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Copper-catalyzed desymmetrization of oxabenzonorbornadienes with aluminum reagents

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ABSTRACT

The desymmetrization of oxabenzonorbornadienes with aluminum reagents and SimplePhos as chiral ligand is described. The corresponding homoallylic alcohols are obtained in high yield, diastereoselectivity, and enantiomeric excess. Furthermore the first *anti* enantioselective desymmetrization with aromatic nucleophiles is reported.

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The copper-catalyzed enantioselective addition of organometallic nucleophiles to activated double bonds is a very important methodology to form C–C bond.[1] Selective creation of multiple stereocenters in one step is a highly valuable process. One way to construct multiple stereocenters is the enantioselective ring-opening reaction of oxabenzonorbornadienes with organometallic nucleophiles.[2] Two different pathways lead to diastereomeric products. The *syn* product is obtained via a carbometallation of the double bond from the less hindered *exo* face.[3] The *anti* product is obtained in the copper-catalyzed reaction via a pure S_N2' mechanism.[4,5]

Formation of the *syn* adduct is extensively documented with a large variety of transition metal complexes as catalyst (Pd, Rh, Ti, Zr).[6] These catalysts have been mainly used in combination with dialkylzinc reagents and more recently with aryl boronic acids. Among all these examples the use of aluminum reagents is rare. The sole report was published by Waymouth and co-workers, in which organoaluminum compounds were used in combination with early transition metals. The desymmetrization of oxabicyclic alkenes could be achieved in good yield with very high enantioselectivity.[6p]

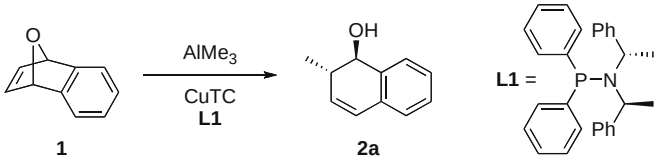
Formation of the *anti* adduct with hard nucleophiles has been less studied. Dialkylzinc reagents were used with phosphoramidite ligands by Pineschi, Feringa, and co-workers.[4] High diastereoselectivity and enantioselectivity were obtained. However a stoichiometric amount of a Lewis acid was necessary and transfer of the useful methyl group gave low yields. The more reactive Grignard reagents have also been applied. The first report was presented by Carretero and co-workers on the non-enantioselective desymmetrization of oxabicyclic alkenes with PPh_3 as ligand.[7] Following their work, Zhou and co-workers described the enantioselective version of the same reaction using chiral *spiro* phosphoramidite as ligand, and more recently they improved their results with *spiro* phosphine ligands.[8] However the use of commercially available and inexpensive trialkylaluminum reagents was not reported so far.

There are only a few reports of allylic alkylation with organoaluminum reagents. They have been employed in the copper-catalyzed desymmetrization of bicyclic hydrazines[9] and allylic substitution of allylic phosphates.[10]

Herein we wish to report the use of organoaluminum reagents in the copper-catalyzed desymmetrization of oxabenzonorbornadienes in presence of SimplePhos[9d] as chiral ligand (Scheme 1). The aim of the use of trialkylaluminum reagents was mainly to transfer the methyl group in high yield, diastereoselectivity, and enantioselectivity.

The initial tests were conducted on the oxabenzonorbornadiene **1**. Different copper salt and solvent were screened as the choice of the reaction conditions is known to have a large impact on the outcome of the reaction.[11]

It appears that the counter-ion of the copper salt plays a very important role on the reaction. When OTf was used as the counter-ion, the desired alcohol was not detected. Only aromatization product was obtained (Table 1, entries 1 and 2).[12] The halogen series of counter ion was studied and going from the chloride to the bromide and finally the iodide led to a decrease in conversion, diastereoselectivity, and enantioselectivity. While CuCl gave an interesting 80% de with 81% ee (Table 1, entry 3), CuBr or CuBr·Me_2S gave only 60% de, 50% ee (Table 1, entries 4 and 5) and CuI did not catalyze the reaction (Table 1, entry 6). With $Cu(OAc)_2 \cdot H_2O$ a high



1 **2a**

Scheme 1. Desymmetrization of **1**.

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Table 1
Screening of copper salt and solvent[a]

Entry	Copper	Solvent	Conversion[b] (%)	*anti:syn*[c]	ee[c] (%)
1	$Cu(OTf)_2$	CH_2Cl_2	—[d]	—	—
2	$CuOTf{\cdot}C_6H_6$	CH_2Cl_2	—[d]	—	—
3	CuCl	CH_2Cl_2	40[d]	90:10	81
4	CuBr	CH_2Cl_2	35	80:20	50
5	$CuBr{\cdot}Me_2S$	CH_2Cl_2	36	80:20	50
6	CuI	CH_2Cl_2	0	—	—
7	$Cu(OAc)_2{\cdot}H_2O$	CH_2Cl_2	30	95:5	89
8	$Cu(CH_3CN)_4{\cdot}BF_4$	CH_2Cl_2	66[e]	95:5	88
9	CuTC	CH_2Cl_2	54	99:1	89
10	CuTC	Et_2O	90	91:9	90
11	CuTC	THF	0	—	—
12	CuTC	PhMe	15	—	—
13	CuTC	MTBE	100 (93)	99:1	91
14[f]	CuTC	MTBE	100	99:1	92

[a] Reaction conditions: **1** (0.5 mmol), **L1** (3 mol %), Cu (3 mol %), solvent (3 ml), Me_3Al (1.2 equiv), rt, 20 h.
[b] Determined by ^1H NMR, isolated yield in parentheses.
[c] Determined by chiral GC.
[d] No traces of desired alcohol were detected.
[e] 1-Naphthol and 1-methylnaphthalene were detected as by-products.
[f] Reaction preformed at 0 °C.

enantioselectivity was observed but the conversion remained low (Table 1, entry 7). The weakly coordinated $Cu(CH_3CN)_4{\cdot}BF_4$ led to the formation of substantial amount of by-products despite good conversion and enantioselectivity (Table 1, entry 8). Finally, copper thiophene-2-carboxylate (CuTC) appeared as the most efficient copper salt as after 20 h 54% conversion was reached with complete diastereoselectivity and 89% ee (Table 1, entry 9). In order to improve the reactivity, we investigated other solvents. Diethyl ether increased the reactivity as well as the enantioselectivity (Table 1, entry 10). Changing the solvent to THF led to no conversion (Table 1, entry 11), while employment of toluene resulted in only 15% conversion after 20 h (Table 1, entry 12). Finally, with the safe and environmentally friendly methyl *tert*-butyl ether (MTBE), the reaction proceeded to completion in 20 h, with complete diastereoselectivity and 91% ee (Table 1, entry 13). Performing the reaction at 0 °C did not improve the result (Table 1, entry 14).

The next step was to study the influence of the ligand on the reaction under optimized conditions (Fig. 1). The high tunability of the SimplePhos family around both the phosphorous atom and the amine moiety was used to increase the bulk around each part. We also took advantage of the coordinating solvent to test phosphoramidite ligands.[9c]

First, the bulk around the phosphorous part was increased with **L2**. Alcohol **2a** was obtained with full conversion in a very good *anti/syn* ratio with 90% ee (Table 2, entry 2). This value was slightly lower than that obtained with **L1** (Table 2, entry 1). The bulk around the amine part was then increased by using **L3** and once more total conversion to **2a** was obtained with nearly perfect diastereoselectivity and ee in the same range than previously observed (Table 2, entry 3). It appears that the outcome of the reaction is not sensible to the bulk of the ligand. We next turned our attention on another class of successful ligands in asymmetric allylic alkylation, the phosphoramidite ligands (**L4**–**L6**). They were compatible with the reaction conditions as the reaction was carried out in coordinating solvent.[9c] A *match/mismatch* effect was pointed out by testing the diastereomeric pair **L4** and **L5**. (*S,S,S*)-**L4** is the *match* ligand with 66% ee (Table 2, entry 4), while the other diastereomer (*R,S,S*)-**L5** is the *mismatch* one with only 45% ee (Table 2, entry 5). We also noticed that the side of the attack was dictated by the binaphthol part. The *tropos* **L6** gave a result in between with 57% ee. However the phosphoramidite ligands were less efficient than the SimplePhos ligands for this transformation. The SimplePhos **L1** was Selected as ligand for the next part of the study.

The scope of the reaction was then studied by modifying the substrate (Scheme 2). The electron density around the aromatic part was modified. It was decreased by adding two fluorine atoms **3** and increased by adding two methoxy groups in different positions **4** and **5**.

Table 2
Modification of the ligand[a]

Entry	Ligand	Conversion[b] (%)	*anti:syn*[c]	ee[c] (%)
1	**L1**	100	99:1	91 (−)
2	**L2**	100	99:1	90 (−)
3	**L3**	100	99:1	92 (−)
4	(*S,S,S*)-**L4**	100	99:1	66 (+)
5	(*R,S,S*)-**L5**	100	99:1	45 (−)
6	**L6**	100	99:1	57 (−)

[a] Reaction conditions: **1** (0.5 mmol), CuTC (3 mol %), ligand (3 mol %), MTBE (3 ml), Me_3Al (1.2 mmol), rt, 20 h.
[b] Determined by ^1H NMR.
[c] Determined by chiral GC.

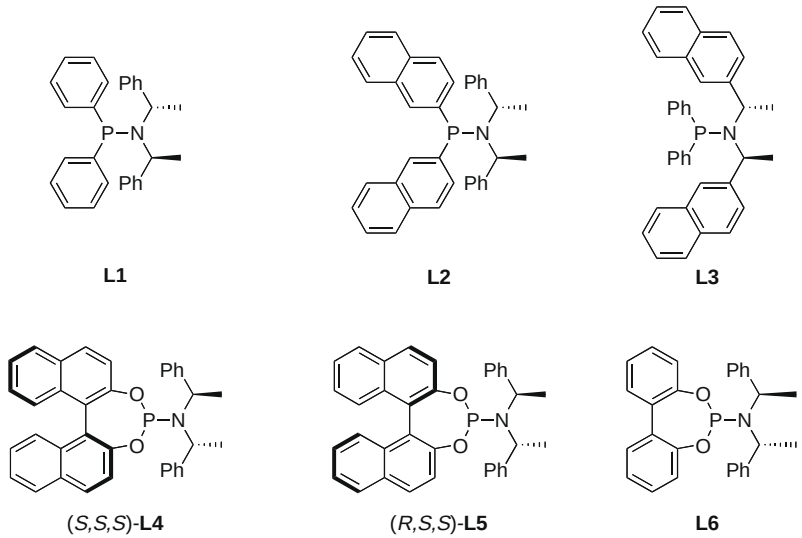
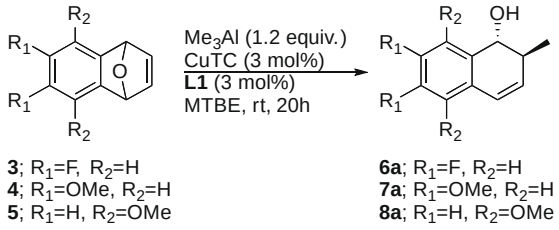


Figure 1. Ligands used in this study.



Scheme 2. Substrate scope.

The different substrates are compatible with the reaction conditions. The electron-deficient alcohol **6a** was isolated in good yield with a slightly lower diastereoselectivity but a high enantiomeric excess (Table 3, entry 2). Electron-rich substrates were also good candidates for this reaction as the corresponding alcohols were isolated in good yield with good diastereoselectivity and 87–88% ee (Table 3, entries 3 and 4).[13] The developed conditions appeared to accept substrates with different electron density around the aromatic part.[14]

A large range of trialkylaluminum reagents are commercially available and we wanted to check if our methodology could be applied to other aluminum reagents.

The substrates **1**, **4,** and **5** were then tested with different trialkylaluminum reagents. When the chain length was increased, the same level of enantioselectivity was maintained (Table 4, entries 1–3). Bulky *i*-Bu_3Al gave the highest enantioselectivity with 94% ee, a good isolated yield, and a high diastereoselectivity (Table 4, entry 4). Electron-rich alcohols **7b** and **8b** were obtained in high diastereoselectivity with the same level of enantioselectivity as for the reaction with Me_3Al (Table 4, entries 5 and 6). Only the more hindered *i*-Bu_3Al is not a good nucleophile as the reaction resulted in the aromatization of the substrate (Table 4, entry 7).

Very recently, the group of Hoveyda[15a] and our group[15b] described tandem lithium/aluminum exchange from aryl lithium reagents followed by an asymmetric conjugate addition. The ratio of the transferred aryl group is very high and the product is obtained in high enantioselectivity. We envisaged that this approach could be used to perform the desymmetrization of oxabenzonorbornadienes with aryl nucleophiles (Scheme 3).

Two reactants were used to transmetallate from lithium to aluminum. When Et_2AlCl was used the ratio of phenyl group versus ethyl group transfer was 40:60 with 84% ee and 94% ee, respectively. To increase the amount of phenyl group transfer we decided to use the more hindered *i*-Bu_2AlCl as transmetallating agent. Unfortunately the effect on the aryl/alkyl transfer was not the expected one as more alkyl group was transferred.

We have shown that organoaluminum reagents are efficient and cheap reagents for the desymmetrization of oxabenzonorbornadienes. The methyl group can be transferred in high yield and with high enantioselectivity.[16] The reaction can be extended to other alkyl group. We also have shown that the tandem lithium aluminum exchange desymmetrization reaction can be applied in this case. This work is currently under development, especially the transfer of aryl group and new tandem reactions.

Table 3
Scope substrate with Me_3Al

Entry	Substrate	Product	Yield[a] (%)	*anti*:*syn*[b]	ee[c] (%)
1	**1**	**2a**	93	99:1	91
2	**3**	**6a**	85	94:6	91
3	**4**	**7a**	69	99:1	88
4	**5**	**8a**	88	93:7	87

[a] Isolated yield of the *anti* alcohols.
[b] Determined by ^1H NMR.
[c] Determined by chiral GC or chiral SFC.

Table 4
Reactions with various trialkylaluminum reagents

Entry	Substrate	R	Product	Yield[a] (%)	*anti*:*syn*[b]	ee[c] (%)
1	**1**	Et	**2b**	79	99:1	92
2	**1**	*n*-Pr	**2c**	50	95:5	87
3	**1**	*n*-Bu	**2d**	95	99:1	87
4	**1**	*i*-Bu	**2e**	71	99:1	94
5	**4**	Et	**7b**	95	99:1	89
6	**5**	Et	**8b**	(100)	99:1	88
7	**5**	*i*-Bu	**8e**	—	—	—

[a] Isolated yield of the *anti* alcohols, conversion in parentheses
[b] Determined by ^1H NMR.
[c] Determined by chiral GC or chiral SFC.

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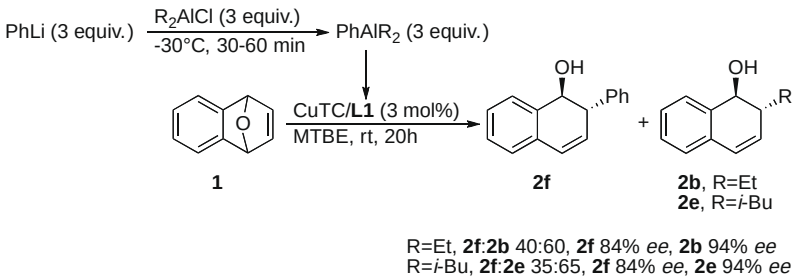
References and notes

1. (a) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823; (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824–2852.
2. (a) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48–58; (b) Pineschi, M. *New J. Chem.* **2004**, *28*, 657–665.
3. Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804–1805.
4. Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703–2705.
5. Persson, E. S. M.; van Klaveren, M.; Grove, D. M.; Bäckvall, J. E.; van Koten, G. *Chem. Eur. J.* **1995**, *1*, 351–359.
6. For palladium catalysis see: (a) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971–1973; (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834–6839; (c) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, R.; Carretero, J. C. *Chem. Commun.* **2002**, 2512–2513; (d) Lautens, M.; Hiebert, S. *J. Am. Chem. Soc.* **2004**, *126*, 1437–1447; (e) Cabrera, S.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3944–3947;



Scheme 3. Tandem Li–Al exchange desymmetrization reaction.

(f) Dotta, P.; Kuwar, P. G. A.; Pregosin, P. S.; Albinati, A.; Rizzato, S. *Organometallics* **2004**, *23*, 2295–2304; (g) Li, M.; Yan, X.-X.; Hong, W.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 2833–2835; (h) Imamoto, T.; Sugita, K.; Yoshida, K. *J. Am. Chem. Soc.* **2005**, *127*, 11934–11935; (i) Cabrera, S.Gómez Arrayás, R.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 17938–17947; (j) Imamoto, T.; Kumada, A.; Yoshida, K. *Chem. Lett.* **2007**, *36*, 500–501; (k) Zhang, T.-K.; Yuan, K.; Hou, X.-L. *J. Organomet. Chem.* **2007**, *692*, 1912–1919; (l) Imamoto, T.; Saitoh, Y.; Koide, A.; Ogura, T.; Yoshida, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8636–8639; (m) Zhang, T.-K.; Mo, D.-L.; Dai, L.-X.; Hou, X.-L. *Org. Lett.* **2008**, *10*, 3689–3692; For rhodium catalysis (n) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390–391; (o) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311–1314; For Ti and Zr catalysis see (p) Millward, D. B.; Sammis, G.; Waymouth, R. M. *J. Org. Chem.* **2000**, *65*, 3902–3909.

7. (a) Gomez Arrayas, R.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333–1336; (b) Gomez Arrayas, R.; Cabrera, S.; Carretero, J. C. *Synthesis* **2006**, 1205–1219.
8. (a) Zhang, W.; Wang, L.-X.; Shi, W.-J.; Zhou, Q.-L. *J. Org. Chem.* **2005**, *70*, 3734–3736; (b) Zhang, W.; Zhu, S.-F.; Qiao, X.-C.; Zhou, Q.-L. *Chem. Asian J.* **2008**, *3*, 2105–2111.
9. (a) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605–3607; (b) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Pure Appl. Chem.* **2006**, *78*, 463–467; (c) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581–3584; (d) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465.
10. Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Amer. Chem. Soc.* **2008**, *130*, 446–447.
11. Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.
12. 1-Naphthol and 2-methylnaphthalene were obtained. For $Cu(OTf)_2$ catalyzed aromatization of oxabenzonorbornadienes see: Peng, F. Z.; Fan, B. M.; Shao, Z. H.; Pu, X. W.; Li, P. H.; Zhang, H. B. *Synthesis* **2008**, 3043–3046.
13. The lower yield in **7a** is mainly due to aromatization during the purification steps.
14. Non-benzylic substrates were not reactive under the reaction conditions.
15. (a) May, T. L.; Brown, M. K.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7358–7362; (b) Hawner, C.; Li, K. Y.; Cirriez, V.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8211–8214.
16. *Typical procedure*: In a dried Schlenck tube under nitrogen atmosphere were placed CuTC (2.9 mg, 0.015 mmol, 3 mol %) and **L1** (6.8 mg, 0.015 mmol, 3 mol %). MTBE was added (3 ml) and mixture was stirred at room temperature for 20 min. The oxabicyclic alkene (0.5 mmol) was added. R_3Al in hexanes (0.6 mmol) was added dropwise over a period of 3 min. The reaction was stirred for 20 h and then quenched with water and HCl (1 N). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated. The crude was purified by flash chromatography (*c*-Hex then EtOAc:*c*-Hex 15:85). The alcohol **2a** was obtained with 90% yield (80 mg). $[\alpha]_D^{20}$ −242.6 (*c* = 0.69, $CHCl_3$, ee 91%). ^1H NMR (400 MHz, $CDCl_3$): 7.38 (d, *J* = 6.2 Hz, 1H), 7.29–7.19 (m, 2H), 7.09 (d, *J* = 6.2 Hz, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 5.91 (dd, *J* = 9.5, 4.4 Hz, 1H), 4.44 (d, *J* = 5.8 Hz, 1H), 2.68–2.56 (m, 1H), 1.74 (d, *J* = 5.8 Hz, 1H), 1.05 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 135.7, 132.3, 128.3, 127.6, 127.2, 126.4, 125.8, 125.7, 74.1, 37.4, 16.9.