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Highly Enantioselective Quinoline Synthesis via Ene-type Cyclization of 1,7-Enynes Catalyzed by a Cationic BINAP−Palladium(II) Complex

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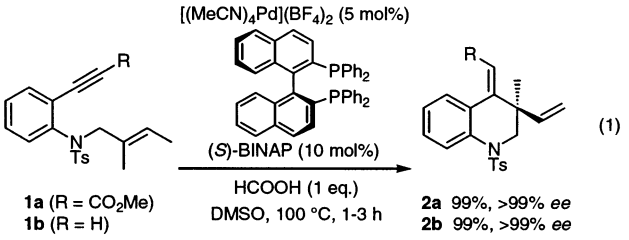
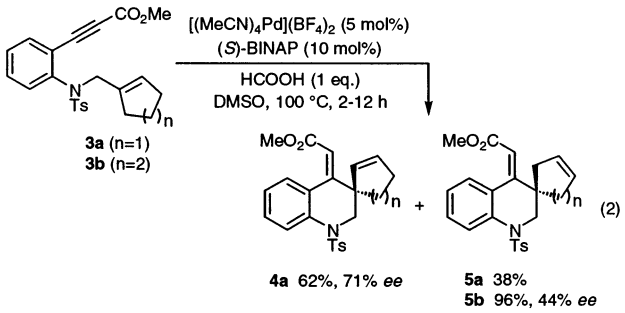
Catalytic asymmetric syntheses of chiral quinoline derivatives are of great importance, because many biologically and pharmacologically active alkaloids bear this skeleton.[1,2] Thermal and transition metal-catalyzed[3] syntheses of quinolines have thus been amply investigated. For the construction of these heterocycles, the cycloisomerization and ene-type cyclization of 1,6-enynes catalyzed by transition metal complexes to form a five-membered ring have attracted much interest.[4] Asymmetric versions with high enantiomeric excesses have been developed by using chiral Rh and Pd complexes as catalysts.[5−8] Despite the synthetic potential of 1,7-enyne, there has been no report of transition metal-catalyzed asymmetric six-membered ring formation from 1,7-enyne, due to the difficulty in forming a six-membered ring as compared to forming a five-membered ring. Herein, we report the first efficient asymmetric synthesis of six-membered quinoline derivatives bearing a quaternary carbon center or a spiro-ring, by the ene-type cyclization of 1,7-enynes catalyzed by the cationic BINAP−Pd(II) complex.[9,10]



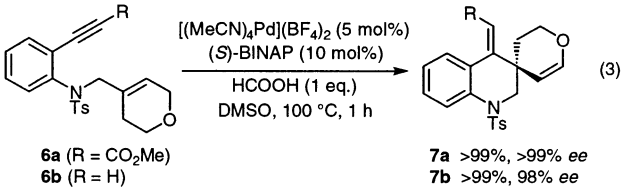
The reaction of 1,7-enynes was performed by a combination of 5 mol % of a cationic Pd(II) catalyst such as $[(MeCN)_4Pd](BF_4)_2$, 10 mol % of (*S*)-BINAP as a chiral bidentate PP-ligand, and 1 equiv of formic acid, in DMSO. Cyclization of substrate **1** leads to quinoline **2** with a quaternary carbon center (eq 1). For **1a**, of which the terminal acetylene is functionalized by a carbomethoxy group, cyclization gave **2a** as a *single enantiomer* and in quantitative yield within 3 h. Substrate **1b** also cyclized under the same conditions within 1 h to afford the corresponding chiral quinoline **2b** bearing an exomethylene moiety. Remarkably, the presence of this highly reactive terminal acetylene does not lead to side reactions such as polymerizations.[11] By contrast, aryl- or silyl-protecting groups (R = Ph or Me_3Si) could not give the corresponding quinolines at all, leading to the full recovery of starting materials. Moreover, the *ortho*-substituted benzene skeleton is essential, because non-benzo-fused 1,7-enynes provide no six-membered products.

The formation of these quinolines can be easily followed by the variation of coloration of the reaction. Usually, the color of the mixtures containing Pd(II) species is yellow to dark red-brown for the common palladium-catalyzed reactions such as the Mizoroki−Heck reaction, the Suzuki−Miyaura cross-coupling reaction, the allylation reaction, or even the ene-type cyclization.[12] However, in the present ene-type reactions leading to the chiral quinolines, the coloration changed from the initial light yellow to deep green after only 2 min at 100 °C. The color was deep green, but the mixture was still a clear solution. The color became pale as the reactions proceeded, and finally turned yellow-orange.

The success in the enantioselective quinoline-cyclizations of **1** to **2** prompted us to challenge the enantioselective construction of spiro-quinoline rings. Enyne substrate **3a**, which has a five-membered cyclic olefin, gave the desired spiro-ring product **4a** but in 62% yield and 71% ee, along with the *achiral* olefin-migration[13] product **5a** (38% yield) (eq 2). The six-membered ring substrate



3b gave completely olefin-migrated spiro-quinoline **5b** as the sole product (96%) with 44% ee. The moderate yield and/or enantioselectivity obtained for **4** and **5** might be due to the migration of the olefin at this high temperature and long reaction time: The desired product **4a** was indeed, under the reaction conditions, transformed to **5a** by the Pd(II) catalyst. To avoid this olefin-migration problem and to clarify the real enantioselectivity for spiro-systems, transformation of substrate **6**, with a pyran as a cyclic olefin, was examined (eq 3).



With both functionalized and naked terminal acetylenes, cyclizations of **6a** and **6b** proceeded successfully to give **7a** and **7b**, respectively, achieving the spiro-ring formation in quantitative yield and 98% ee. The structures of the spiro-pyran products **7a** and **7b** were confirmed by X-ray diffraction analysis.[14,15] The ORTEP drawings are shown in Figure 1. For **7a**, a π-stacking interaction between the tosyl moiety and methyl ester moiety is observed, with a nearest length of only 3.59 Å. On the other hand, in **7b**, the tosyl moiety is directed outside, and no π-stacking structure is observed.

Finally, the spiro-quinoline formation was applied to a large membered ring. Substrate **8**, bearing a 15-membered cyclic olefin

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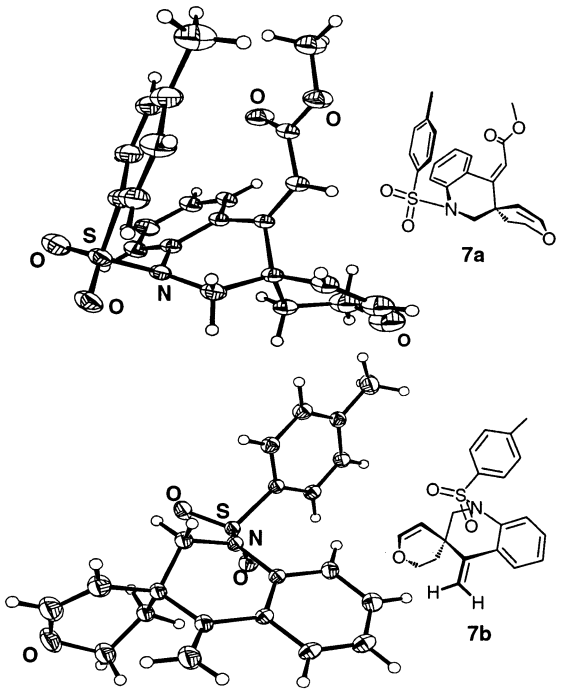
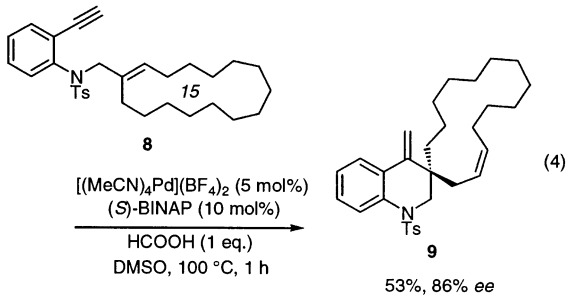


Figure 1. ORTEP drawings of the spiro-quinolines **7a** and **7b**.

and a terminal acetylene, was cyclized under the previously described conditions to give the olefin migration product **9** in moderate yield (53%) but good enantioselectivity (86% ee) (eq 4).



(4)

In conclusion, we have developed a highly enantioselective method for the synthesis of quinoline via ene-type cyclization of 1,7-enynes catalyzed by the cationic BINAP−palladium(II) complex. This is the first example of asymmetric ene-type cyclization affording six-membered ring compounds, with a quaternary carbon center or a spiro-ring.

Acknowledgment. This work is dedicated to Professor Frederick E. Ziegler of Yale University on the occasion of his 65th birthday on March 29, 2003.

Supporting Information Available: Typical experimental procedures and spectral data for **1**−**9** and crystallographic data collection parameters for spiro-ring products (**4a**, **7a**, **7b**) (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystal data for **7a** in X-ray analysis: formula $C_{23}H_{23}NO_5S$, triclinic, space group *P*-1 (No. 2), $a = 8.7188(5)$ Å, $b = 14.5607(7)$ Å, $c = 8.5946(5)$ Å, $\alpha = 99.563(3)°$, $\beta = 89.5260(1)°$, $\gamma = 73.718(4)°$, $V = 1031.05(10)$ Å^3, $Z = 2$, and $D = 1.371$ g cm^{-3}. X-ray diffraction data were collected on a Rigaku R-AXIS CS diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71069$ Å) at − 40 °C, and the structure was solved by direct methods (SIR97). The final cycle of full-matrix least-squares refinement was based on 4233 observed reflections ($I > 3\sigma(I)$) and 271 variable parameters and converged to $R = 0.0647$ and $R_w = 0.1817$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-196469. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
(15) Crystal data for **7b** in X-ray analysis: formula $C_{21}H_{21}NO_3S$, monoclinic, space group $P2_1/c$ (No. 14), $a = 9.3996(2)$ Å, $b = 19.4020(4)$ Å, $c = 9.8885(2)$ Å, $\beta = 92.8800(1)°$, $V = 1801.10(6)$ Å^3, $Z = 4$, and $D = 1.355$ g cm^{-3}. X-ray diffraction data were collected on a Rigaku R-AXIS CS diffractometer with graphite-monochromated Mo Kα ($\lambda = 0.71069$ Å) at −40 °C, and the structure was solved by direct methods (SIR97). The final cycle of full-matrix least-squares refinement was based on 4115 observed reflections ($I > 3\sigma(I)$) and 235 variable parameters and converged to $R = 0.0508$ and $R_w = 0.1391$. Crystallographic data have been deposited as no. CCDC-196470.

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