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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 formations¹ 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 oxabicycles¹² 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 Et₂Zn in the ring-opening of oxabenzonorbornadiene **1** (Scheme 1) showed complete regioselectivity (only the S_N2'

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

Table 1. Catalytic Enantioselective Addition of R₂Zn to Oxabenzonorbornadiene **1**^a

entry	R	L*	<i>anti/syn</i>	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>i</i> -Pr ^e	2	70/30	55 (3c)	91
5	<i>n</i> -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.

(88%) in 24 h with an *anti/syn* ratio of 98:2 (entry 1, Table 1).^{15,16}

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). Me₂Zn 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*-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*-Bu)₂Zn proceeds with high diastereo- and enantioselectivity (entry 5).

Next, the ring opening with Et₂Zn 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 Et₂Zn 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 Et₂Zn alone (140 h, rt) gave only starting material and trace amounts of *syn*-adduct **4a**. On the other hand, the addition of Et₂Zn 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–Me₂S, CuI. Solvents screened were THF, CH₃CN, CH₂Cl₂, 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 $\text{Et}_2\text{Zn}/\text{Cu}(\text{OTf})_2/2^a$

entry	Substrate	time (h)	Product	yield (%) ^b	<i>anti</i> / <i>syn</i>	ee (%)
1		70		58	83/ 17	80
2		70		65	90/ 10	88
3		16		90	99/ 1	>99
4		48		82	90/ 10	97
5		40		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 resolution¹⁹ 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 allyl-copper intermediate **18**. Subsequently, the allyl intermediate **18** undergoes a reductive elimination, with retention of configuration, at the less hindered secondary terminus.⁶

Control experiments¹³ 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 $\text{Zn}(\text{OTf})_2$ in this case caused a rapid rearrangement of **16** to 4-methyl-1-naphthol. Although deleterious in this case, the role of $\text{Zn}(\text{OTf})_2$ in these ring-opening reactions seems to be that of a Lewis acid favoring the ionization of the bridgehead carbon–oxygen bond.