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Copper-catalyzed asymmetric ring opening of oxabicyclic alkenes with organolithium reagents[†]

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A highly efficient method is reported for the asymmetric ring opening of oxabicyclic alkenes with organolithium reagents. Using a copper/chiral phosphoramidite complex together with a Lewis acid (BF₃·OEt₂), full selectivity for the *anti* isomer and excellent enantioselectivities were obtained for the ring opened products.

In the past decade, a variety of methods were developed for the transition-metal catalyzed ring opening of meso heterobicyclic alkenes 1 using various nucleophiles.^{1,2} This process is especially valuable as multiple stereocenters can be introduced simultaneously with high stereocontrol. In particular the enantioselective palladium-catalyzed ring opening using organozinc reagents, developed by Lautens et al., proceeds with high selectivity for the syn diastereomers and is a highly valuable transformation for the synthesis of multifunctional building blocks.^{3,4} Previously, racemic syn products could also be accessed from organolithium reagents and organocuprates in moderate to good yields.^{5–9} It is important to note that in the case of organocuprates, suprastoichiometric amounts are necessary (2.5-5 eq.). To the best of our knowledge there is only one example reported in which organolithium reagents are used for the asymmetric ring opening of oxabicyclic alkenes. The group of Lautens was able to convert an oxabicyclic compound using (-)-sparteine together with *n*-butyllithium providing the syn product with moderate enantioselectivity (51%) and yield (61%).⁷

The use of transition-metal catalysis has allowed for the development of methods applying softer organometallic reagents. In general most asymmetric ring opening procedures with carbon nucleophiles give the *syn* product as a result of *exo* attack of the nucleophile to the oxabicyclic alkene.² Exceptions leading to high *anti* selectivity are reported in our copper-catalyzed ring opening reactions using organozinc reagents in combination with a Lewis acid,¹⁰ and related methods using Grignard reagents^{11–14} and trialkylaluminium reagents.^{14,15}

Recently, our group developed the first copper-catalyzed asymmetric allylic alkylation protocol using organolithium reagents as nucleophiles (see Scheme 1).¹⁶ By excluding or



Scheme 1 Catalytic asymmetric allylic alkylation with organolithium reagents (for the ligand structure see Fig. 1).

minimizing the amount of ethereal solvents we were able to prevent the formation of highly reactive organolithium species, and by selecting dichloromethane as a solvent we were able to enhance the catalytic reaction selectively. Based on the excellent enantio- and regioselectivities obtained, we envisioned that this novel methodology could be extended towards the asymmetric ring opening of oxabicyclic alkenes. Organolithium reagents are arguably among the most widely used organometallic reagents in chemistry and are in general cheaper than their organozinc, Grignard or organoaluminium counterparts.^{17,18} Methodologies in which organolithium reagents can be applied directly as the enantioselective carbon–carbon bond forming reagents are therefore highly desirable, but challenging in view of their very high reactivity.

The asymmetric ring opening of oxabicyclic alkenes with organolithium reagents can lead to four products namely the desired *anti* product **3aa** and its *syn* diastereomers **4**, 1-naphthol **5** as a result of acid-catalyzed ring opening/aromatization and alkyl naphthalene **6** as a result of elimination of water followed by aromatization of product **3aa** or **4**. In our initial experiment



Fig. 1 Ligands used for the ring opening of oxabicyclic alkenes with organolithium reagents.

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Table 1 Screening of ligands and conditions with *n*-butyllithium (Scheme 2)^{*a*}

Entry	L	$BF_3 \cdot OEt_2$	<i>T</i> /°C	Solvent	Conversion (%)	Anti : syn	ee ^b (%)
1	L1	_	-80	CH_2Cl_2	_	_	nd
2^c	L2		-30	$C_2H_4Cl_2$	50	3:97	nd
3^d	L2		0	$C_2H_4Cl_2$	45	16:84	nd
4^d	L2		0	MTBE	Full ^e	3:97	nd
5^c	L2	Yes	-40	$C_2H_4Cl_2$	Full		nd
6	L2	Yes	-80	CH_2Cl_2	Full	>99:1	97
7	L3	Yes	-80	CH_2Cl_2	76	98:2	-69
8	L4	Yes	-80	CH_2Cl_2	53	93:7	-77
9	L5	Yes	-80	CH_2Cl_2	75	>99:1	-76
10^g	L2	Yes	-80	CH_2Cl_2	Full	>99:1	97

^{*a*} Reagents and conditions: **1a** (0.2 mmol), *n*-butyllithium (1.5 eq.), CuBr·Me₂S (5 mol%), L (6 mol%), solvent, temperature, 2 h. ^{*b*} % ee of the *anti* product. ^{*c*} 16 h. ^{*d*} 5 h. ^{*e*} Formation of side products. ^{*f*} Formation of **5** and **6** (1 : 1). ^{*g*} *n*-Butyllithium (1.1 eq.), 16 h.



Scheme 2 Copper-catalyzed asymmetric ring opening of oxabicyclic alkenes using *n*-butyllithium.

the optimized conditions using Taniaphos L1 as a ligand for the allylic alkylation of allylic bromides were employed (Table 1, entry 1).¹⁶ Unfortunately, no ring opening of the oxabicyclic alkene occurred at -80 °C.

We anticipated that higher temperatures were needed but in order to raise the temperature the solvent had to be changed to 1,2-dichloroethane in order to prevent carbene formation.^{19,20} This led to 50% conversion and syn selectivity for the ringopening reaction giving a racemic product due to the uncatalyzed reaction (Table 1, entry 2). We also switched to phosphoramidite ligands²¹ because they have been shown to perform very well both with organolithium reagents in the allylic alkylation¹⁶ as well as in the copper-catalyzed ring opening of oxabicyclic alkenes using organozinc reagents developed by our group.¹⁰ Increasing the temperature even further did not lead to higher conversion or selectivity (Table 1, entry 3). Switching solvents from 1,2-dichloroethane to methyl tert-butyl ether (MTBE) led to mainly syn product together with a considerable amount of side products (Table 1, entry 4). We then added a Lewis acid $(BF_3 \cdot OEt_2, 1.1 \text{ eq.})$ to activate the substrate and performed the reaction at -40 °C overnight (Table 1, entry 5). In this case full conversion was reached, but a 1 : 1 mixture of 1-naphthol 5, originating from Lewis acid-catalyzed ring opening, and *n*-butyl naphthalene **6**, originating from addition of the butyl group followed by elimination/aromatization, was observed (Table 1, entry 6).

Upon lowering the temperature to -80 °C in dichloromethane full conversion was obtained after 2 h, after which the reaction had to be stopped to prevent side-reactions.²² Using phosphoramidite ligand (*R*,*R*,*R*)-L2 (Fig. 1) exclusive

Table 2 Cu-catalyzed ring opening of 1a and 1b (Scheme 3)^a

Entry	Substrate	RLi	Anti : syn	$\operatorname{Yield}^{b}3(\%)$	ee 3 (%)
1	1a	<i>n</i> -BuLi (2a)	>99:1	84	97
2	1b	n-BuLi (2a)	>99:1	82	95
3	1a	EtLi (2b)	>99:1	80	98
4	1b	EtLi (2b)	>99:1	71	97
5	1a	<i>n</i> -HexLi (2c)	>99:1	81	97
6	1b	<i>n</i> -HexLi (2c)	>99:1	82	93
7	1a	<i>i</i> -BuLi (2d)	>99:1	86	97
8	1b	<i>i</i> -BuLi (2d)	>99:1	96	93
9	1a	TMSCH ₂ Li (2e)	>99:1	65 ^c	43

^{*a*} Reagents and conditions: **1** (0.2 mmol), *n*-butyllithium (1.1 eq.), CuBr·Me₂S (5 mol%), L (6 mol%), BF₃·OEt₂ (1.1 eq.), CH₂Cl₂, -80 °C, full conversion after 16 h. ^{*b*} Isolated yield. ^{*c*} Conversion \approx 70%.



Scheme 3 Copper-catalyzed ring opening of oxabicyclic alkenes 1a and 1b with organolithium reagents.

formation of the *anti* diastereomers was observed with excellent enantioselectivity (97% ee) (Table 1, entry 6). The use of other phosphoramidite ligands resulted in lower enantioselectivity compared to the values obtained with ligand (R,R,R)-L2 although excellent *anti* : *syn* ratios were achieved in all cases (Table 1, entries 7–9). The amount of organolithium reagent could be lowered to 1.1 eq. without affecting the selectivities (Table 1, entry 10). In this case the reaction mixture was stirred overnight to ensure full conversion while undesired side reactions were prevented.

After optimization of the reaction conditions the use of several organolithium reagents was examined for the ring opening of oxabicyclic alkenes **1a** and **1b** (Table 2). In all cases full conversion was obtained after stirring overnight using only a slight excess of organolithium reagent (1.1 eq.) and the *anti* product was formed exclusively (Scheme 3).

The ring opening of **1b** using *n*-butyllithium gave a slightly lower enantioselectivity than **1a** (Table 2, entry 2). Both ethyllithium as well as *n*-hexyllithium gave excellent enantioselectivities and isolated yields (Table 2, entries 3–6). Furthermore, the use of the more bulky reagent *i*-butyllithium also resulted in an excellent yield and enantioselectivity of the desired product **3ad** (Table 2, entries 7 and 8). The use of a trimethylsilyl-substituted organolithium reagent led to a decrease in reactivity and enantioselectivity (Table 2, entry 9).

Organolithium reagents commercially available as solutions in ethereal solvents were not effective under the optimized reaction conditions and no conversion was observed. Furthermore, substrates bearing electron donating groups were not compatible under the reaction conditions, leading to elimination of the alcohol group and aromatization of the naphthyl group. This substrate incompatibility has also been observed in the copper-catalyzed ring opening of oxabicyclic alkenes with aluminium and Grignard reagents.^{12,14} Financial support from The Netherlands Organization for Scientific Research (NWO-CW) is acknowledged. M.P. thanks the Xunta de Galicia for an Angeles Alvariño contract and Fondo Social Europeo.

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