ORGANIC
LETTERS

2012
Vol. 14, No. 14
3576–3579

Significant Asymmetric Amplification in Enantioselective Cu/DiPPAM-catalyzed 1,6- and 1,4-Conjugate Additions of Diethylzinc to (Di)enones

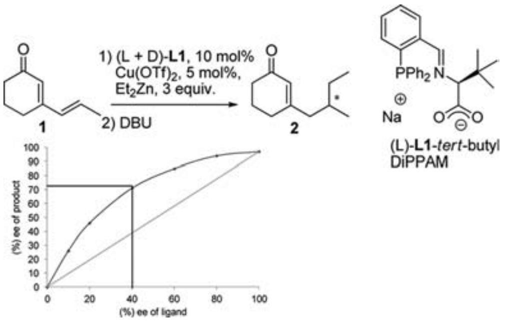
Magaly Magrez,[†,§] Joanna Wencel-Delord,[†,§] Alexandre Alexakis,[*,‡]
Christophe Crévisy,[*,†,§] and Marc Mauduit[*,†,§]

Ecole Nationale Supérieure de Chimie de Rennes, CNRS, UMR 6226, Avenue du Général Leclerc, CS 50837, 35708 Rennes Cedex 7, France, Department of Organic Chemistry, University of Geneva, Quai Ernest Ansermet 30, 1211 Geneva, Switzerland, and Université Européenne de Bretagne, 5 Bd Laënnec, 35000 Rennes, France

crevisy@ensc-rennes.fr; marc.mauduit@ensc-rennes.fr; Alexandre.Alexakis@unige.ch

Received April 5, 2012

ABSTRACT



An unprecedented and strong positive nonlinear effect (NLE) was observed in Cu/DiPPAM-catalyzed asymmetric 1,6-conjugate addition of Et_2Zn on (*E*)-3-(prop-1-en-1-yl)cyclohex-2-enone (71% ee reached with a 40% ee ligand). Moreover, similar behaviors were observed in Cu/DiPPAM-catalyzed 1,4-asymmetric conjugate additions of Et_2Zn on both cyclohexenone and (*E*)-3-non-3-en-2-one (83% and 70% ee, respectively, reached with a 40% ee ligand).

In order to extend the application of asymmetric catalysis, particularly for industrial purposes, there is a need for new chiral ligands that can be synthesized in very short and efficient routes. In this context, we have recently developed the DiPPAM family, which can be easily obtained from diphenylphosphinobenzaldehyde and an amino acid. These ligands, which are a simplified version of Hoveyda's salen-peptide ligands,[1] proved to be efficient in Cu-catalyzed 1,4-conjugate additions of dialkylzinc to both cyclic and acyclic enones[2,3] and also in 1,6-conjugate addition of dialkylzinc on cyclic dienones.[4] Although preliminary mechanistic studies had already been undertaken dealing with the 1,4-conjugate addition reaction, they had to be pursued and extended to the 1,6-conjugate addition. The observation of nonlinear effect (NLE) can help

---

[†] Ecole Nationale Supérieure de Chimie de Rennes.

[§] Université Européenne de Bretagne.

[‡] University of Geneva.

(1) (a) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755–756. (b) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 13362–13363. (c) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306–5310. (d) Kacprzynski, M. A.; Kazane, S. A.; May, T. L.; Hoveyda, A. H. *Org. Lett.* **2007**, *9*, 3187–3190.

(2) (a) Wencel, J.; Rix, D.; Crévisy, C.; Mauduit, M. PCT Int Appl WO 2009050284, 2009. (b) Wencel, J.; Rix, D.; Jennequin, T.; Labat, S.; Crévisy, C.; Mauduit, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1804–1809.

(3) Magrez, M.; Wencel-Delord, J.; Crévisy, C.; Mauduit, M. *Tetrahedron* **2012**, *68*, 3507–3511.

(4) Wencel-Delord, J.; Alexakis, A.; Crévisy, C.; Mauduit, M. *Org. Lett.* **2010**, *12*, 4335–4337.

(5) For a recent review on NLE: Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456–494.

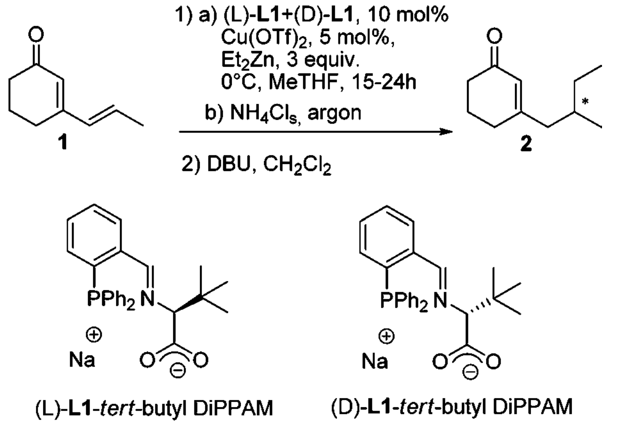
(6) For general reviews on Cu-catalyzed ACA, see: (a) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039–1075. (b) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796–2823.

10.1021/ol300866p

explain reaction mechanisms.[5] NLEs have been already observed in Cu-catalyzed 1,4-conjugate additions to enones.[6] Early observations were reported in 1994 by Pfaltz[7] and van Koten[8] with Grignard reagents. In the case of addition of organozinc nucleophiles, both negative and positive NLEs were reported. Moderate depletions were observed by Feringa in the Cu/phosphoramidite-catalyzed addition on cyclohexenone and chalcone,[9] Fu in the Cu/phosphaferrocene–oxazoline catalyzed addition on 4-chlorochalcone,[10] and Ito in the Cu/phosphino-phenol-catalyzed addition to chalcone.[11] An amplification (58% ee was reached with a 40% ee ligand) in agreement with the Kagan ML_2 model was observed by Hu in the Cu/bidentate phosphite–pyridine-catalyzed addition on chalcone.[12] In 2004, Alexakis and van Koten observed a positive NLE in the Cu/aminoarenthiolate-catalyzed addition on cyclohexenone (50% ee was obtained with a 36% ee ligand).[13]

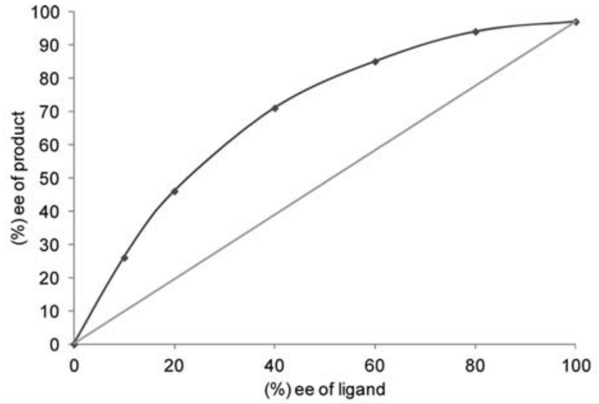
Nevertheless, it must be underlined that similar observation has never been reported to date on the Cu-catalyzed 1,6-conjugate addition reaction.

Scheme 1. Cu(II)/DiPPAM-Catalyzed 1,6-ACA



We decided to study the relationship between optical purities of the *tert*-butyl DiPPAM ligand **L1** and the product, and we report our results here.

The 1,6-conjugate addition was studied using diethylzinc and (*E*)-3-(prop-1-en-yl)cyclohex-2-enone **1** under the experimental conditions reported previously:[4] 5 mol % of $Cu(OTf)_2$ and 10 mol % of the ligand were used, and the reactions were run in Me-THF at 0 °C. After acidic quenching, the product being partially reconjugated, the reconjugation step was completed in the presence of DBU (Scheme 1). DiPPAM ligands **L1** having different optical purities were first prepared by reacting diphenylphosphinobenzaldehyde with various mixtures of L- and D-*tert*-leucine (L/D ratio of 100/0, 90/10, 80/20, 70/30, 60/40, 55/45, 50/50; method A). The ligands of optical purities between 10 and 80% were tested two or three times to secure the reproducibility (see Supporting Information). The results are presented in Figure 1.



ee ligand (%)	ee product (%)[a,b]	Isol. Yield (%)[b]
100	97	60
80	94	56
60	85	61
40	71	53
20	46	46
10	26	23
0	0	-

Figure 1. NLE in Cu(II)/DiPPAM-catalyzed 1,6-ACA.

[a] ee was determined on chiral GC using a Betadex column. [b] Average values from multiple experiments (see supporting information for details).

A strong positive NLE was observed as, for instance, the product was obtained in 71% ee when a ligand having a ee of 40% was used. It was checked first that the preparation mode of the ligand did not have any influence on the result. To that aim, (L)-**L1** and (D)-**L1** ligands were first prepared separately then mixed in a 60/40 ratio before being used in the catalysis (method B). In this case, the product was isolated in a similar ee (45%) to this which was obtained using method A. To check that the removal of the hexane from the Et_2Zn solution before the addition of solvent and reagents did not interfere with the result, an experiment was run without the removal of hexanes using a 20% ee ligand. In this case, the reaction was slower, but a similar ee value was reached (43%). Moreover the evolution of the ee value in the course of time was monitored in the reaction using a ligand having an optical purity of 20%: seven reactions were run simultaneously in the same conditions but quenched at different times (from 1 h 30 to 24 h), and it was observed that in all cases the ee's were somewhat constant (ranging from 37% to 50%). Besides, it can be noted that the isolated yields dropped when low ee ligands were used (10–40%). First, it was observed that the conversion of the conjugate addition step was lower when a

---

(7) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467–4478.

(8) van Koten, G. *Pure Appl. Chem.* **1994**, *66*, 1455–1462.

(9) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865–2878.

(10) Shintani, R; Fu, G. C. *Org. Lett.* **2002**, *4*, 3699–3702.

(11) Ito, K.; Eno, S.; Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2005**, *46*, 3981–3985.

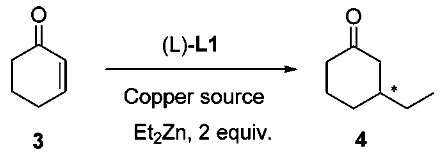
(12) Hu, Y.; Liang, X.; Zheng, Z.; Hu, X. *Tetrahedron: Asymmetry* **2003**, *14*, 2771–2774.

(13) Arink, A. M.; Braam, T. W.; Keeris, R.; Jastrzebski, J. T. B. H.; Benhaim, C.; Rosset, S.; Alexakis, A.; van Koten, G. *Org. Lett.* **2004**, *6*, 1959–1962.

low ee ligand was used. Moreover, the difficulties within this reaction may arise mainly from the DBU-mediated reconjugation step. Indeed, although the amount of non-conjugated product was not dependent on the optical purity of the ligand used, the reconjugation step was more difficult when reaction was run with low ee ligand, requiring the addition of more (2×) DBU. Thus, the lower yields observed in these cases may arise from the excess of DBU which probably causes partial decomposition of products.[14]

We then tried to evidence NLE in Cu-DiPPAM-catalyzed 1,4-ACA. Experiments were first done on cyclohexenone **3** and diethylzinc. Although the reaction was originally developed using Cu(I) triflate,[2] efficiency of Cu(I) and Cu(II) sources were first compared (Table 1).

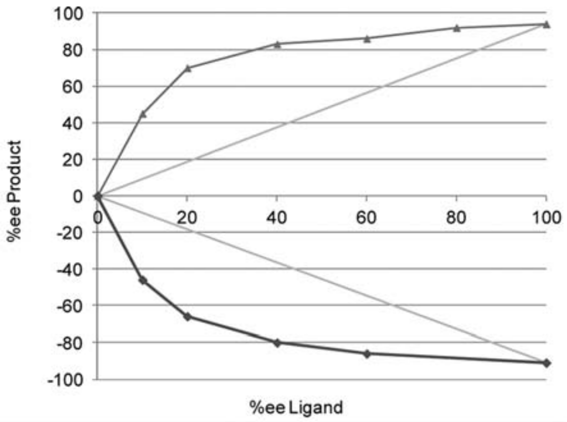
Table 1. Cu/DiPPAM-Catalyzed 1,4-ACA on Cyclohexenone **3**



cosolvent	copper source[c]	Cu/L	Cu (mol %)	temp (°C)	time[d] (h)	ee[a] (%)
AcOEt	$(\mathrm{CuOTf})_2$	2/1	2	rt	2	89
AcOEt	$(\mathrm{CuOTf})_2$	2/1	2	−18	6	93−98
THF	$\mathrm{Cu(OTf)_2}$	1/1	2	rt	2	94
THF	$\mathrm{Cu(OTf)_2}$	1/1	2	−18	6	96[b]
AcOEt	$\mathrm{Cu(OTf)_2}$	1/1	1	rt	3.5	92
AcOEt	$\mathrm{Cu(OTf)_2}$	1/1	1	−18	5	91
THF	$\mathrm{Cu(OTf)_2}$	2/1	2	rt	2	94

[a] ee was determined by chiral GC on a GTA column. [b] 62% isolated yield. [c] $(\mathrm{CuOTf})_2\cdot C_7H_8$ was used as Cu(I) triflate source. [d] Full conversion was obtained in all experiments.

Slightly better results were reached at room temperature when a 1/1 Cu(II)/ligand ratio was used in THF/hexanes.[15] Thus, the following experiments were performed in the latter conditions, using method A. (Figure 2).[16] A significant positive NLE was observed as, for instance, the product was obtained in 83% ee when a ligand having a ee of 40% was used. It was observed that the reaction was slower with ligands having a low ee; nevertheless, conversions > 90% were obtained in all cases after 2−4 h reaction at rt. In addition, it was found that similar shapes were obtained whatever the configuration (L or D) of the ligand used in excess was (Figure 2). Moreover, the evolution of the ee in the course of time was monitored in the reaction using ligand having an optical purity of 20%: four reactions were run simultaneously in the same conditions but quenched at different times (from 1 to 4 h). The determination of the ee values showed that it was constant with the progress of reaction (69, 67, 67, and 65%, respectively, were obtained).



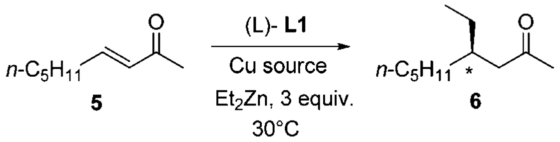
ee ligand (%) L Major	ee product (%)	ee ligand (%) D Major	ee product (%)
100	94	100	91
80	92		
60	86[a]	60	86[a]
40	83[a]	40	80[a]
20	70[a]	20	66[a]
10	45[a]	10	46[a]
0	0	0	0

Figure 2. NLE in Cu(II)/DiPPAM-catalyzed 1,4-ACA on **3**.

[a] Average values from multiple experiments (see supporting information for details).

The study was then extended to acyclic enones[17] using non-3-en-2-one **5** as the substrate. Although the reaction

Table 2. Cu/DiPPAM-Catalyzed 1,4-ACA on Acyclic Enone **5**



cosolvent	copper source[e]	Cu/L	Cu (mol %)	time[d] (h)	ee[a] (%)
AcOEt	$(\mathrm{CuOTf})_2$	2/1	2	4	96
THF	$\mathrm{Cu(OTf)_2}$	1/1	2	20	77[b]
AcOEt	$\mathrm{Cu(OTf)_2}$	1/1	2	1.5	97[c]

[a] Determined on chiral GC on a GTA column. [b] Average value from two experiments. [c] 64% isolated yield. [d] Full conversions were reached in all experiments. [e] $(\mathrm{CuOTf})_2\cdot C_7H_8$ was used as Cu(I) triflate source.

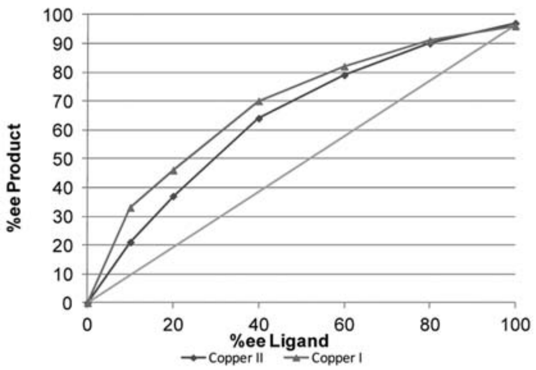
---

(14) The re-conjugation step using DBU is required to convert the nonconjugate product and consequently to isolate a pure conjugated product after chromatography. Nevertheless, NMR studies using internal standard showed that the yield in the conjugate product is not increased but slightly decreased after the DBU treatment. According to a recent report, DBU mediated re-conjugation in 1,6-ACA products appears problematic: Nishimura, T.; Noishiki, A.; Hayashi, T. *Chem. Commun.* **2012**, *48*, 973–975.

(15) Hexanes from the Et_2Zn solution was not removed as its elimination has deleterious consequences on the conversions and ee's.

(16) When method B was used with a 20% ee ligand, the product was isolated with an ee (71%) similar to that which was obtained using method A.

(17) An outstanding NLE has recently been achieved in the La-catalyzed 1,4-addition of thioglycolates to chalcone: Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Cai, Y.; Lin, L.; Liu, X.; Feng, X *Angew. Chem., Int. Ed.* **2010**, *49*, 4290–4293.



ee ligand (%) L major	ee product (%) using Cu(I)	ee product (%) using Cu(II)	Isolated yield (%)
100	96	97	64
80	91	90	
60	82[a]	79[a]	
40	70[a]	64[a]	
20	46[a]	37[a]	70
10	33[a]	21[a]	
0	0	0	

Figure 3. NLE in Cu(I)- and Cu(II)/DiPPAM-catalyzed 1,4-ACA on **5**.

[a] Average values from multiple experiments (see supporting information for details).

was originally developed using Cu(I) triflate,[2] efficiencies of Cu(I) triflate and Cu(II) triflate were first compared (Table 2).

The ee values obtained using a 2/1 Cu(I)/ligand ratio were similar to those obtained with a 1/1 $Cu(OTf)_2$/ligand ratio, but the reaction was faster in the latter case. NLE experiments were run in AcOEt/hexanes at 30 °C with 3 equiv of Et_2Zn and using both copper sources (Figure 3).[18] It can be seen that NLE was little more pronounced when $(CuOTf)_2$ was used and less important to the effect observed when cyclohexenone was employed as the substrate.

It must be noted that, contrary to what was observed in the 1,6-ACA, the optical purity of the ligand has no influence on the isolated yield. This difference of behavior may be explained by the absence of reconjugation step in the 1,4-addition reaction. Finally, the evolution of the ee versus the catalyst loading was studied using a 20% ee ligand, and no significant differences could be noticed, both with Cu(I) and Cu(II) triflates. For instance, ee's of 33%, 38%, and 31% were obtained using, respectively, 1, 2, and 4 mol % of $Cu(OTf)_2$.

To conclude, a strong positive NLE was evidenced for the first time in the Cu-catalyzed 1,6-conjugate addition of dialkylzinc on dienones. A similar effect was observed in the 1,4-conjugate addition on both cyclic and acyclic enones. This effect probably arises from the presence of di(oligo)meric species in Cu/DiPPAM-catalyzed conjugate additions. All attempts (mass spectrometry, liquid or solid NMR, X-ray) to determine the structure of these oligomeric species have not been a success until now, but efforts will continue to reach this goal.

Acknowledgment. This work was supported by the Ministère de la Recherche et de la Technologie and by the Université Européenne de Bretagne (grant to J.W.-D and M.M.). The authors thank Pr. Henri Kagan for fruitful exchange of information.

Supporting Information Available. Experimental procedures and spectral and chromatographic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript was published ASAP on June 28, 2012. Reference 18 was erroneously removed during production. The corrected version was reposted on July 3, 2012.

---

(18) When method B was employed with a 20% ee ligand and the Cu(II) source, the product was isolated in a similar ee (33%) to this which was obtained using method A, but the ee was lower (32%) when Cu(I) source was used. This is probably connected to the poorer reproducibility of the reaction with Cu(I) triflate.

The authors declare no competing financial interest.