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Copper Phosphoramidite Catalyzed Enantioselective Ring-Opening of Oxabicyclic Alkenes: Remarkable Reversal of Stereocontrol

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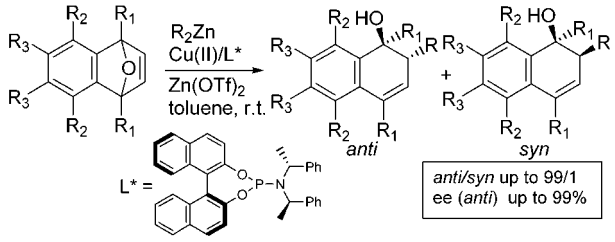
ABSTRACT



An unprecedented copper phosphoramidite catalyzed enantioselective alkylative ring-opening reaction of oxabenzonorbornadiene derivatives with dialkylzinc reagents is reported. The reaction shows high levels of *anti*-stereoselectivity (up to *anti*/*syn* >99:1), complementary to the Pd(0)-catalyzed *syn*-selective ring-opening protocol, allowing a new entry to *anti*-dihydronaphthols with high enantioselectivity (up to 99% ee).

In recent years, a number of catalytic asymmetric C−C bond formations[1] with excellent levels of stereocontrol have been developed using organozinc reagents in the presence of copper complexes of chiral phosphoramidite ligands.[2] Methodology includes 1,4-additions to enones and dienones,[3] tandem 1,4-additions and ring-annulations,[4] kinetic resolution of cycloalkenones,[5] and regiodivergent kinetic resolutions leading to cyclohexenols.[6] Remarkably high stereoselectivity was achieved using these novel monodentate ligands in catalytic asymmetric hydrogenations and Heck reactions.[7] As part of our program to further explore chiral copper phosphoramidite catalysts, ring-opening reactions using dialkylzinc reagents were investigated.

Ring-opening reactions of oxabicyclic compounds with a variety of organometallic reagents and other nucleophiles have emerged as attractive strategies to cyclic and acyclic compounds with multiple stereocenters.[8] Recently, Lautens

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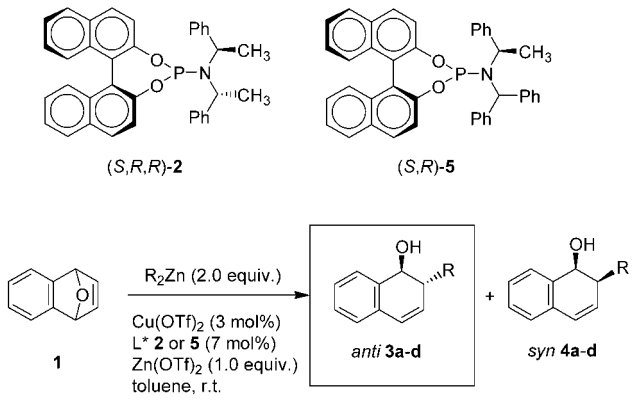
and co-workers developed a nickel-catalyzed hydroalumination,[9] a rhodium-catalyzed alcoholysis,[10] and a palladium-catalyzed alkylative-*syn*-selective-ring-opening of oxabicycles,[11] all featuring high enantioselectivities.

As organocuprates are effective in ring-opening of oxabicycles[12] and copper phosphoramidite catalysts show high regio- and enantioselectivities in ring-opening of diene-monoepoxides with dialkylzinc reagents,[6] we envisioned that copper-catalyzed asymmetric ring-opening of oxabicycles might be feasible.

We report here that monodentate phosphoramidites are effective chiral ligands for a copper-catalyzed ring-opening with excellent enantioselectivities (up to >99% ee). In sharp contrast to the palladium-catalyzed ring-opening reactions, high *anti*-selectivities (up to *anti*/*syn* >99:1) are found.

Preliminary experiments using $Cu(OTf)_2$, phosphoramidite **2**, and Et_2Zn in the ring-opening of oxabenzonorbornadiene **1** (Scheme 1) showed complete regioselectivity (only the S_N2'

Scheme 1



addition mode was observed), but the reaction was extremely slow (57% conversion after 120 h at room temperature). However, the stereoselectivities of the reaction were encouraging, affording a 4/1 mixture of adducts *anti*-**3a** (88% ee) and *syn*-**4a** (0% ee).[13] In the absence of the copper phosphoramidite catalyst, no significant reaction takes place.[13] We examined various reaction parameters (solvents, Lewis acids, copper salts, and ligands).[14] Much to our delight, by employing the in situ prepared catalyst derived from $Cu(OTf)_2$ and ligand **2** in the presence of 1 equiv of dry $Zn(OTf)_2$,[11] ring-opened product **3a** was obtained in high yield (88%) in 24 h with an *anti*/*syn* ratio of 98:2 (entry 1, Table 1).[15,16]

Table 1. Catalytic Enantioselective Addition of R_2Zn to Oxabenzonorbornadiene **1**[a]

entry	R	L*	anti/syn	yield[b] (%)	ee[c] (%)
1	Et	2	98/2	88 (**3a**)	90
2	Et	5	97/3	92 (**3a**)	94
3	Me[d]	2	99/1	17 (**3b**)	88
4	*i*-Pr[e]	2	70/30	55 (**3c**)	91
5	*n*-Bu	5	99/1	95 (**3d**)	92

[a] All reactions were run as described in the typical procedure.[16] Conversions of compound **1** were >98% unless stated otherwise. [b] Isolated yield of the anti products **3a**–**d**. [c] Determined by HPLC (Chiralcel OD or AD) for **3a**–**d**. [d] 35% conversion. [e] Reaction performed at −15 °C.

Moreover, the use of the new phosphoramidite **5** as the chiral ligand provided *anti*-**3a** with a 94% ee in 13 h (entry 2). The relative and absolute configuration of the *anti*-S_N2' adduct (1*S*,2*R*)-**3a** was unequivocally demonstrated by single-crystal X-ray analysis (see the Supporting Information). To extend the scope of the reaction, other dialkylzinc reagents were investigated (Table 1). Me_2Zn displayed lower reactivity, although the corresponding adduct *anti*-**3b** was obtained as a single diastereomer with 88% ee (entry 3). On the other hand, the use of a more reactive secondary dialkylzinc reagent such as $(i\text{-Pr})_2Zn$ afforded a consistent amount (30%) of the corresponding *syn*-S_N2'adduct **4c** as a racemate, probably arising from a $Cu(OTf)_2$-catalyzed (without interference of the phosphoramidite) or $Zn(OTf)_2$-mediated syn addition mode (entry 4).[13] The catalyzed addition of $(n\text{-Bu})_2Zn$ proceeds with high diastereo- and enantioselectivity (entry 5).

Next, the ring opening with Et_2Zn of oxabenzonorbornadienes **6**–**10**, bearing substituents in various positions with respect to the endocyclic oxygen, was examined. Chiral phosphoramidite **2** (7 mol %) and $Cu(OTf)_2$ (3 mol %) gave the best results with respect to the stereoselectivities of the addition.[17] As illustrated in Table 2, the presence of substituents of different nature and in various positions resulted in high diastereo- and enantioselectivities.[18] In particular, the catalyzed addition of Et_2Zn to 5,8-dimethyl derivative **8** delivered the corresponding adduct **13** as a single diastereoisomer with >99% ee (entry 3). Furthermore, it should be

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(13) All the minor *syn*-adducts obtained throughout this work are racemic. The copper phosphoramidite catalyst appears to be essential to obtain the *anti*-selective pathway. In fact, the addition of Et_2Zn alone (140 h, rt) gave only starting material and trace amounts of *syn*-adduct **4a**. On the other hand, the addition of Et_2Zn to **1** catalyzed by $Cu(OTf)_2$ (3.0 mol %) gave only the *syn*-adduct **4a** (full conversion, 55% isolated yield after 18 h at room temperature). The reaction performed in the presence of $Zn(OTf)_2$ (1.0 equiv) afforded *syn*-**4a** (42%) and α-naphthol (24%).

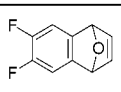
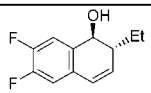
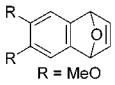
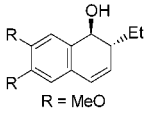
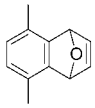
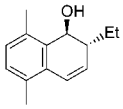
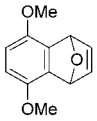
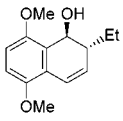
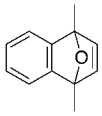
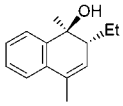
(14) The following Cu salts were examined: CuCN, CuBr–Me_2S, CuI. Solvents screened were THF, CH_3CN, CH_2Cl_2, and diglyme. In all cases, complex reaction mixtures containing racemic *syn*-adduct **4a** and only trace amounts of *anti*-adduct **3a** were obtained.

(15) The *anti*-stereochemistry was assigned on the basis of ^1H NMR analysis (Supporting Information) and comparison with NMR data of independent prepared *syn*-adducts.[11]

(16) For a typical procedure, see the Supporting Information.

(17) Chiral phosphoramidite **5** afforded compounds **11**–**15** with a slight decrease (2–3%) in stereoselectivity.

Table 2. Catalytic Enantioselective Ring-Opening of Oxabenzonorbornadiene Substrates **6**−**10** with $Et_2Zn/Cu(OTf)_2/2$[a]

entry	Substrate	time (h)	Product	yield (%)[b]	*anti* /*syn*	ee (%)
1	 **6**	70	 **11**	58	83/ 17	80
2	 **7**	70	 **12**	65	90/ 10	88
3	 **8**	16	 **13**	90	99/ 1	>99
4	 **9**	48	 **14**	82	90/ 10	97
5	 **10**	40	 **15**	85	92/ 8	92

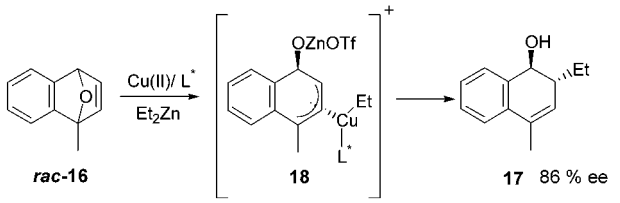
[a] All reactions were run as described in the typical procedure.[16] [b] Isolated yields of anti products.

noted that it was possible to obtain the *anti*-adduct **15**, containing a tertiary benzylic alcohol function, with a high level of diastereo- and enantioselectivity (entry 5).

In addition, the kinetic resolution[19] of an unsymmetrical substrate, i.e., racemic **16** (Scheme 2), with Et_2Zn afforded unreacted **16** in 92% ee at 56% conversion and exclusively *anti*-dihydronaphthol **17** (86% ee), which is regioisomeric to the tertiary alcohol obtained by the Pd-catalyzed protocol.[11a]

(18) The present copper-catalyzed protocol gave so far only very low yields of addition products when nonbenzylic oxabicyclic alkenes were employed.

Scheme 2



The selective ionization at the tertiary center of **16** points to a π-allyl pathway involving activation of the carbon−oxygen bond and *anti*-attack of the alkylcopper to form the allylcopper intermediate **18**. Subsequently, the allyl intermediate **18** undergoes a reductive elimination, with retention of configuration, at the less hindered secondary terminus.[6]

Control experiments[13] showed that the phosphoramidite ligand governs the *anti*-selective pathway in these reactions as the catalytic ring-opening of **1** in the absence of ligands **2** or **5** resulted in *syn*-**4a** exclusively.

In summary, we have developed a new copper-catalyzed nucleophilic ring-opening of oxabicyclic compounds using dialkylzinc reagents. The reaction shows an unprecedented high level of *anti*-stereoselectivity. It is complementary, both with respect to regio- and stereoselectivity, to the Pd(0)-catalyzed *syn*-selective ring-opening reported by Lautens, allowing the formation of *anti*-dihydronaphthols with high enantioselectivity. We are currently investigating the scope and mechanism of this methodology.

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Supporting Information Available: Experimental details describing the synthesis, characterization, and HPLC analysis of the ee's of products **3a**−**d**, **4a**−**d**, **11**−**15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Reactions performed for 60 h with 0.75 equiv of Et_2Zn and **2** (7 mol %). The use of $Zn(OTf)_2$ in this case caused a rapid rearrangement of **16** to 4-methyl-1-naphthol. Although deleterious in this case, the role of $Zn(OTf)_2$ in these ring-opening reactions seems to be that of a Lewis acid favoring the ionization of the bridgehead carbon−oxygen bond.