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Catalyzed Asymmetric Diels–Alder Reaction of Benzoquinone. Total Synthesis of (–)-Ibogamine†

James D. White* and Younggi Choi

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@orst.edu

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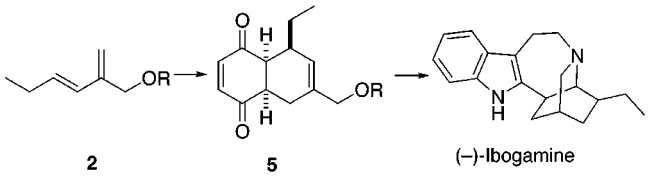
ABSTRACT



2 5 (–)-Ibogamine

The Diels–Alder addition of diene 2 with benzoquinone catalyzed by (*S*)-BINOL–$TiCl_2$ produced cycloadduct 5 in >65% yield and 87% ee. The cycloadduct was transformed into (–)-ibogamine in nine steps (10% overall yield from benzoquinone). A model for the transition state leading to 5 is proposed.

The catalyzed asymmetric Diels−Alder reaction is among the most powerful constructs for assembling a six-membered ring in a stereocontrolled fashion.[1] Many cycloadditions of this class rely on two-point ligation of a chiral catalyst to the dienophile, often a β-dicarbonyl system, so that only one face of the dienophile is exposed to the diene partner. Single-point ligation of an achiral dienophile to an asymmetric catalyst will generally require a secondary interaction, either electronic or steric, between the dienophile and catalyst for good enantioselectivity. A few catalyzed asymmetric Diels−Alder reactions of this latter type have been reported,[2] including one involving naphthoquinone,[3] but to our knowledge none has involved benzoquinone as the dienophile. We now describe a cycloaddition of benzoquinone to an achiral diene which proceeds with high enantioselectivity in the presence of a chiral catalyst, and we further demonstrate the utility of this process in an asymmetric synthesis leading to the indole alkaloid (−)-ibogamine (**1**).[4,5]

The diene **2** selected for this study was prepared from 1-butyne by hydroboration with catecholborane[6] followed by Suzuki cross-coupling[7] with bromo ether **3**. Completion of the uncatalyzed cycloaddition of benzoquinone to **2** required several hours at 80 °C, although the reaction was cleanly *endo* selective. By contrast, the reaction of **2** with benzoquinone in the presence of the (*S*)-BINOL complex **4**[3] (30 mol %) was complete in 0.5 h at room temperature and afforded the unstable *endo* adduct **5** in good yield. This diketone was reduced under Luche conditions[8] to give hydroxy ketone **6** (65% from **2**) which was converted to its

† This paper is dedicated to the memory of Professor George Büchi.

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(4) Previous syntheses of (±)-**1**: (a) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1965**, *87*, 2073. (b) Büchi, G.; Coffen, D. L.; Kocsis, K.; Sonnet, P. E.; Ziegler, F. E. *J. Am. Chem. Soc.* **1966**, *88*, 3099. (c) Sallay, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 6762. (d) Nagata, W.; Hirai, S.; Okumura, T.; Kawata, K. *J. Am. Chem. Soc.* **1968**, *90*, 1650. (e) Ikezaki, M.; Wakamatsu, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1969**, 88. (f) Rosenmund, P.; Haase, W. H.; Bauer, J.; Frische, R. *Chem. Ber.* **1975**, *108*, 1871. (g) Atta-ur-Rahman; Beisler, J. A.; Harley-Mason, J. *Tetrahedron* **1980**, *36*, 1063. (h) Imanishi, T.; Yagi, N.; Hanaoka, M. *Chem. Pharm. Bull.* **1985**, *33*, 4202. (i) Huffman, J. W.; Shanmugasundaram, G.; Sawdaye, R.; Raveendranath, P. C.; Desai, R. C. *J. Org. Chem.* **1985**, *50*, 1460. (j) Kuehne, M. E.; Reider, P. J. *J. Org. Chem.* **1985**, *50*, 1464. (k) Herdeis, C.; Hartke-Karger, C. *Justus Liebigs Ann. Chem.* **1991**, 99. (l) Henry, K. J., Jr.; Grieco, P. A.; Dubay, W. J. *Tetrahedron Lett.* **1996**, *37*, 8289.

(5) An asymmetric synthesis leading to an 80:20 mixture of enantiomers of ibogamine favoring (+)-**1** was accomplished by Trost (see Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930).

(6) (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1971**, *93*, 1816. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370.

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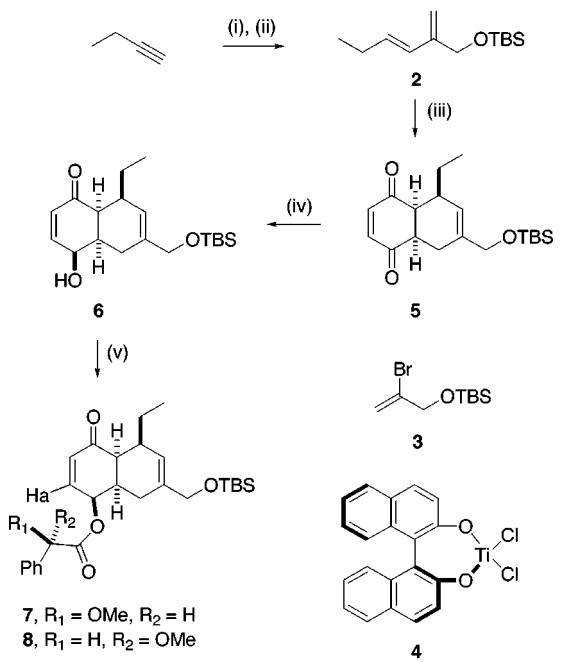
Mosher ester;[9] the ee of **5** determined from both ^{1}H and ^{19}F NMR measurements on this ester was 87%. Decreasing the reaction temperature of the Diels−Alder reaction to 0 °C led to only a slight increase in yield and ee, but the protocol used to obtain the chiral catalyst **4** had a profound effect on the reaction. The catalyst prepared in situ by the method of Mikami[3] (BINOL + $(i\text{-PrO})_2TiCl_2$) gave consistently good yields and ee's of **5**, but an alternative method[10] (BINOL + $(i\text{-PrO})_4Ti$ + $SiCl_4$) for obtaining **4** resulted in significantly lower yields and enantioselectivity. The catalyst TADDOL−Ti[11] also gave low ee values (26−58%) and yields (25−41%) of **5** (Scheme 1).

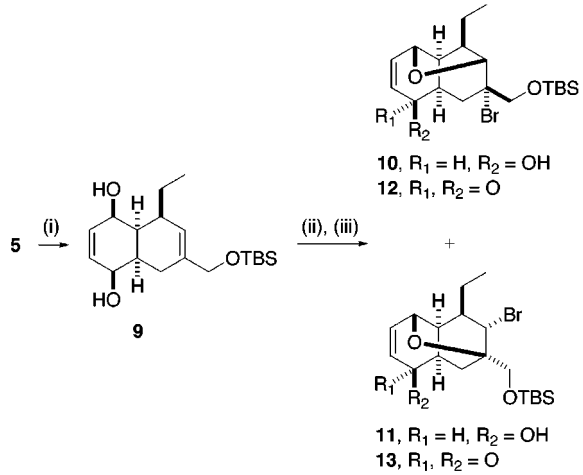
Scheme 1[a]



[a] Reagents and conditions: (i) Catechol-borane, THF, 24 h, 70 °C, 82%; (ii) **3**, $Pd(PPh_3)_4$, NaOEt, THF, 7 h, 70 °C, 67%; (iii) Benzoquinone, **4** (30 mol %), toluene, 0.5 h, rt; (iv) $NaBH_4$, $CeCl_3$•7 H_2O, MeOH, 1 h, 0 °C, 65% from **2**; (v) (*R*)- or (*S*)-PhCH(OMe)CO_2H, DCC, DMAP, CH_2Cl_2, 0.5 h, rt, 82%.

The absolute configuration of **6**, and hence **5**, was determined from the ^{1}H NMR spectra of mandelates **7** and **8**. The Mosher model as applied to mandelates by Trost[12] predicts that H_a in (*R*)-mandelate **7** will be shielded by the phenyl substituent relative to the corresponding proton in the (*S*) diastereoisomer **8**, and this is indeed the case ($\Delta\delta$ = 0.20 ppm). Further proof of the absolute configuration of **5** was obtained by its exhaustive reduction to **9** under Luche conditions,[8] followed by treatment of **9** with *N*-bromosuccinimide (Scheme 2). This gave a 3:2 mixture of inseparable

Scheme 2[a]



[a] Reagents and conditions: (i) $NaBH_4$, $CeCl_3$•7H2O, MeOH, 8 h, rt, 62% fom **2**; (ii) NBS, THF, 1 h, rt, 91%; (iii) PDC, NaOAc, CH_2Cl_2, 73%.

bromo ethers **10** and **11** which was oxidized to enones **12** and **13**. Ketone **12** crystallized from this mixture, and X-ray analysis using anomalous dispersion confirmed its absolute configuration as shown.[13]

Diol **9** was the pivotal substance in our plan for the synthesis of natural (−)-ibogamine (**1**) which was patterned after an earlier synthesis of the racemic alkaloid by Sallay.[4c] Clean saturation of both olefinic bonds was accomplished by hydrogenation over rhodium on alumina and resulted in *endo* orientation of all four substituents on the cis-fused decalin framework. Oxidation of the diol then gave diketone **14** (Scheme 3). Selective protection of the less hindered ketone as its dimethyl ketal was accompanied by loss of the *tert*-butyldimethylsilyl ether to yield **15**, but this inadvertent cleavage was turned into an advantage since it proved necessary to blockade the primary alcohol with the more robust triisopropylsilyl protecting group for a subsequent Beckmann rearrangement.

The triisopropylsilyl ether of **15** was converted to *anti* oxime **16** which underwent smooth Beckmann rearrangement in the presence of *p*-toluenesulfonyl chloride to afford lactam **17**.[14] Elaboration of **17** into the azatricyclic core of **1** was initially attempted through amino alcohol **18**, obtained by reduction of the lactam with Red-Al followed by cleavage of the silyl ether. However, neither a Mitsunobu reaction[15] nor any other method[16] for effecting intramolecular displace-

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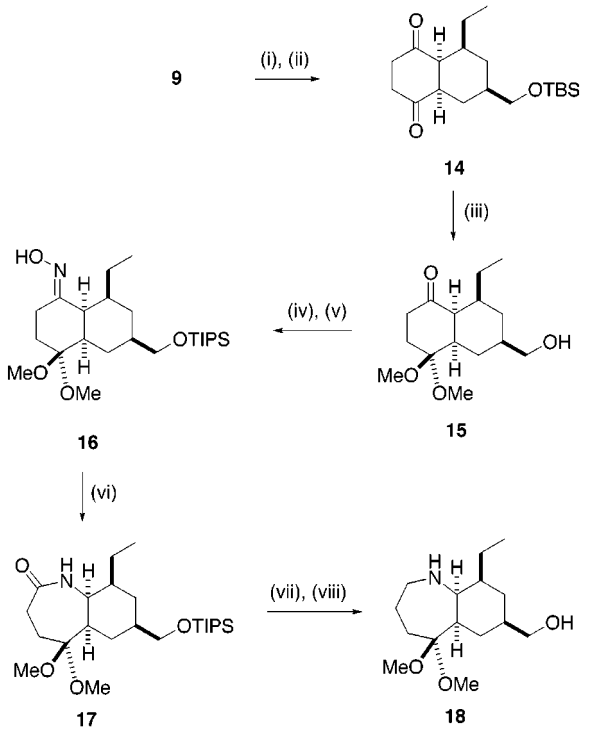
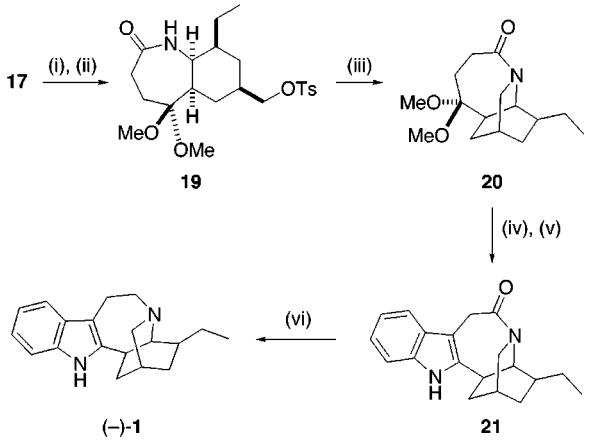
(13) It is noteworthy that the absolute configuration of **5** corresponds to that observed by Mikami (ref 3) for the Diels−Alder adduct obtained from the reaction of 1-methoxybutadiene with naphthoquinone catalyzed by (*S*)-**4**.
(14) For a contemporary view of the classical Beckmann rearrangement, see: Nguyen, M. T.; Raspoet, G.; Vanquickenborne, L. G. *J. Am. Chem. Soc*. **1997**, *119*, 2552.

Scheme 3[a]



[a] Reagents and conditions: (i) H_2, Rh/Al_2O_3, EtOAc, 24 h, 94%; (ii) PDC, CH_2Cl_2, 4 h, rt, 88%; (iii) MeOH, PPTS (cat), MeOH, 3 h, 55 °C, 89%; (iv) TIPSCl, Imidazole, DMF, 2 h, rt, 93%; (v) HONH2.HCl, NaOAc, MeOH, 3 h, reflux, 81%; (vi) *p*-TsCl, Et_3N, DMAP (cat), CH_2Cl_2, 3 h, rt, 74%; (vii) Red-Al, C_6H_6, 1 h, reflux, 92%, (viii) TBAF, THF, 1 h, rt, 95%.

Scheme 4[a]



[a] Reagents and conditions: (i)TBAF, THF, 1 h, rt, 99%; (ii) *p*-TsCl, Et_3N, DMAP (cat), CH_2Cl_2, 3 h, rt, 100%; (iii) NaH, THF, 1.5 h, 0 °C, then 1 h, reflux, 71%; (iv) Me_2CO, *p*-TsOH, 12 h, rt, 86%; (v) $PhNHNH_2$, AcOH, 1 h, 50 °C, then $BF_3 \bullet OEt_2$, 12 h, 80 °C, 77%; (vi) $NaBH_4$, $BF_3 \bullet OEt_2$, THF, 3 h, rt, 78%.

ment of the hydroxyl substituent by the secondary amine was successful, and it became clear from examination of a molecular model that the conformation of **18** needed to connect N and C1 creates a transannular steric repulsion between the interior hydrogen of the CH_2N moiety and the endo OMe group of the dimethyl ketal. This analysis suggested that lactam **17**, in which the offending sp^3 carbon is replaced by a carbonyl, would be a more tractable substrate for constructing the alicyclic framework of **1**, and to this end the TIPS ether **17** was advanced to tosylate **19** (Scheme 4). Exposure of the latter to sodium hydride resulted in clean cyclization to furnish **20**. After transketalization of **20** with acetone, the resultant keto lactam was subjected to Fischer indolization[17] to yield **21**. Reduction of this lactam proved unexpectedly difficult and could not be accomplished with conventional hydride reagents. Fortunately, **21** was reduced efficiently with borane generated in situ[18] and produced crystalline (−)-ibogamine [mp 156−157 °C, $[\alpha]_D^{23}$ −45.8 (*c* 0.2, EtOH)] identical with a sample of the natural alkaloid [mp 159−161 °C (lit.[19] 162−163 °C); $[\alpha]^{23}$ −45.0 (*c* 1.29, EtOH) (lit.[19] −36.4, $CHCl_3$)] by comparison of IR and NMR spectra. (−)-Ibogamine was obtained in 14 steps and 10% overall yield from benzoquinone by this route.

A possible transition state for the enantioselective and regioselective **endo** Diels−Alder addition leading to **5** is shown in Figure 1. This model postulates a $\pi-\pi$ interaction between catalyst **4** and benzoquinone which allows exposure of only one face of one of the two double bonds of the quinone to the diene.[20] Further studies, particularly with other dienes, are needed to evaluate this model, but the superior

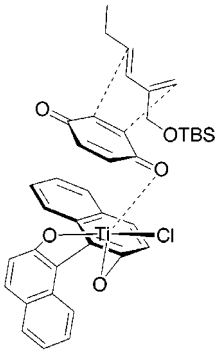


Figure 1. Proposed (*S*)-Binol−$TiCl_2$−benzoquinone complex in which the top face of the more remote double bond of the quinone is exposed for *endo* cycloaddition of **2**, leading to **5**.

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asymmetric induction observed with **4** as catalyst indicates that efficient enantioselective cycloaddition with a dienophile such as benzoquinone is indeed possible.

Acknowledgment. We are grateful to Dr. Alexandre F. T. Yokochi for the X-ray crystal structure of **12** and to Professor John Huffman, Clemson University, for a sample of natural ibogamine. Financial support was provided by the National Science Foundation (9711187-CHE).

Supporting Information Available: Characterization data and procedures for preparation of **2**, **5**−**17**, **19**−**21**, and (−)-**1**; X-ray crystallographic data for **12**. This material is available free of charge via the Internet at http://pubs.acs.org

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(20) No evidence for a charge-transfer band was found in the UV−visible spectrum of a mixture of **4** and benzoquinone. However, the solution containing these compounds was an intense red-brown color.