Palladium-Catalyzed Enantioselective Alkylative Ring Opening

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We have been investigating the stereochemical outcome in ring-opening reactions of oxabicyclic compounds and now report a new enantioselective transformation that significantly expands the scope and utility of this reaction.[1]

We have shown that the enantioselective reductive ring-opening using a nickel catalyst and a chiral phosphine in the presence of DIBAL-H works well for a variety of oxabicyclic compounds, including the very sensitive oxabenzonorbornadiene class of substrates **1**, which are readily prepared from a benzyne and furan. This strategy led to a rapid and efficient synthesis of the important antidepressant agent, Sertraline.[2]

Many other bioactive molecules, which contain a substituted tetrahydronaphthalene core,[3−5] led us to examine the possibility of developing the enantioselective ring-opening using other nucleophiles. For example, carbanionic ring-opening of oxabicyclo[3.2.1]-, -[2.2.1]-, and oxabenzonorbornene systems are now well established (Scheme 1), but no general enantioselective process has been reported.[6−8,12] Recently, Cheng,[9] Fiaud,[10] and Kosugi[11] reported that palladium catalyzed the addition of iodoarenes, iodoalkenes, and stannylarenes to 7-oxabenzonorbornadiene derivatives (Scheme 1), but the use of chiral phosphines[10] led to low yields and/or low enantioselectivities.

Our previous attempts to achieve an enantioselective ring-opening utilizing organolithium reagents in the presence of a catalytic amount of sparteine,[13] or a Grignard reagent in the presence of a catalytic amount of $Ni(COD)_2$ and a chiral ligand,[14] gave poor to modest results.[13,14b] However, we now report that changing the nucleophile from one based on magnesium or lithium to one derived from zinc and using a palladium catalyst and a chiral ligand gives ring-opened substrates with excellent yields and enantiomeric excesses (ee's).[15]

Scheme 1

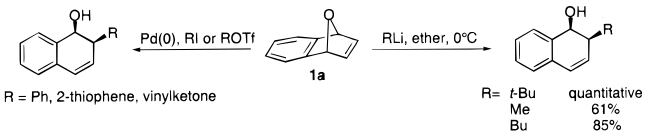
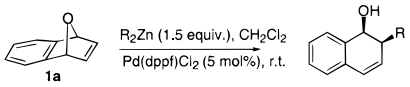


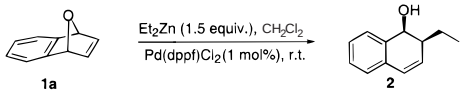
Table 1. Addition of Various Dialkylzincs



R	yield[a] (%)	de[b] (%)
Me	80	>98
Et	92	>98
t-Bu	72	>98
vinyl	55	>98
$TMSCH_2$	67	>98

[a] Isolated yield. [b] Determined by ^1H NMR

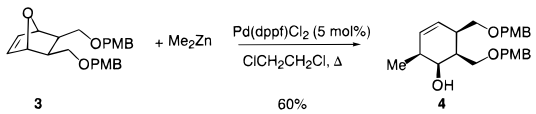
We first sought a nucleophile that was unreactive in the absence of catalyst, to minimize the noncatalyzed reaction that would ultimately diminish the ee in any enantioselective process. Dialkylzinc reagents were ideal since, in the absence of the catalyst, they reacted slowly with **1a** to give a mixture of products (including naphthol derivatives). The best results were obtained using $(dppf)PdCl_2$ or $(dppb)PdCl_2$ rather than $(Ph_3P)_2PdCl_2$, *N*,*N*′-dimethylethylenediamine palladium dichloride, or $(Ph_3P)_2NiCl_2$. Indeed, in the presence of only 1 mol % of $Pd(dppf)Cl_2$ and 1.5 equiv of Et_2Zn, **2** was obtained as a single diastereomer in 79% yield under very mild conditions. When the amount of palladium catalyst was increased to 5 mol %, the yield improved to 92%, and no naphthol was observed.



The different reactivities of the metal−ligand complexes might be explained by the difference in the P−Pd−P and Cl−Pd−Cl angles, as Hayashi and Higuchi proposed for the cross-coupling of secondary and primary alkyl Grignard reagents with an aryl or alkenyl halide.[16] Our results parallel those of Hayashi and Higuchi in cross-coupling reactions but are opposite to those for the asymmetric hydrophenylation of **1a**, where it appears that monodentate phosphines give better results.[9−11]

We investigated the scope of the reaction with primary, tertiary, and vinylzinc reagents (Table 1), and in all cases, the yield was good to excellent (55−92%) and the alcohol was obtained as a single diastereomer.

The ring-opening of various substituted oxabenzonorbornadienes was studied, and the results are reported in Table 2. Yields were generally above 70%, even for electron-rich compounds (entries 4 and 6). Less reactive oxabicycles such as an oxabicyclo-[2.2.1]heptene failed to open at room temperature, but heating **3** in refluxing dichloroethane gave **4** in 60% yield.



(1) a) Lautens, M.; Rovis, T. *J. Am. Chem. Soc.* **1997**, *119*, 11090. (b) Lautens, M.; Rovis, T. *Tetrahedron* **1998**, *54*, 1107. (c) Lautens, M.; Ma, S.; Chiu, P. *J. Am. Chem. Soc.* **1997**, *119*, 6478. (d) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. *J. Am. Chem. Soc.* **1995**, *117*, 532. (e) Lautens, M.; Chiu, P.; Colucci, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281.

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

(3) Kamal, A.; Gayatri, N. L. *Tetrahedron Lett.* **1996**, *37*, 3359 and references therein.

(4) Snyder, S. E.; et al. *J. Med. Chem.* **1995**, *38*, 2395.

(5) Kim, K.; Guo, Y.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 6866.

(6) (a) Lautens, M.; Klute, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442. (b) Arjona, O.; de Dios, A.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 3906. (c) Lautens, M.; Abd-El-Aziz, A. S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305. (d) Lautens, M.; Di Felice, C.; Huboux, A. *Tetrahedron Lett.* **1989**, *30*, 6817.

(7) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954.

(8) (a) Lautens, M. *Synlett* **1993**, 177−185. (b) Chiu, P.; Lautens, M. *Topics Curr. Chem.* **1997**, *190*, 1.

(9) a) Duan, J. P.; Cheng, C. H. *Tetrahedron Lett.* **1993**, *34*, 4019. (b) Duan, J. P.; Cheng, C. H. *Organometallics* **1995**, *14*, 1608. (c) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C. H. *J. Org. Chem.* **1999**, *64*, 3538.

(10) Moinet, C.; Fiaud, J. C. *Tetrahedron Lett.* **1995**, *36*, 2051.

(11) Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 477.

(12) Caple, R.; Chen, G. M. S.; Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874.

(13) Lautens, M.; Gadja, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193.

(14) (a) Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246. (b) Ma, S. Ph.D. Thesis, University of Toronto, 1996.

(15) Waymouth has shown that he could obtain a 96% ee for the ring-opening of **3** using Et_3Al and bis(neoisomenthylindenyl)zirconium dichloride as a chiral catalyst; private communication.

(16) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

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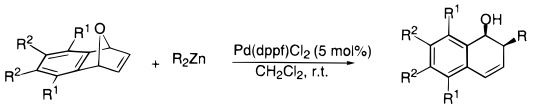
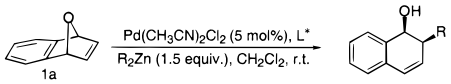
Table 2. Addition to Other Oxabicycles



entry	R	substrate	R^1	R^2	yield[a] (%)
1	Me	**1b**	H	F	73
2	Me	**1c**	Me	Br	71
3	Me	**1d**	Me	H	65
4	Me	**1e**	H	$O(CH_2)O$	quant.
5	Et	**1b**	H	F	89
6	Et	**1e**	H	$O(CH_2)O$	83

[a] Isolated yield.

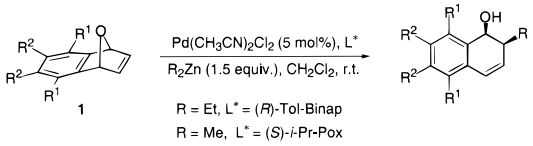
Table 3. Enantioselective Ring-Opening of Oxabenzonorbornadiene **1a**



entry	R	yield (%)	ee[c] (%)	L*
1	Me	97	67	(*R*)-Binap
2	Me	92	76	(*R*)-Tol-Binap
3	Me	90	89	*i*-Pr-Pox
4	Me[a]	77	88	*i*-Pr-Pox
5	Me[b]	–	90	*i*-Pr-Pox
6	Et	91	89	(*R*)-Binap
7	Et	98	96	(*R*)-Tol-Binap
8	Et	21	20	*i*-Pr-Pox
9	$TMSCH_2$	81	92	(*R*)-Tol-Binap

[a] The reaction was carried out in refluxing dichloromethane. [b] Less than 50% conversion after 20 h at 0 °C. [c] Determined by HPLC (Chiracel OD or OJ column).

Table 4. Enantioselective Addition to Other Oxabenzonorbornadienes



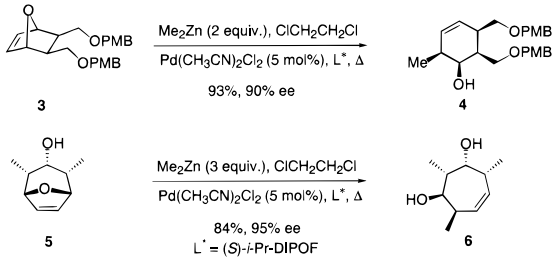
entry	R	substrate	R^1	R^2	yield[a] (%)	ee[b] (%)
1	Me	**1b**	H	F	87	90
2	Me	**1c**	Me	Br	67	90
3	Me	**1d**	Me	H	76	89
4	Me	**1e**	H	$O(CH_2)O$	85	91
5	Et	**1b**	H	F	89	92
6	Et	**1e**	H	$O(CH_2)O$	91	92

[a] Isolated yield. [b] Determined by HPLC (Chiracel OD or OJ column).

We next tried to react **1** with a palladium catalyst and a chiral ligand in order to determine the viability of an enantioselective ring-opening. We found that (*R*)-Tol-BINAP gave the highest ee's for the addition of diethylzinc, and (4*S*)-2-(2-(diphenylphosphino)-phenyl)-4-isopropyl-1,3-oxazoline (abbreviated as *i*-Pr-POX) worked best when dimethylzinc was added (Table 3).[17,18] It is not clear why this change in ligand is necessary and why we observed a difference in the enantioselectivities for the methyl and ethyl addition with the *i*-Pr-POX ligand (entries 3 and 8). Very little effect on the ee was observed when the reaction was carried out at 0 °C compared to refluxing dichloromethane (entries 3−5)!

The ee's obtained from the carbanionic ring-opening of several oxabenzonorbornadienes substituted on the aromatic moiety are summarized in Table 4. Changing the electronic or steric properties of the aromatic ring has little influence on the enantioselectivity.

The enantioselective opening was also achieved with less reactive substrates such as **3** and **5**. The cyclohexenol **4** was



obtained in 75% ee when the *i*-Pr-POX ligand was used, but much better results were obtained when a ferrocene-derived DIPOF ligand was used.[19] Thus, both [2.2.1] and [3.2.1] oxabicyclic derivatives react to give **4** and **6** in 90 and 95% ee, respectively.

Either enantioselective carbopalladation or enantioselective ionization of the bridging carbon−oxygen bond could be the enantioselectivity-determining step.[20] Carbopalladation of the alkene would be followed by elimination of the β-oxygen, perhaps assisted by complexation to the Lewis acidic zinc. Alternatively, an allylic substitution via a π-allyl palladium intermediate, in analogy with the well-documented results obtained using allylic leaving groups, palladium catalysts, and chiral ligands, could also be occurring.[21] The overall pathway is one of retention, so a retention−retention or a double inversion is possible.

The intermediate formed following the ionization is closely related to the π-allyl species proposed by Trost in his work on desymmetrization of meso-diesters.[21a] However the regioselectivity reported in these studies is different. Whereas Trost isolated the product from attack of the nucleophile distal to the alkoxide, no trace of this isomer was detected in our studies. It is possible that the major regioisomer is formed due to a difference in the nucleophile, or this may be evidence in support of a carbometalation mechanism.

In summary, we have developed a new catalytic nucleophilic ring-opening reaction of oxabicyclic compounds using dialkylzinc reagents. This method is applicable to the enantioselective synthesis of cyclohexenols, cycloheptenol, and dihydronaphthols. Our ongoing experiments are focused on defining the scope of this methodology and determining the utility of the reaction in the synthesis of biologically interesting molecules.

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Supporting Information Available: Experimental details, characterization data, and spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) A ligand study will be published in a forthcoming full paper.

(18) For the preparation and use of (4*S*)-2-(2-(diphenylphosphino)phenyl)-4-isopropyl-1,3-oxazoline (abbreviated as *i*-Pr-POX), see: (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) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1. (e) Pfaltz, A. *Synlett* **1999**, 835.

(19) For the synthesis of 2(*S*)-(diphenylphosphino)-1-[4(*S*)-isopropyl-2-oxazolin-2-yl]ferrocene (abbreviated as (*S*)-*i*-Pr-DIPOF), see: (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377. (b) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79. (c) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74. (d) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *62*, 10.

(20) Based our results with unsymmetrical substrates, an S_N2' mechanism is unlikely. The details will be reported in the full account of this work.

(21) (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (b) Pfaltz, A.; Lautens, M. *Comp. Asym. Ca.* Springer-Verlag, **1999**, 833.