ORGANIC LETTERS

2000
Vol. 2, No. 13
1971−1973

# Enantioselective Ring Opening of Aza and Oxabicyclic Alkenes with Dimethylzinc

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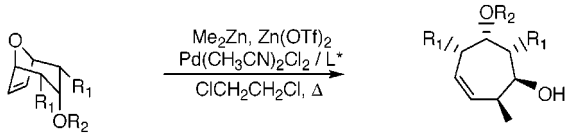
**Received May 12, 2000**

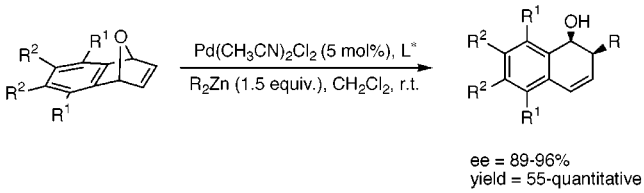
## ABSTRACT




**A system for efficient, asymmetric alkylative ring opening of azabenzonorbornadienes and [2.2.1] and [3.2.1] oxabicyclic alkenes was developed. The use of $Pd(CH_3CN)_2Cl_2$ and chiral phosphinooxazoline ligands gives the dihydronaphthalenes, cyclohexenols, and cycloheptenols in excellent yields and enantiomeric excesses.**

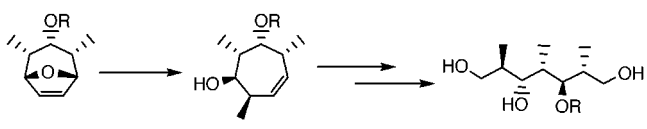
We have recently described the first efficient, enantioselective carbanionic ring opening of oxabenzonorbornadiene derivatives catalyzed by palladium in the presence of dialkylzinc reagents[1] (Scheme 1)

**Scheme 1**




We sought to extend this methodology to the less reactive [2.2.1] and [3.2.1] substrates, since ring opening and cleavage of the double bond provides a rapid, efficient, and enantioselective route to polypropionate and polyacetate subunits[2] (Scheme 2). The most useful nucleophile is one derived from a suitable methyl anion, but the decreased reactivity of the methyl-metal reagents vs other alkyl-metals has limited the use of this methodology.

**Scheme 2**




We now report our results in the enantioselective ring opening of [2.2.1] and [3.2.1] oxabicyclic compounds, and for the first time an efficient enantioselective ring opening of azabicyclic alkenes with dimethylzinc and a palladium−chiral ligand complex.

Our first attempts to open the [2.2.1] oxabicycle **1a** using the conditions we previously reported gave no ring opening, and only starting material was recovered. However, by increasing the reaction temperature to 80 °C (refluxing dichloroethane, Table 1), cyclohexenol **2a** was obtained in 60% yield.

We next tried the reaction of **1a** with palladium and a chiral ligand in order to determine the viability of the enantioselective process. The reaction was first conducted using *i*-Pr−POX as a ligand,[3] because it had given good results with oxabenzonorbornadiene.[1] Using these conditions,

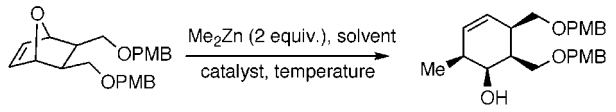
(1) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804.

(2) (a) Lautens, M.; Belter, R. K. *Tetrahedron Lett.* **1992**, *33*, 2617. (b) Chiu, P.; Lautens, M. *Topics Curr. Chem.* **1997**, *190*, 1. (c) Lautens, M. *Synlett* **1993**, 177.

(3) For the preparation and use of (4*S*)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-1,3-oxazoline (abbreviated as *i*-Pr-POX) (a) Williams, J. M. J. *Synlett* **1996**, 705 and references therein. (b) Spinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. (c) Von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. For a review on oxazolines and bisoxazolines, see: (d) Pfaltz, A. *Synlett* **1999**, 835.

10.1021/ol006052a CCC: $19.00 
**Published on Web 06/06/2000**

**Table 1.** Ring Opening of the [2.2.1] Oxabicycle



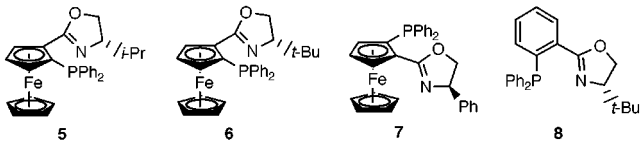

1a 2a

| | solvent | temp. | catalyst | yield[a] | ee[b] |
|---|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | rt | $Pd(dppf)Cl_2$ | N.R. | |
| 2 | $CH_2Cl_2$ | Δ | $Pd(dppf)Cl_2$ | N.R. | |
| 3 | $ClCH_2CH_2Cl$ | Δ | $Pd(dppf)Cl_2$ | 60 | |
| 4 | $ClCH_2CH_2Cl$ | Δ | $Pd(CH_3CN)_2Cl_2$/i-Pr-POX | 70 | 75 |
| 5 | $ClCH_2CH_2Cl$ | Δ | $Pd(CH_3CN)_2Cl_2$/i-Pr-DIPOF | 93 | 90 |
| 6 | $ClCH_2CH_2Cl$ | Δ | $Pd(CH_3CN)_2Cl_2$/BINAP | 56 | 19 |

[a] Isolated yield. [b] Determined by HPLC (Chiral OD column).

cyclohexenol **2a** was obtained in only 75% ee; however, much better results were obtained using the structurally related ferrocene-derived DIPOF ligand **5** (Scheme 3),[4] which gave alcohol **2a** in 93% yield and 90% ee.

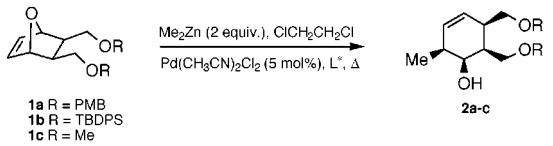
**Scheme 3**




5 6 7 8

In an effort to improve the enantiomeric excess, a series of chiral ferrocene ligands were screened (Table 2). We were

**Table 2.** Enantioselective Opening of the [2.2.1] Oxabicycle




**1a** R = PMB
**1b** R = TBDPS
**1c** R = Me

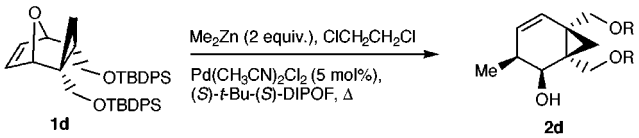
**2a-c**

| | substrate | yield[a] | ee[b] | L* |
|---|---|---|---|---|
| 1 | **1a** | 87 | 91 | (*S*)-*t*-Bu-(*S*)-DIPOF |
| 2 | **1b** | 81 | 95 | (*S*)-*i*-Pr-(*S*)-DIPOF |
| 3 | **1b** | 80 | 92 | (*S*)-*i*-Pr-(*R*)-DIPOF |
| 4 | **1b** | 90 | 98 | (*S*)-*t*-Bu-(*S*)-DIPOF |
| 5 | **1b** | 77 | −87 | (R)-Ph-(*R*)-DIPOF |
| 6 | **1c** | 58 | 91 | (*S*)-*t*-Bu-(*S*)-DIPOF |

[a] Isolated yield. [b] Determined by HPLC (chiral OD column).

able to obtain alcohol **2a** and **2b** in 91% and 98% ee, respectively, with the (*S*)-*t*-Bu-DIPOF ligand **6**. An increase in ee is seen as the size of the substituent on the oxazoline ring increases from Ph to *i*-Pr to *t*-Bu. It is interesting to note that, as in allylic substitution reactions catalyzed by palladium and a chiral ligand,[5] changing the planar chirality of the ferrocene does not affect the sense of the enantioselectivity (entries 2 and 3, Table 2). Rather, it is the chirality on the oxazoline ring that determines the product stereochemistry (entry 5, Table 2).

Other [2.2.1] substrates such as the methyl-protected analogue **1c** (entry 6) and **1d**, which contains a cyclopropane ring, gave slightly lower yields but comparable ee's (91% and 98% respectively).

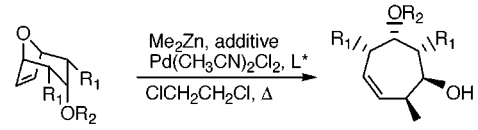



**1d** **2d**

68%, 98%ee

Next, we extended our study to the [3.2.1] substrates **3a**−**e** and were able to obtain the cycloheptene diols **4a** and **4b** in good yields (70−91%) and in good ee's (75−95%). Surprisingly, ligand **6** did not give the best ee's, as observed with the [2.2.1] system (Table 3, entries 2 and 4). However, ligand

**Table 3.** Enantioselective Opening of the [3.2.1] Oxabicycle




**3a** $R^1$ = H, $R^2$ = H
**3b** $R^1$ = Me, $R^2$ = H
**3c** $R^1$ = H, $R^2$ = TBDPS
**3d** $R^1$ = Me, $R^2$ = TBDPS
**3e** $R^1$ = Me, $R^2$ = TIPS

**4a** $R^1$ = H, $R^2$ = H
**4b** $R^1$ = Me, $R^2$ = H
**4c** $R^1$ = H, $R^2$ = TBDPS
**4d** $R^1$ = Me, $R^2$ = TBDPS
**4e** $R^1$ = Me, $R^2$ = TIPS

| | substrate | L* | additive | yield[a] | ee[b,c] |
|---|---|---|---|---|---|
| 1 | **3a** | **5** | | 84 | 90 |
| 2 | **3a** | **6** | | 72 | 75 |
| 3 | **3b** | **5** | | 84 | 95 |
| 4 | **3b** | **6** | | 76 | 89 |
| 5 | **3b** | **7** | | 91 | −75 |
| 6 | **3c** | **5** | | 58 | 87 |
| 7 | **3c** | **7** | | 27 | −72 |
| 8 | **3c** | **8** | | 31 | 90 |
| 9 | **3d** | **5** | | 19 | 87 |
| 10 | **3d** | **6** | | 38 | 90 |
| 11 | **3d** | **7** | | 40 | −85 |
| 12 | **3c** | **5** | $Zn(OTf)_2$ | 92 | 88 |
| 13 | **3c** | **6** | $Zn(OTf)_2$ | 83 | 88 |
| 14 | **3c** | **8** | $Zn(OTf)_2$ | 60 | 91 |
| 15 | **3d** | **5** | $Zn(OTf)_2$ | 70 | 87 |
| 16 | **3e** | **5** | $Zn(OTf)_2$ | 73 | 93 |
| 17 | **3e** | **6** | $Zn(OTf)_2$ | 75 | 93 |

[a] Isolated yield. [b] Determined by HPLC (Chiral OD column). [c] A negative number refers to the enantiomeric product.

**5** provided cycloheptenols **4a** and **4b** in 90% and 95% ee, respectively (Table 3, entries 1 and 3). The protected alcohols

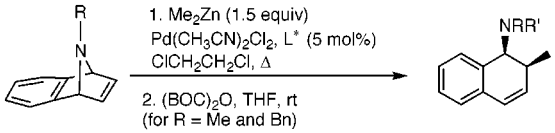
**3c**−**e** have previously been shown to be unreactive with methyllithium,[2a,6] but with this new catalytic system alcohols **4c**−**e** were obtained in moderate yields and up to 90% ee (Table 3, entries 6−11). For the first time, we were able to open a [3.2.1] system containing a protected alcohol.

Significant improvement in the yield of the reaction was observed upon addition of zinc triflate, $Zn(OTf)_2$ (60−92%, Table 3, entries 12−17), with very little change in the ee's. The exact role of the zinc triflate is unclear at this time, but it might be acting as a Lewis acid, generating MeZnOTf by an exchange reaction, or interacting with the catalyst to form a more reactive species.

We next sought to extend this methodology to the ring opening of azabicyclic substrates, in particular the azabenzonorbornadienes. Alkylative ring opening of these compounds would provide access to a variety of natural products and bioactive molecules which contain a substituted aminotetrahydronaphthalene core, such as analogues of sertraline, which was previously synthesized in our laboratories by an asymmetric reductive ring opening.[7]

The azabicycles are less reactive than their oxygen analogues, and previous studies have shown that the transition from oxa to azabicycles is not trivial with frequent decreases in yields and enantiomeric excesses being observed. However, good results were obtained when the reactions were carried out in refluxing dichloroethane. Using the POX ligands, which were shown to work best for the oxabenzonorbornadienes, we were able to obtain excellent ee's (Table 4). The R group on the nitrogen had a small effect on the enantioselectivity but a large effect on the yield, with the electron-withdrawing phenyl group giving the best yields.

**Table 4.** Enantioselective Opening of Azabenzonorbornadiene




**9** **10**

| | R | R′ | yield[a] | ee[b] | L* |
|---|---|---|---|---|---|
| 1 | Me | BOC | 60 | 98 | (*S*)-*i*-Pr-POX |
| 2 | Bn | BOC | 20 | 92 | (*S*)-*i*-Pr-POX |
| 3 | Ph | H | 99 | 98 | (*S*)-*i*-Pr-POX |
| 4 | Me | BOC | 26 | >99 | (*S*)-*i*-Pr-POX |
| 5 | Bn | BOC | 3 | 97 | (*S*)-*i*-Pr-POX |
| 6 | Ph | H | 92 | 98 | (*S*)-*i*-Pr-POX |

[a] Isolated yield. [b] Determined by HPLC (Chiral OD column).

In summary, we have reported a new catalytic nucleophilic ring opening reaction of [2.2.1] and [3.2.1] oxabicycles and azabenzonorbornadienes using dimethylzinc. Product cycloalkenes were obtained in good yields and good ee's (up to 99%). This method represents a significant enhancement to the oxabicyclic methodology developed in our laboratory. Further work is being pursued toward the addition of other dialkylzinc species to these aza- and oxabicyclic substrates, as well as studies into the mechanism of this reaction.

**Acknowledgment.** We thank AstraZeneca Research Centre in Montreal, the Ontario Research and Development Challenge Fund (ORDCF), NSERC (Canada), and the University of Toronto for financial support of this work. J.L.R. thanks the Ministère Francais des Affaires Etrangères for a Bourse Lavoisier. S.H. thanks NSERC (Canada) for financial support in the form of a postgraduate fellowship.

**Supporting Information Available:** Experimental procedures and full characterization for compounds **2a**−**d**, **4a**−**e**, and **10a**,**c** and and $^1$H NMR of **10b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006052A

(4) For the synthesis of 2(*S*)-(diphenylphosphino)-1-[4(*S*)-isopropyl-2-oxazolin-2-yl]ferrocene (abbreviated as (*S*)-*i*-Pr-DIPOF) and other ferrocene type ligands, see: (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (b) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (c) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *62*, 10.

(5) You, S.-L.; Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X. *Chem. Commun.* **1998**, 2765.

(6) (a) Lautens, M.; de Frutos, O.; Stammers, T. A. *Tetrahedron Lett.* **1999**, *40*, 8317. (b) Lautens, M.; Chiu, P. *Tetrahedron Lett.* **1993**, *34*, 773.

(7) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246.