymmetric hydrogenation,[17] Heck coupling,[18,19] allylic alkylation,[18] and allylic amination.[20] Third, the enantioselectivity of the conversion of **3** to **5** increased with the increasing donicity/polarity of the solvent (Table 1, entries 6−11), although employment of strongly donating solvents led to a significant decrease in reaction rate (Table 1, entry 7).[15] Fourth, although the nature of the silver source had no significant effect on the reaction (Table 1, entries 10 and 11),[15] the Pt/Ag ratio was important. In particular, employment of a 1:2 ratio of Pt/Ag led to a significant decrease in both the yield and the enantioselectivity of hydroarylation (Table 1, entries 3 and 4). This observation suggests that monomeric dicationic platinum complexes are not effective catalysts for asymmetric hydroarylation.[13]

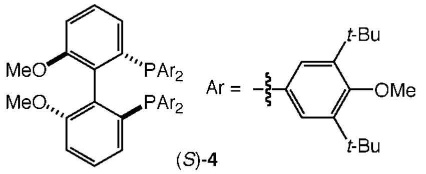
**Table 1.** Effect of Ligand and Solvent on the Platinum-Catalyzed Asymmetric Hydroarylation of **3**



**3** (E = $CO_2Me$)

**5**

| entry | P–P | solvent | time (h) | yield[a] (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | (*S*)-BINAP | dioxane | 22 | 82 | ≤5 |
| 2 | (*S*)-Tol-BINAP | dioxane | 24 | 83 | 21 |
| 3 | (*R*)-3,5-Xylyl-BINAP | dioxane | 24 | 81 | 41 |
| 4 | (*R*)-3,5-Xylyl-BINAP | dioxane | 24 | 66 | 21[b] |
| 5 | (*R*)-3,5-*i*-Pr-MeOBIPHEP | dioxane | 24 | 86 | 63 |
| 6 | (*S*)-**4** | dioxane | 23 | 88 | 87 |
| 7 | (*S*)-**4** | $CH_3CN$ | 24 | 7 | —[c] |
| 8 | (*S*)-**4** | THF | 23 | 92 | 89 |
| 9 | (*S*)-**4** | acetone | 21 | 83 | 90 |
| 10 | (*S*)-**4** | MeOH | 20 | 93 | 90 |
| 11 | (*S*)-**4** | MeOH | 20 | 95 | 89[d] |



(*S*)-**4**

[a] Isolated product ≥95% purity. [b] AgOTf (20 mol %) was employed. [c] Enantiomeric purity not determined. [d] $AgBF_4$ (10 mol %) was employed.

Asymmetric hydroarylation of 2-alkenyl indoles catalyzed by a 1:1 mixture of [(*S*)-**4**]$PtCl_2$ and AgOTf tolerated either an *N*-benzyl or an *N*-allyl group and either an electron-donating or an electron-withdrawing group on the indole moiety (Table 2, entries 1−4). The protocol tolerated heteroatom and alkyl substitution at the C(1) or C(2) position of the 4-pentyl chain, although the bis(pivaloate)-substituted indole **6** cyclized with low enantioselectivity (Table 2, entries 5−9). Similarly, 2-(1,1-dimethyl-4-pentenyl)indole cyclized

---

(10) (a) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (b) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070. (c) Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649. (d) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635.

(11) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536.

(12) A preliminary result in this area has been described[9] but was unfortunately reported incorrectly. See: Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10493.

(13) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19*, 5160.

(14) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) C*atalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000.

(15) See the Supporting Information for a more detailed description of the optimization studies.

(16) Two control experiments ruled out the possibility of acid- or silver-catalyzed asymmetric hydroarylation. In one experiment, a solution of **3** that contained a catalytic mixture of (*S*)-**4** (10 mol %), HCl (10 mol %), and HOTf (10 mol %) in methanol was heated at 60 °C for 24 h. GC analysis of the crude reaction mixture revealed no consumption of **3**. In a second experiment, a solution of **3** and a catalytic mixture of (*S*)-**4** (10 mol %) and AgOTf (5 mol %) in methanol was heated at 60 °C for 24 h. GC analysis of the crude reaction mixture again revealed no consumption of **3**.

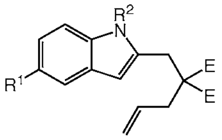
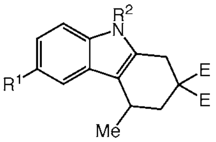
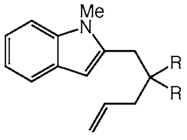
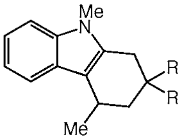
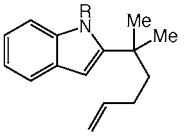
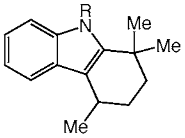
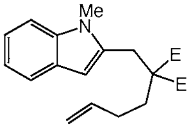
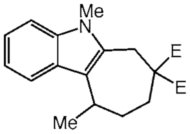
(17) (a) RajanBabu, T. V.; Ayers, T. A.; Casalnuovo, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 4101. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Müller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131. (c) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867.

(18) Trabesinger, G.; Albinati, A.; Feiken, N.; Kunz, R. W.; Pregosin, P. S.; Tschoerner, M. *J. Am. Chem. Soc.* **1997**, *119*, 6315.

(19) Tschoerner, M.; Pregosin, P. S. *Organometallics* **1999**, *18*, 670.

(20) (a) Selvakumar, K.; Valentini, M.; Pregosin, P. S. *Organometallics* **2000**, 19, 1299. (b) Faller, J. W.; Wilt, J. C. *Org. Lett.* **2005**, *7*, 633.

**Table 2.** Asymmetric Hydroarylation of 2-Alkenyl Indoles Catalyzed by a Mixture of [(*S*)-4]$PtCl_2$ (10 mol %) and AgOTf (10 mol %) in Methanol at 60 °C for 20−48 h (*e* = $Co_2Me$)

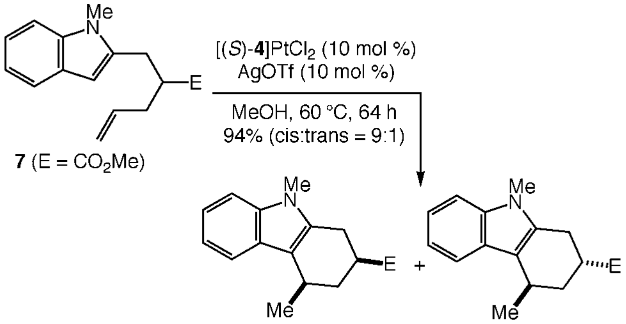
| entry | alkenyl indole | product | yield[a] (%) | ee (%) |
|---|---|---|---|---|
| |  |  | | |
| 1 | $R^1$ = H, $R^2$ = Bn | | 93 | 88 |
| 2 | $R^1$ = H, $R^2$ = allyl | | 91 | 87 |
| 3 | $R^1$ = OMe, $R^2$ = Me | | 96 | 87 |
| 4 | $R^1$ = F, $R^2$ = Me | | 93 | 88 |
| |  |  | | |
| 5 | R = $CH_2OH$ | | 82 | 73 |
| 6 | R = $CH_2OPiv$ (**6**) | | 94 | 48 |
| 7 | R = COO*t*-Bu | | 56 | 86 |
| 8 | R = Me | | 90 | 68 |
| |  |  | | |
| 9 | R = Me | | 93 | 71 |
| 10 | R = H | | 90 | 47 |
| 11 |  |  | 69 | 74 |

[a] Isolated product of ≥95% purity.

in good yield but with low enantioselectivity (Table 2, entry 10). Platinum-catalyzed asymmetric hydroarylation was also applied to the formation of a seven-membered ring (Table 2, entry 11).

We sought to evaluate the effect of an existing asymmetric carbon atom on the stereoselectivity of platinum-catalyzed hydroarylation. To this end, treatment of **7**, which possessed a single carbomethoxy group at the C(2) position of the 4-pentenyl group, with a catalytic 1:1 mixture of [(*S*)-**4**]$PtCl_2$ and AgOTf (10 mol %) at 60 °C for 64 h led to the isolation of **8** in 94% yield as a 9:1 mixture of cis (*cis*-**8**) and trans (*trans*-**8**) isomers (Scheme 1).[21] Whereas the major diastereomer *cis*-**8** was formed with no significant enantiomeric purity (≤5% ee), *trans*-**8** was formed with ≥90% ee. This result indicates that the stereochemistry of the substrate and not the catalyst is most responsible for determining the stereochemistry of the product. The preferential formation of *cis*-**8** from the catalytic hydroarylation of **7** appears to be a general feature of cationic platinum bis(phosphine) complexes. For example, reaction of **7** with a catalytic 1:1 mixture of [(±)-BINAP]$PtCl_2$ and AgOTf (10 mol %) formed a 25:1 mixture of *cis*-**8** and *trans*-**8** in 93% yield. In contrast, the reaction of **7** with a catalytic mixture of $PtCl_2$ (2 mol %) and HCl (5 mol %) formed a 1:2 mixture of *cis*-**8** and *trans*-**8** in 98% yield.[9]

**Scheme 1**



**7** (E = $CO_2Me$)

*cis*-**8** (≤ 5% ee) *trans*-**8** (≥ 90% ee)

Because platinum complexes of the form $[(P-P)PtCl]^+$ are known to form stable dicationic chloride-bridged dimers,[13] we probed for the potential involvement of dicationic platinum complexes in the catalytic hydroarylation of alkenyl indoles. To this end, the enantioselectivity of the conversion of **3** to **5** catalyzed by a 1:1 mixture of (3,5-Xylyl-BINAP)-$PtCl_2$ (**9**) and AgOTf was determined as a function of the enantiomeric purity of **9** over the range 0−99% ee. The linear plot of the enantiomeric purity of **5** versus the enantiomeric purity of **9** strongly suggests that the active catalyst is monomeric and that dicationic diplatinum complexes are either not formed or dissociate rapidly under reaction conditions (Figure 1).[22]

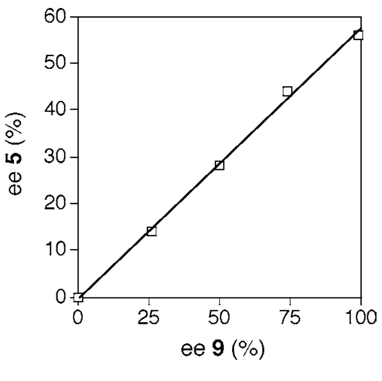


**Figure 1.** Plot of the enantiomeric purity of **5** vs the enantiomeric purity of (3,5-xylyl-BINAP)$PtCl_2$ (**9**) for the conversion of **3** to **5** catalyzed by a 1:1 mixture of **9** and AgOTf in methanol at 60 °C.

In summary, we have developed a mild and efficient Pt-catalyzed protocol for the asymmetric hydroarylation of 2-(4-pentenyl)indoles. We continue to work toward the identification of more-effective catalysts for the asymmetric

---

[21] Compounds **8** were isolated along with ~5% of an unidentified impurity. Analytically pure 25:1 and 1:2 mixtures of *cis*-**8** and *trans*-**8** were obtained through cyclization of **7** catalyzed by [(±)-BINAP]$PtCl_2$/AgOTf and $PtCl_2$,[9] respectively.

[22] Girard, C.; Kagan, H. B. *Angew Chem., Int. Ed.* **1998**, *37*, 2922.

hydroarylation of alkenes and toward the elucidation of the mechanism of Pt-catalyzed asymmetric hydroarylation.

**Acknowledgment** is made to the NSF (CHE-0304994 and CHE-0555425) for support of this research. We thank Dr. Rudolf Schmid (Hoffmann−La Roche) for a generous gift of (*R*)-3,5-*i*-Pr-MeOBIPHEP and (*S*)-**4**.

**Supporting Information Available:** Experimental procedures and spectroscopic data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL061441B