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Copper-Catalyzed Anti-Stereocontrolled Ring Opening of Oxabicyclic Alkenes with Grignard Reagents

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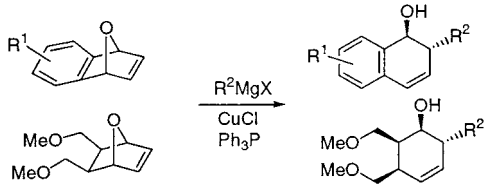
ABSTRACT



A general copper-catalyzed procedure for the stereoselective ring opening of [2.2.1]-oxabicyclic alkenes with Grignard reagents is described. In the presence of catalytic amounts of CuCl/PPh_3 the reaction occurs with very high or complete anti selectivity in all cases.

The efficient construction of stereochemically complex carbocyclic compounds through the ring opening of oxabicyclic alkenes has become an important reaction for C−C and C−X bond formation.[1] Pioneering work in this field as well as the exploration of its synthetic potential in enantioselective synthesis and synthesis of natural products was first described by Lautens and co-workers.[1,2]

Among the carbon nucleophiles capable of inducing this transfomation, organolithium[3] and cuprate[4] reagents were the first class of nucleophiles used, affording the corresponding syn addition products. Later, softer organometallic species such as phenylstannane,[5] alkylaluminums,[6] dialkylzincs,[7] alkylzinc halides,[8] and arylboronic acids,[9] in the presence of a variety of metal catalysts, also proved to be efficient reagents for the syn-stereoselective ring-opening addition.[10] Although remarkable progress in the transition-metal-catalyzed ring opening of oxa-bridged bicyclic alkenes has been achieved, some limitations still remain. For example, the vast majority of the reported methods occur with syn selectivity as a result of the exo attack to the oxabicyclic unit. In fact, the rhodium-catalyzed addition of malonates to oxabenzonorbornadienes, reported by Lautens and co-workers,[11] and the addition of dialkylzinc reagents catalyzed by a chiral copper phosphoramidite in the presence of Zn-

(1) For reviews, see: (a) Lautens, M. *Synthesis* **1993**, 177−185. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(2) For natural product synthesis, see: (a) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247. (b) Lautens, M.; Rovis, T. *Tetrahedron* **1999**, 8967−8976. (c) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. *Org. Lett.* **2002**, *4*, 1879−1882.

(3) Caple, R.; Chen, G. M.-S.; Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874−2876. (b) Arjona, O.; de la Pradilla, R. F.; García, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437−6440. (c) Lautens, M.; Gajda, C.; Chiu, P. *J. Chem. Soc., Chem. Commun.* **1993**, 1193−1194.

(4) Lautens, M.; Smith, A. C.; Abd-El-Aziz, A. S.; Huboux, A. H. *Tetrahedron Lett.* **1990**, *31*, 3523.

(5) Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 477−478.

(6) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902−3909.

(7) (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971−1973. (b) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839.

(8) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679−1682.

(9) (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390−391. (b) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311−1314.

(10) Alkylative ring-opening reactions of oxabenzonorbornadienes with organic halides in the presence of palladium or nickel catalyst have been also reported: (a) Duan, J.-P.; Cheng, C.-H. *Tetrahedron Lett.* **1993**, *34*, 4019−4022. (b) Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051−2052. (c) Duan, J.-P.; Cheng, C.-H. *Organometallics* **1995**, *14*, 1608−1618. (d) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538−3543.

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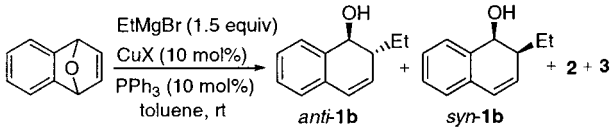
$(OTf)_2$, recently reported by Feringa and co-workers,[12] constitute the only current examples of stereoselective anti ring opening of [2.2.1]-oxabicyclic compounds with carbon nucleophiles.[13] Despite the great interest of these procedures, especially their high enantioselectivity, the synthetic scope seems to be limited to the case of oxabenzonorbornadienes and a narrow structural diversity of carbon nucleophiles (malonates and primary dialkyl-substituted zinc reagents).

In this context, it is surprising that the more reactive and readily available Grignard reagents have been scarcely studied. Thus, Lautens has reported the nickel-catalyzed ring opening of [2.2.1]-oxabicyclic alkenes with a large excess of Grignard reagents to give mainly syn-substituted products.[14,15] We report herein that the ring-opening of benzo- and alkyl-substituted oxabicyclic alkenes with a wide variety of Grignard reagents occur with very high regioselectivity and anti stereoselectivity in the presence of substoichiometric amounts of CuCl and PPh_3.

We began our studies by searching for the optimal copper-catalyst system. In our initial experiment, treatment of a toluene solution of oxabenzonorbornadiene with ethylmagnesium bromide (1.5 equiv) in the presence of 10 mol % of CuI provided a 90:10 mixture of the anti/syn ring-opened compounds **1b**[16] (60%), accompanied by 1,2-dihydronaphthalen-1-ol (**2**, 35%),[17] and a small amount of naphthalene (**3**, 5%). In the absence of copper salt, no reaction took place. Significant yield and anti/syn ratio (95:5, 73%) enhancements were observed when PPh_3 (10 mol %) was added as a chelating ligand.[18] Encouraged by the high anti stereoselectivity shown by this catalytic Cu/PPh_3 system, the effect of several commercially available copper salts on the reaction were surveyed. As depicted in Table 1, CuTC[19,20] (entry 8) and especially CuCl (entry 3) produced the best results in terms of reactivity and stereoselectivity. Consequently, to establish the synthetic scope of this copper-catalyzed reaction, CuCl was chosen for subsequent experiments.

The results of the addition of a variety of Grignard reagents to oxabenzonorbornadiene in the presence of CuCl (10 mol %)[21] and PPh_3 (10 mol %)[22] in toluene[23] at room temperature are detailed in Table 2. Interestingly, primary, secondary, and benzyl alkylmagnesium bromides and chlorides afforded the corresponding dihydronaphthalenols in good chemical

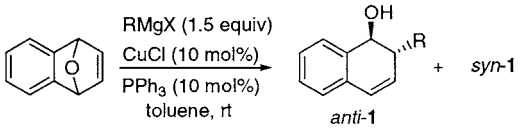
Table 1. Ring Opening of Oxabenzonorbornadiene with Ethylmagnesium Bromide Catalyzed by Various Copper Salts



entry	copper salt[a]	*anti*-**1b**/*syn*-**1b**/**2**/**3**[b]
1	CuI	69:4:10:17
2	CuBr	85:4:7:4
3	CuCl	97:3:—:—
4	$(CuOTf)_2 \cdot C_6H_6$	80:5:4:11
5	CuCN	36:9:—:43[c]
6	$CuCl_2$	78:3:8:11
7	$Cu(OTf)_2$	17:1:37:—[c]
8	CuTC	90:5:—:5
9	$Cu(CN)_4PF_6$	73:4:—:—[c]

[a] 10 mol %. [b] Determined by ^1H NMR from the crude reaction mixture; **2** = 1,2-dihydronaphthalen-1-ol; **3** = naphthalene. [c] Oxabenzonorbornadiene was also detected.

Table 2. Cu-Catalyzed Ring Opening of Oxabenzonorbornadiene with Grignard Reagents



entry	X	R	product	t (h)	anti/syn[a]	yield[b]
1	Br	Me	**1a**	6	>98:<2	92
2[c]	Br	Et	**1b**	0.3	97:3	76
3	Br	Et	**1b**	0.3	95:5	83
4	Br	*i*-Bu	**1c**	3	>98:<2	89
5	Cl	decyl	**1d**	4	90:10	66
6	Cl	Cy	**1e**	2	>98:<2	51
7[c]	Cl	Cy	**1e**	1	>98:<2	64
8	Br	Bn	**1f**	12	>98:<2	47[d]
9	Br	Ph	**1g**	2	>98:<2	90
10[c]	Br	Ph	**1g**	4	>98:<2	84
11[c]	Br	(*p*-OMe)C_6H_4	**1h**	12	>98:<2	92[e]
12	Br	(*p*-F)C_6H_4	**1i**	1.5	>98:<2	94

[a] Determined by ^1H NMR. [b] Yield (%) of anti product after chromatography. [c] 10 mol % of CuTC (copper thiophene-2-carboxylate) was used instead of CuCl. [d] Yield in converted product (10% of starting material was recovered); 35% of naphthalene was also obtained. [e] Yield of converted product (15% of starting material was recovered).

(11) Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171. (b) Lautens, M.; Schmid, G. A.; Chau, A. *J. Org. Chem.* **2002**, *67*, 8043−8053.

(12) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703−2705.

(13) The copper-catalyzed addition of Grignard reagents to 3-aza-2-oxabicyclo[2.2.1]hept-5-ene systems has been recently reported: Surman, M. D.; Mulvihill, M. J.; Miller, M. J. *J. Org. Chem.* **2002**, *67*, 4115−4121.

(14) Lautens, M.; Ma, S. *J. Org. Chem.* **1996**, *61*, 7246−7247.

(15) Some examples of ring opening of [3.2.1]-oxabicycles with Grignard reagents with zirconocene catalysts are found within ref 6.

(16) For previous synthesis of *anti*-**1b**, see: (a) Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B. L. *Chem. Commun.* **2001**, *24*, 2606−2607 and ref 12. For previous synthesis of *anti*-**1a**, see: (b) Jeffrey, A. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1975**, *97*, 4427−4428. (c) Tsang, W. S.; Griffing, G. W.; Horning, M. G.; Stillwell, W. G. *J. Org. Chem.* **1982**, *47*, 5339−5353 and ref 12.

(17) Compound **2** likely results from the reductive ring opening caused by a β-hydride transfer from the Grignard reagent.

(18) Upon screening other commonly used ligands for copper such as dimethyl ethylenediamine, BINAP,or bisoxazolines, it was found that the use of Ph_3P was crucial for achieving good yield and high anti selectivity.

(19) CuTC = copper thiophene-2-carboxylate: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

(20) For the use of CuTC in copper-catalyzed S_N2' addition of Grignard reagents to allylic chlorides, see: Alexakis, A.; Croset, K. *Org. Lett.* **2002**, *4*, 4147−4149.

(21) Lower catalyst loading was also studied: the reaction of oxabenzonorbornadiene with EtMgBr in the presence of 5 mol % of CuCl and 5 mol % of Ph_3P provided *anti*-**1b** in lower yield due to the formation of **2** (8%) and **3** (7%) in the reaction mixture.

(22) In the absence of PPh_3, CuCl alone gave a 60:35:5 mixture of *anti*-**1b**, naphthalenol **2** and naphthalene (**3**), respectively.

yields and very high anti selectivity.[24] The easy delivery of a methyl group under these conditions (entry 1) contrasts with the low reactivity displayed by Me_2Zn in the Cu-catalyzed ring opening of oxabenzonorbornadiene.[12] Although in general CuTC provides poorer results compared to CuCl, the addition of CyMgCl in the presence of CuTC afforded a better yield of the addition product (entry 7). Remarkably, the less reactive aryl Grignard reagents provided the ring-opened products with complete anti-stereoselectivity (entries 9−12). The reaction proceeded smoothly with both electron-rich and electron poor aryl derivatives. It should be noted that, to the best of our knowledge, no previous anti ring opening arylations of oxa-bridged bicyclic alkenes have been described.

To extend the scope of this transformation to other bicyclic substrates, substituted oxabenzonorbornadiene derivatives were examined. We chose MeMgBr and (*p*-F)C_6H_4MgBr as model examples of alkyl- and arylmagnesium reagents. As illustrated in Figure 1, regardless of the electronic nature or

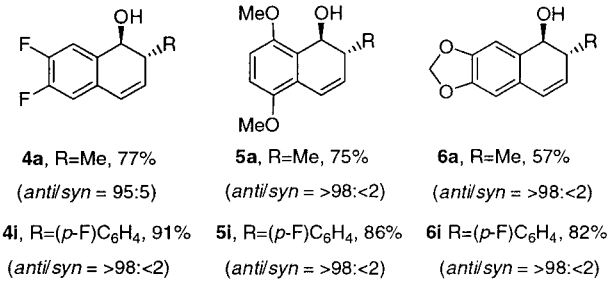


Figure 1. Stereoselective synthesis of 2-substituted 1,2-dihydro-1-naphthols.

the position of the substituents, the corresponding 2-substituted 1,2-dihydro-1-naphthalenols **4**−**6** were obtained in good yields with practically complete regioselectivity and anti stereocontrol.

Next, less reactive bicyclic substrates such as nonaromatic oxabicyclic alkenes were examined. Despite the lower reactivity shown by the alkyl-substituted [2.2.1]-oxabicycle **7**, its reaction with a variety of alkyl Grignard reagents afforded, in moderate to good yields, the corresponding cyclohexenols **8** with complete regioselectivity and anti stereoselectivity[24] (Table 3, entries 1−6).[25] Interestingly, these are the first examples of highly regioselective anti stereocontrolled ring opening of nonbenzo-fused oxa-bridged bicyclic alkenes with carbon nucleophiles.

(23) While CH_2Cl_2 provided similar results, more coordinating solvents such as Et_2O or THF proved to be much less efficient.

(24) The anti stereochemistry of the ring-opened products were assigned by comparison of their NMR data with those of the reported compounds *anti*-**1a**, *anti*-**1b** (see ref 16), *anti*-**8a** and *anti*-**8g** (see ref 14).

(25) An 87:13 mixture of **8b** and **9** (see below) was obtained in the addition of EtMgBr to **7**. For previous synthesis of **9** via ring opening addition of silyl nucleophiles, see: Lautens, M.; Ma, S.; Belter, R. K.; Chiu, P.; Leschziner, A. *J. Org. Chem.* **1992**, *57*, 4065−4066.

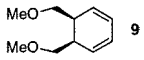
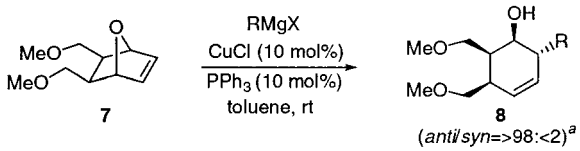


Table 3. Cu-Catalyzed Ring Opening of Oxabicycle **7** with Grignard Reagents



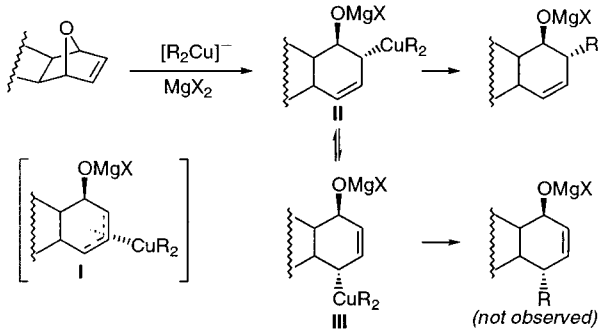
entry	X	R	product	time (h)	yield[b] (%)
1	Br	Me	**8a**	72	69
2[c]	Br	Me	**8a**	12	74
3	Br	Et	**8b**	0.5	61[d]
4	Br	*i*-Bu	**8c**	24	77[e]
5	Br	decyl	**8d**	24	78
6[c]	Cl	Cy	**8e**	12	42[d]
7[c]	Br	Ph	**8g**	12	79

[a] The syn diastereomer was not detected by ^{1}H NMR in the crude reaction mixture. [b] Yield after chromatographic purification. [c] Reaction carried out at 60 °C. [d] Diene **9** (see ref 25) was also isolated. [e] Yield in converted product (13% of starting **7** was recovered).

Aryl Grignard reagents such as PhMgBr failed to react with **7** at room temperature (less than 10% conversion was observed after 2 days).[26] However, we were pleased to find that PhMgBr efficiently reacted with **7** when the reaction temperature was increased to 60 °C, affording cyclohexanol **8g** in 79% yield (entry 7, Table 3). At this temperature, the addition of MeMgBr was complete after 12 h, instead of 3 days required at room temperature (entries 1 and 2).

Although a reaction pathway involving the participation of a (π-allyl)copper(III) intermediate **I**[27] (Scheme 1) cannot

Scheme 1. Mechanistic Proposal for the Cu-Catalyzed Ring-Opening of Oxabicyclic Alkenes with Grignard Reagents.



be ruled out, it would be difficult to explain the complete regioselectivity observed in all cases, even from the alkyl-substituted substrate **7** in which both termini of the allyl unit would have a very similar substitution. Rather, the results are more consistent with a copper-catalyzed S_N2' reaction

(26) The addition of Lewis acids such as $Zn(OTf)_2$, $ZnCl_2$, $CeCl_3$, LiI, or $Yb(OTf)_3$ did not improve the reactivity of the process.

(27) A similar (π-allyl)copper pathway has been suggested for the anti-stereoselective addition of dialkylzincs to oxabenzonorbornadienes; see ref 12.

in which the in situ formed organocuprate would react with the alkene anti with respect to the leaving group (endo attack). The resulting σ-allylic copper **II** would then undergo a reductive elimination to give the observed ring-opened product[28] faster than equilibration to the regioisomeric (σ-allyl)copper **III** through the (π-allyl)copper intermediate **I**. Presumably, triphenylphosphine acts as a ligand of copper, and the oxophilic magnesium salts present in the medium (Schlenk equilibrium) would coordinate the bicyclic oxygen favoring the C−O bond breaking.[29]

(28) It is known that, after an initial π-complexation of Cu^{I} to the double bond and subsequent S_N2' oxidative addition, the resulting (σ-allyl)−Cu^{III} complex can undergo a fast reductive elimination prior to isomerization: (a) Sofia, A.; Karlstrom, E.; Backvall, J.-E. *Chem. Eur. J*. **2001**, *7*, 1981−1989 (and references therein). For the formation of (σ-allyl)copper intermediates leading to anti S_N2' products in allylation of allylic substrates, see: (b) Bertz, S. H.; Copra, A.; Eriksson, M.; Ogle, C. A.; Seagle, P. *Chem. Eur. J*. **1999**, 2680−2691. (c) Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem*. **2001**, *66*, 5881−5889.

(29) It has been reported that the combination of an organocopper reagent and a Lewis acid greatly enhances the S_N2' selectivity. For an excellent review on reaction mechanisms of organocuprate reagents in organic transformations, see: Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed*. **2000**, *39*, 3750−3771.

In conclusion, we have developed an efficient copper-catalyzed anti-stereocontrolled ring-opening of [2.2.1]-oxabicyclic alkenes with Grignard reagents. The reaction is wide in scope for both the Grignard reagent and the oxabicyclic alkene. Extension of this reaction to other types of substrates, such as azabicyclic substrates, is currently under investigation.

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Supporting Information Available: A complete description of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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