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Addition of a Chiral Copper Reagent Derived from Propargylic Oxazolidininone to Aldehydes

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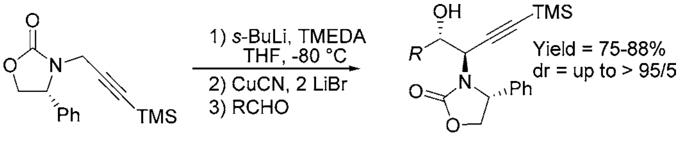
ABSTRACT



R = *i*-Pr, *c*-Hex, *n*-Pr, *t*-Bu, Ph, propenyl, pentynyl

The copper reagent arising from an optically pure propargylic oxazolidinone was found to react regio- and diastereoselectively with aldehydes, leading, in a one-pot procedure, to the *anti* homopropargylic amino alcohols derivatives in good yields.

We have recently disclosed a diastereoselective synthesis of propargylic amino alcohols by addition of metalated propargylic amine derivatives to aldehydes.[1] The *anti* or *syn* selectivity was controlled by a simple change in the nature of the metallic species (copper or zincate), which gave a simple and versatile access to *anti* or *syn* propargylic amino alcohols. Encouraged by these results, we decided to develop an asymmetric version of this methodology.

In this reaction involving a probable metallic allenic species,[2] to obtain an enantioselective transformation, one possibility was to control its axial chirality. We postulated that this could be achieved through the control of the stereochemistry of the nitrogen-substituted carbanion, precursor of the allenic metal, by using a chiral auxiliary attached to nitrogen. To achieved this goal, one of the most convenient way would be the use of a propargylic chiral oxazolidinone.[3] Very recently, building on Marschall's tin chemistry, Hegedus used propargylic oxazolidinones to prepare selectively allenyl tin derivatives that were isolated and then added, in the presence of Lewis acids, to aldehydes to yield the corresponding homopropargylic alcohols with an excellent *syn* selectivity.[4] In our behalf, we decided to develop a one-pot procedure based on our copper methodology.

First, we checked the influence of the nature of the metal on the regioselectivity of the reaction. Oxazolidinone (*R*)-**1** was metalated in THF by a *n*-BuLi/TMEDA mixture[5] at −80 °C. The resulting lithiated derivative **2**, probably diastereomerically defined via the equilibrium depicted in Scheme

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(1) (a) Bernaud, F.; Vrancken, E.; Mangeney, P. *Org. Lett.* **2003**, *5*, 2567−2569. (b) Bernaud, F.; Vrancken, E.; Mangeney, P. *Synlett* **2004**, 1080−1082.

(2) (a) Yamamoto, H. Propargyl and allenyl organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 2, pp 81−98. (b) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31−47.

(3) (a) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546−8548. (b) Tomoyasu, T.; Tomooka, K.; Nakai, T. *Tetrahedron Lett.* **2000**, *41*, 345−349. (c) Gaul, C.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 772−787. (d) Berry, C.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challepan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038−4042. (e) De los Rios, C.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 6541−6543. (f) Hyland, C. J. T.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 8628−8630.

(4) (a) Ranslow, P. B. D.; Hegedus, L. S.; de los Rios, C. *J. Org. Chem.* **2004**, *69*, 105−111. (b) Achmatowicz, M.; Hegedus, L. S. *J. Org. Chem.* **2004**, *69*, 2229−2234.

(5) In the absence of TMEDA, we have observed the formation of variable amounts of the free (NH) oxazolidinone.

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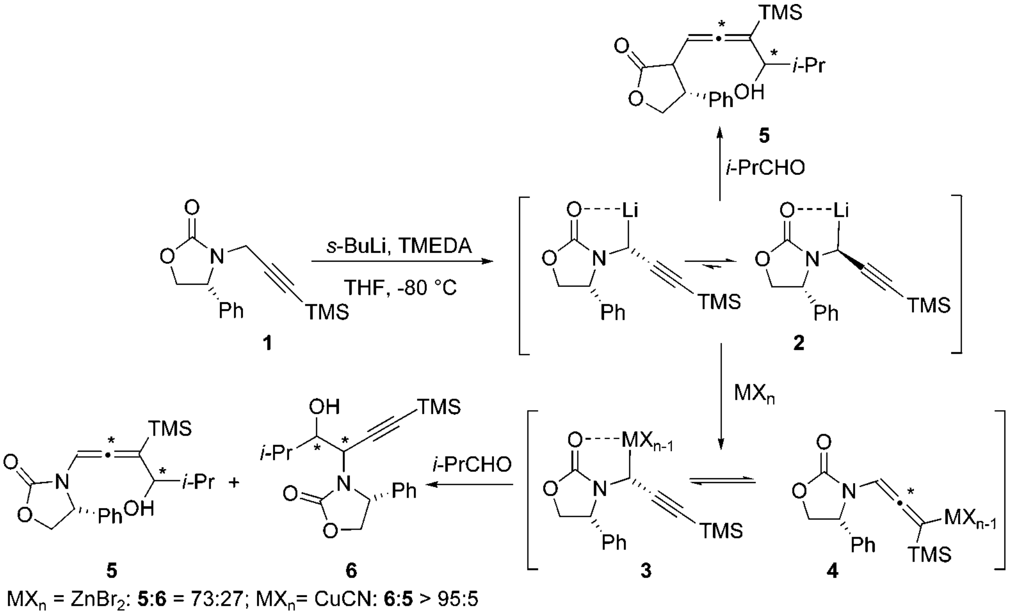
Scheme 1. Influence of the Metal on Regioselectivity



1,[3a] was then either used as is or transmetalated with $ZnBr_2$ or CuCN, 2 LiBr before addition of isobutyraldehyde.

We found that the regioselectivity is dependent on the Lewis acidity of the metal. The very oxophilic lithium remaining in the propargylic position gave only the allenic alcohol **5** as a 72:28 mixture of diastereomers. This result was in good agreement with Seebach's observations for titanium derivatives.[6] The zinc species afforded a mixture of allenic **5** (dr > 95:5) and homopropargylic alcohols **6** (dr 69:31) as the result of a probable metalotropic equilibrium between the propargylic **3** and allenic **4** metal (MX_{n-1} = ZnBr) species. The best result was obtained by the use of the copper derivative, which led with total regioselectivity to homopropargylic alcohol **6**. Due to the general preference of allenic organometallic species for S_e'-type reactions when they react with aldehydes, it is reasonable to involve an allenylcopper intermediate to explain the formation of the homopropargylic alcohol.[7] This alcohol was obtained with a very good diastereoselectivity as a mixture of two diastereomers in a 93:7 ratio (85% yield). The relative and absolute configurations of the new stereogenic centers of both major and minor stereoisomers (the four possible diastereomers are depicted in Figure 1) were determined by X-ray analysis.[8] The major one was found to be *anti* and of (*S*,*R*,*R*) configuration (Figure 2) as the result of an approach of the aldehyde *anti* to the phenyl of the chiral auxiliary to give *anti*$_a$-**6** (Scheme 2). The minor isomer was also of *anti* stereochemistry but of (*R*,*S*,*R*) absolute configuration (Figure 2). This isomer, *anti*$_s$-**6**, results from an attack *syn* to the phenyl group. Thus, in contrast to the amine case where the

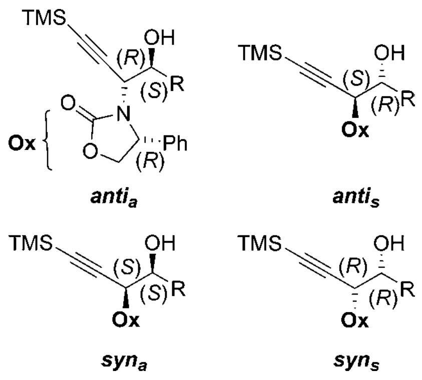


Figure 1. Structure of the four possible diastereomers.

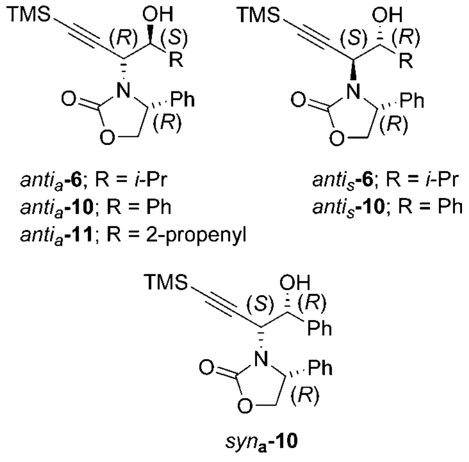


Figure 2. Absolute configurations determined by X-ray analyses.

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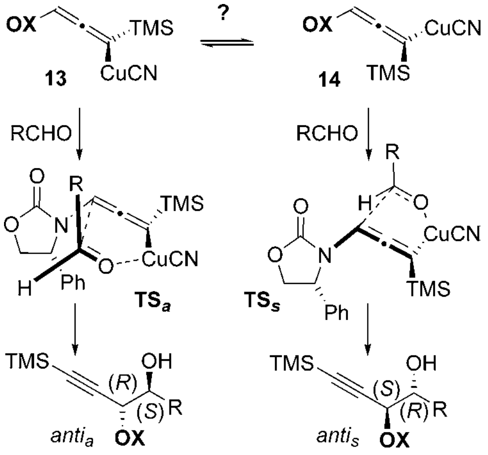
[6] Gaul, C.; Seebach D. *Helv. Chim. Acta* **2002**, *85*, 963−978.

Scheme 2



syn isomer was present (2−5%),[1] no *syn*-**6** isomer (Figure 1) was detected here.

Then, we checked the generality of this reaction with several aldehydes (Table 1). As shown in this table, except for benzaldehyde (entry 5), again only two diastereomers were obtained with a good selectivity. The stereochemistry of the major isomers **6**−**12** was found to be *anti*$_a$ (*S*,*R*,*R* absolute configuration).

Table 1. Addition of Copper Reagent to Several Aldehydes

entry	RCHO	major stereoisomer	yield (%)^a	*anti*$_a$:*anti*$_s$:*syn*$_a$:*syn*$_s$^{b}
1	*i*-PrCHO	*anti*$_a$-**6**	82	93:7:−:−
2	*c*-HexCHO	*anti*$_a$-**7**	88	95:5:−:−
3	*n*-PrCHO	*anti*$_a$-**8**	83	93:7:−:−
4	*t*-BuCHO	*anti*$_a$-**9**	84	100:−:−:−
5	PhCHO	*anti*$_a$-**10**	52	59:9:32:−
6	2-propenylCHO	*anti*$_a$-**11**	78	87:13:−:−
7	2-heptynylCHO	*anti*$_a$-**12**	75	86:14:−:−

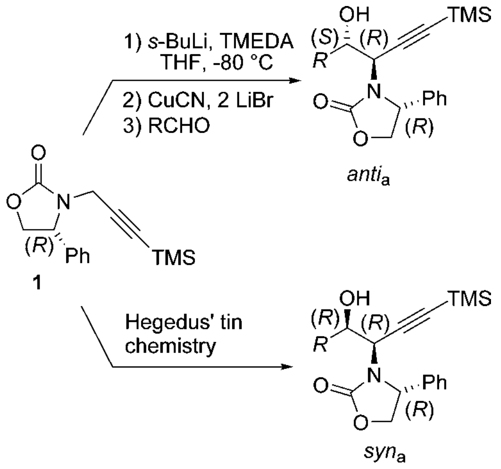
^{a} Isolated yields. ^{b} Determined by ^{1}H NMR of the crude product.

X-ray analysis was obtained for *anti*$_a$-**10** and *anti*$_a$-**11**[9] and the stereochemistry of **7**, **8**, **9**, and **12** was inferred by comparison of NMR spectra. Similarly, the stereochemistry of the minor isomer *anti*$_s$-**10** (Figure 2) was determined by X-ray analysis and found to be (*R*,*S*,*R*).[10] By analogy and by comparison of their NMR spectra, we assumed the same stereochemistry for all minor stereoisomers *anti*$_s$-**6**−**9** and *anti*$_s$-**11**−**12**. Noteworthy, no *syn*$_a$ isomers corresponding to the ones obtained by Hegedus[3] were detected in the crude mixture except in one case (entry 5, Table 1). Indeed benzaldehyde was found to be a particular case, the *syn*$_a$-**10** isomer (Figure 2)[11] being obtained in addition with the usual *anti*$_a$ and *anti*$_s$ isomers. Any attempts to increase the selectivity for this aldehyde, for instance, by adding HMPA or by changing the nature of the copper salt (CuI or CuSCN instead of CuCN) failed.

If we assume an allenylcopper reagent as intermediate, the *anti*$_a$ stereochemistry of the major diastereomers would be in good accordance with the classical Yamamoto−Chodkiewicz cyclic transition state usually involved for similar reactions, occurring *anti* to the oxazolidinone's phenyl group (**TS**$_a$, Scheme 2).[12] Such a model would involve an allenyl copper species **13**, which would be the result of a supra Li−Cu transmetalation process (retention of configuration).[13] This transition state being sterically driven, it could also account for the formation of the minor *syn*$_a$-**10** as a consequence of poor steric interactions between the less hindered face of the oxazolidinone and the phenyl group of the benzaldehyde.

The formation of the *anti*$_s$ minor diastereomers is more surprising. The *anti* relative stereochemistry being the result of a cyclic transition state, the formation of *anti*$_s$ isomers implies the formation of the transient allenyl copper **14** where the copper stands *syn* to the phenyl group (see **TS**$_s$, Scheme 2). Two possible explanations can be brought forward to rationalize the formation of these two diastereomeric allenic-copper derivatives: the transmetalation is not totally stereoselective, or such copper species are not configurationally stable.[14] The fact that the proportion of *anti*$_s$ isomers varies with the nature of the aldehyde seems to rule out the first hypothesis. Indeed lack of stereoselectivity in the transmetalation step should be independent from the electrophile used. Therefore, the sterochemical course of the reaction might arise from a kinetic dynamic resolution of an configurationally unstable allenyl copper species **13** and **14** (Scheme 2).

Scheme 3. Comparison with the Procedure of Hegedus



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(7) For some exemples of Li, Ti, In, and Zn derivatives, see: (a) Reich, H. J.; Holladay, J. E.; Derek Mason, J.; Sikorski, W. H. *J. Am. Soc.* **1995**, *117*, 12137−12150. (b) Nakagawa, T.; Kasatskin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207−3210. (c) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501−1510. (d) Song, Y.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 3543−3545. (e) Marshall, J. A.; Mulhearn, J. J. *Org. Lett.* **2005**, *7*, 1593−1596.

(8) Crystallographic data for the structural analysis have been deposited with the crystallographic Data Center, no. CCDC 283800 for *anti*$_a$-**6** and no. CCDC 273816 for *anti*$_s$-**6**.

(9) Crystallographic data for the structural analysis have been deposited with the crystallographic Data Center, no. CCDC 275717 for *anti*$_a$-**10** and no. CCDC 275719 for *anti*$_a$-**11**.

In conclusion, we have developed a practical and efficient one-pot methodology for the preparation of enantioenriched *anti* homopropargylic-amino alcohols derivatives that is complementary to Hegedus' tin strategy (Scheme 3). This procedure involves the synthesis and the use of an amino-substituted copper reagent for which the real structure and configurational stability still need to be determined. Efforts in this way as well as synthetic applications are in progress and will be published in due course.

Acknowledgment. We thanks Prof. Kamal Boubekeur for crystal structure determinations and Prof. Alex Alexakis and Prof. Jean Normant for many interesting discussions.

Supporting Information Available: Spectral and analytical data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Crystallographic data for the structural analysis of *anti*$_S$-**10** have been deposited with the crystallographic Data Center, no. CCDC 273817.

(11) Crystallographic data for the structural analysis of *syn*$_a$-**10** have been deposited with the crystallographic Data Center, no. CCDC 275718.

(12) Even if, as noticed by one of our referees, one cannot exclude the direct addition of a propargylcopper reagent.

(13) For an exemple of a Li−Cu transmetalation with retention of configuration of a nonmesomerically stabilized lithium derivative, see: Dieter, R. K.; Chen, N.; Watson, R. *Tetrahedron* **2005**, *61*, 3221−3230 and references herein.

(14) (a) Linderman, R.; Griedel, B. D. *J. Org. Chem.* **1991**, *56*, 5491−5493. (b) Hupe, E.; Knochel, P. *Org. Lett.* **2001**, *3*, 127−130. (c) Mohapatra, S.; Bandyopadhyay, A.; Barma, D. K.; Capdevila, J. H.; Falck, J. R. *Org. Lett.* **2003**, *5*, 4759−4762. (d) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. H.; Lu, K.; Watson, R. *J. Org. Chem.* **2004**, *69*, 3076−3086.