

Copper-Catalyzed Asymmetric Conjugate Addition of Dimethylzinc to Acyl-*N*-methylimidazole Michael Acceptors: a Powerful Synthetic Platform

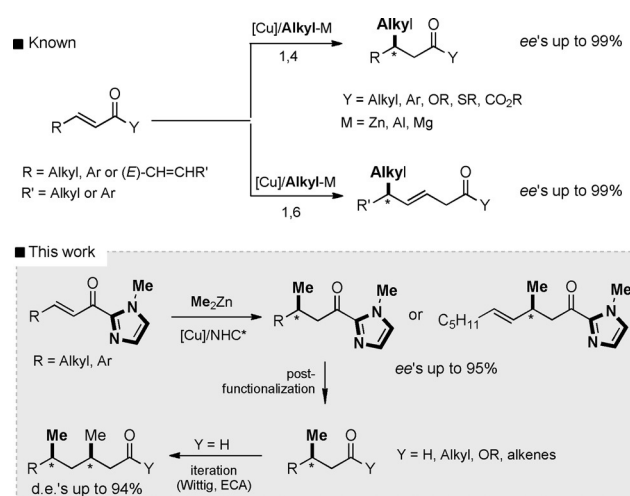
Sammy Drissi-Amraoui, Marie S. T. Morin, Christophe Crévisy, Olivier Baslé, Renata Marcia de Figueiredo, Marc Mauduit,* and Jean-Marc Campagne*

Abstract: An efficient copper-catalyzed enantioselective conjugate addition of dimethylzinc to α,β - and $\alpha,\beta,\gamma,\delta$ -unsaturated 2-acyl-*N*-methylimidazoles has been achieved using a chiral bidentate hydroxyalkyl-NHC ligand. The reactions proceeded with both excellent regio- and enantioselectivity (14 examples, 87–95 % ee) to afford the desired 1,4-adducts, which were easily transformed to the corresponding aldehydes, esters, and ketones. Subsequently, this powerful methodology was therefore successfully applied in the synthesis of natural products. Furthermore, an iterative process was also disclosed leading to highly desirable 1,3-desoxypropionate skeletons (up to 94 % d.e.).

In the last two decades, transition-metal-catalyzed enantioselective conjugate additions (ECA) of organometallic reagents to electron-deficient unsaturated systems have emerged as a versatile and efficient methodology for the asymmetric formation of C–C bonds.^[1] Among the myriad of transition metals studied, tremendous attention has been given to copper catalysis, which resulted in significant breakthroughs,^[2] such as perfect regiocontrol in 1,6- or 1,4-addition with extended Michael acceptors^[3] as well as the subsequent sequential 1,6/1,4 processes.^[4] These recent achievements with a large variety of Michael acceptors and organometallic reagents allowed for the efficient preparation of numerous valuable enantioenriched building blocks^[1] with remarkable applications in total synthesis.^[5] Nevertheless, the enantioselective transfer of a methyl group to form all-carbon methyl-substituted chiral scaffolds, which are present in numerous natural products,^[5] remains a challenge.^[6] On the other hand, the electron-withdrawing group (EWG) of Michael acceptors has to be considered not only as a platform for postfunctionalization but should also be compatible with the methylated organometallic reagents and allow its enantioselective addition. To this end, thioesters have been successfully used with

the methyl-Grignard nucleophile, allowing notably iterative ECA processes to form 1,3-desoxypropionate subunits.^[7] In this context, the acylimidazole function, which has the advantage to be easily transformed into various functional groups such as aldehydes, ketones, and esters^[8] should be considered as a promising EWG. Nevertheless, despite numerous successful uses in additions of stabilized nucleophiles,^[9] to the best of our knowledge the ECA of unstabilized organometallics with unsaturated 2-acyl-*N*-methylimidazoles has been confined to alkylboron compounds.^[10] Herein, we report the first efficient copper-catalyzed enantioselective conjugate addition of a dialkylzinc reagent to either α,β - or $\alpha,\beta,\gamma,\delta$ -unsaturated 2-acyl-*N*-methylimidazoles and its applications in the synthesis of natural molecules or towards iterative processes leading to 1,3-desoxypropionate units (Scheme 1).

We started our study by screening various classes of chiral nonracemic ligands in the conjugate addition of dimethylzinc to the α,β -unsaturated 2-acyl-*N*-methylimidazole **1a** as model reaction (for a complete survey, see the Supporting Information, SI). Binap-type atropisomeric ligands were first evaluated. Initial experiments with Binap^[11] highlighted the potential of Me₂Zn in these reactions to achieve good conversions and 1,4-regioselectivity at room temperature, albeit with only modest enantioselectivities up to 26 %. Control experiments showed that both ligand and metal are essential: no conversion could be observed in the absence of



[*] S. Drissi-Amraoui, Dr. R. Marcia de Figueiredo, Prof. Dr. J.-M. Campagne
Institut Charles Gerhardt Montpellier, UMR 5253 CNRS-UM-ENSCM
Ecole Nationale Supérieure de Chimie
8 Rue de l'Ecole Normale, 34296 Montpellier Cedex 5 (France)
E-mail: jean-marc.campagne@enscm.fr

Dr. M. S. T. Morin, Dr. C. Crévisy, Dr. O. Baslé, Dr. M. Mauduit
Ecole Nationale Supérieure de Chimie de Rennes, UMR CNRS 6226
11 Allée de Beaulieu, CS 50837, 35708 Rennes Cedex 7 (France)
E-mail: marc.mauduit@ensc-rennes.fr

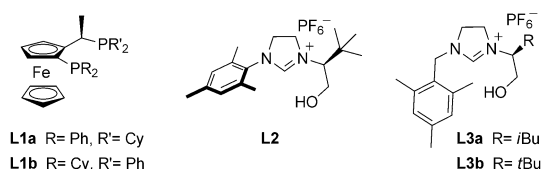


Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201506189>.

Scheme 1. Copper-catalyzed enantioselective conjugate addition of alkyl-metal hard nucleophiles to (extended) Michael acceptors.

copper. The use of more reactive organometallic reagents such as Me_3Al or MeMgBr ^[12] led only to racemic 1,4-product **2a** or a mixture of 1,2/1,4 adducts, respectively (see SI). When other atropisomeric classical ligands such as tol-binap,^[11] Segphos,^[13] difluorophos,^[14] and phosphoramidites^[15] were used, unsatisfying enantioselectivities were observed that did not exceed 70%. Higher selectivity was observed with Josiphos **L1a**^[16] (87% *ee*) whereas less than 5% *ee* was observed with the structural isomer **L1b** (Scheme 2; Table 1, entries 1–3). We next evaluated our home-made hydroxy-alkyl-NHC ligands **L2** and **L3**^[17–19] and the best results were observed with the last generation **L3b** (Table 1, entry 6).^[2e] The copper-NHC catalyst prepared in situ by deprotonation of **L3b** with *n*-butyllithium in the presence of copper(II) triflate (2 mol%) promoted the methyl 1,4-addition efficiently, allowing the formation of **2a** with complete regioselectivity, good yield (85%), and excellent 95% *ee*.

With these optimized reaction conditions in hands, the reaction with alternative organometallic species was re-investigated (Table 1, entries 7–10). In the presence of

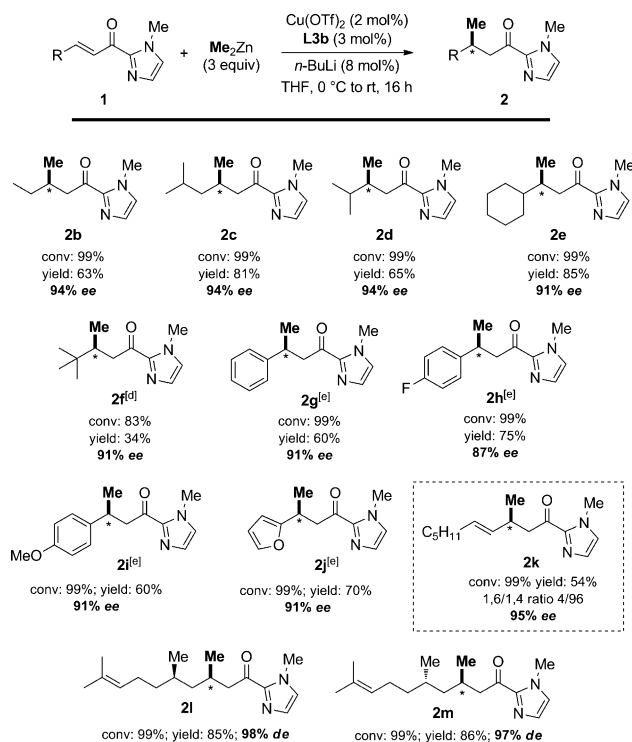


Scheme 2. Selected chiral nonracemic ligands involved in the copper-catalyzed 1,4-addition of dimethylzinc to α,β -unsaturated 2-acyl-*N*-methylimidazoles.

Table 1: Screening of chiral ligands **L1**–**L3** for copper-catalyzed ECA of organometallic nucleophiles to α,β -unsaturated 2-acyl-*N*-methylimidazole **1a**.

Entry	L	R-Metal	Method	T [°C]	Conv [%] ^[a]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	L1a	Me_2Zn	A	0	99	44	87
2	L1a	Me_2Zn	B	rt	99	74	85
3	L1b	Me_2Zn	B	rt	87	64	2
4	L2	Me_2Zn	C	rt	99	80	75
5	L3a	Me_2Zn	C	rt	99	79	85
6	L3b	Me_2Zn	C	rt	99	85	95
7	L3b	Me_3Al	C	−78	99	78	0
8	L3b	MeMgBr	C	−78	99 ^[d]	25	4
9	L3b	Et_2Zn	C	rt	99	84	19
10	L3b	Ph_2Zn	C	rt	99	94	18

Method A: CuTC (5 mol%), ligand **L1** (5 mol%), R-M (3 equiv), THF, −78 °C, −10, 0 °C or room temperature, 16 h. Method B: Method A with $\text{Cu}(\text{OTf})_2$ as copper source. Method C: $\text{Cu}(\text{OTf})_2$ (2 mol%), ligand **L** (3 mol%), *n*BuLi (8 mol%), R-M (3 equiv), 0 °C to room temperature, 16 h. [a] Determined by ^1H NMR spectroscopy. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC on a chiral stationary phase. [d] A mixture of 32/68 1,4/1,2-adducts was obtained. CuTC = copper(I)-thiophene-2-carboxylate.



Scheme 3. Substrate scope for the copper-catalyzed ECA of dimethylzinc with β -substituted α,β -unsaturated 2-acyl-*N*-methylimidazoles **1** catalyzed by **L3b**/ $\text{Cu}(\text{OTf})_2$. [a] The conversion was determined by ^1H NMR spectroscopy. [b] Yield of isolated product. [c] Enantiomeric excesses were determined by HPLC on a chiral stationary phase. [d] Reaction performed with $\text{Cu}(\text{OTf})_2$ (8 mol%), with the same ratio of $\text{Cu}/\text{L3b}/n\text{BuLi}$. [e] Reaction performed with $\text{Cu}(\text{OTf})_2$ (4 mol%), with the same ratio of $\text{Cu}/\text{L3b}/n\text{BuLi}$.

AlMe_3 or MeMgBr , low selectivities were observed (Table 1, entries 7 and 8). Not surprisingly, with diethylzinc and diphenylzinc reagents (Table 1, entries 9 and 10), despite a good control of the chemical reactivity and the 1,4-regioselectivity, low enantioselectivity was observed, further demonstrating the important role of the ligand in the enantio-discriminating step.

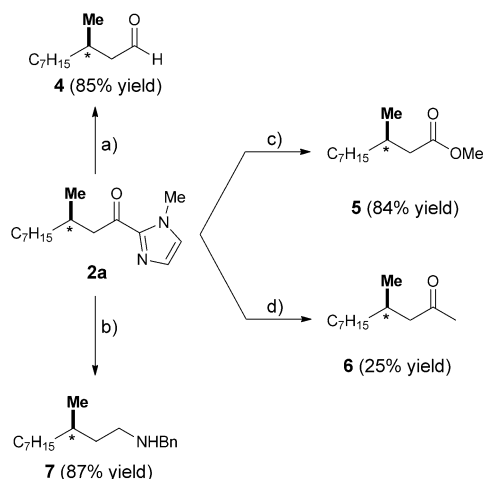
The scope of the reaction was next investigated on a collection of differently substituted α,β -unsaturated 2-acyl-*N*-methylimidazole derivatives (Scheme 3). Either aliphatic or aromatic substituents are well tolerated, though lower catalytic loadings are usually required for reactions involving aliphatic substituents (2 and 4 mol% $\text{Cu}(\text{OTf})_2$, respectively). As illustrated with compounds **2b** and **2c**, the enantiodiscrimination remains excellent (94% *ee*) with less bulky substituents. On the other hand, the use of more bulky branched alkyl substituents is also efficient as illustrated in the selective access to compounds **2d** and **2e** (94% and 91% *ee*, respectively).

Remarkably, the addition of dimethylzinc to the more sterically demanding substrate **1f** bearing a *tert*-butyl group was also successful affording the 1,4-adduct **2f** with up to 91% *ee*; however, the yield remained moderate (34%) despite the use of 8 mol% of the copper catalyst. To the best of our knowledge this is the first time that a methyl group is enantioselectively transferred to a β -substituted *tert*-butyl

Michael acceptor.^[20] This could lead to valuable highly hindered aliphatic substrates, which are present in many natural products.^[21] It should also be emphasized that these reactions are carried out under non-cryogenic conditions (0 °C to rt) at low catalyst loadings.

Differently substituted aromatic derivatives afforded conjugate addition products with good yields in the presence of 4 mol % of copper to reach full conversion with high levels of enantioselectivity (87–91 % *ee*). Using a furan-substituted substrate did neither affect the yield nor the enantiomeric excess. Regioselectivity (i.e., 1,6- versus 1,4-addition) on extended unsaturated systems was next investigated. Gratifyingly, highly regioselective (> 96:4) 1,4-addition was observed on model compound **1k**, giving **2k** in good yield and with an enantioselectivity of up to 95 %. This 1,4-selectivity is in sharp contrast to the selectivities usually obtained with extended conjugated systems.^[4b,12] This highlights the crucial role of the *N*-Me imidazole moiety in the addition mechanism. DFT studies are currently in progress to unveil the role of the imidazole moiety in the catalytic cycle. Finally, when starting from the two enantiomers of the unsaturated acyl-imidazole derived from enantiomerically pure citronellal (see SI for details), the corresponding 1,3-desoxypropionate units **2l** and **2m** have been obtained in good yields and excellent diastereoselectivities.

This diastereoselectivity outcome highlights the prominent role of the catalyst in the double stereodifferentiation and paves the way for future work on iterative 1,4-addition. This iterative 1,4-addition will thus require ready access to a newly created unsaturated acyl-imidazole. The transformation of acylimidazole **2a** was thus explored (Scheme 4). As previously stated,^[8] the acyl-imidazole moiety can be easily transformed into a wide range of carbonyl and carboxyl



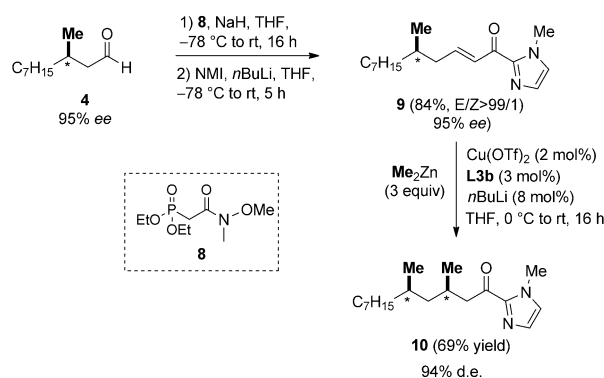
Scheme 4. Post-transformation of the acyl-*N*-methylimidazole 1,4-adduct **2a** into the corresponding enantioenriched aldehyde **4**, ester **5**, ketone **6**, and amine **7**. Reaction conditions: a) 1) NaBH₄, MeOH, 2 h, rt; 2) MeI, EtOAc, 16 h, 60 °C; 3) NaOH 2 M, glycine, toluene, 5 h, 80 °C. b) 1) NaBH₄, MeOH, 2 h, rt; 2) MeI, EtOAc, 16 h, 60 °C; 3) NaOH 2 M, BnNH₂, toluene, 5 h, 80 °C. c) 1) MeOTf, CH₂Cl₂, 2 h, rt; 2) DBU, MeOH. d) 1) MeMgCl, THF, 2 h, rt; 2) MeI, EtOAc, 16 h, 60 °C; 3) DBU, toluene, 16 h, 80 °C. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

derivatives such as aldehyde **4**, methyl ester **5**, and methyl ketone **6** with high yielding procedures. It is also noteworthy that the unprecedented transformation of acylimidazole **2a** into amine **7** could be successfully accomplished in very good yield (87 %).

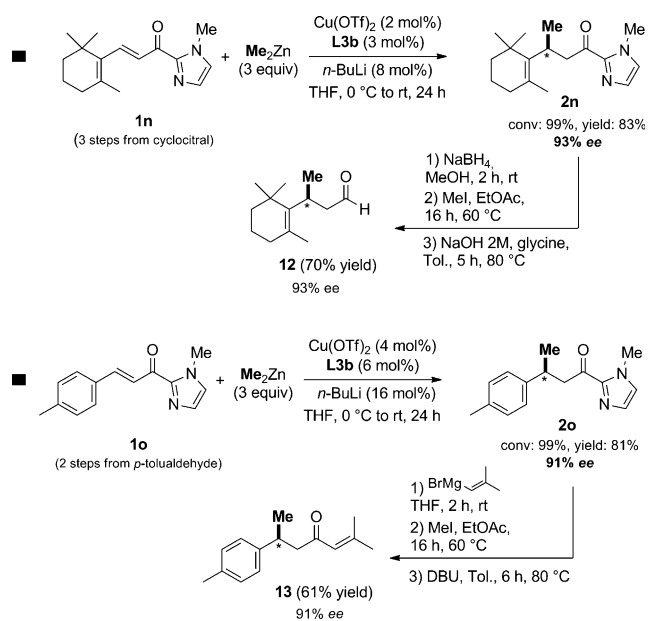
Having a direct and efficient access to aldehyde **4**, the iterative introduction of a second methyl group was thus explored (Scheme 5). Indeed unsaturated acyl imidazole **9** was obtained in high yield and *E/Z* selectivity in two steps from **4**.

As previously observed with citronellal derivatives (see **2l** and **2m**, Scheme 3), the iterative introduction of a second methyl group proved efficient leading to **10** in 69 % yield and 94 % d.e.

The synthetic potential of this methodology has been highlighted in two applications (Scheme 6). Firstly, starting from **1n** (obtained in three steps from cyclocitral), the addition of dimethylzinc enabled the selective formation of



Scheme 5. Enantioselective iterative process for the synthesis of 1,3-desoxypropionate units.



Scheme 6. Application in the asymmetric synthesis of ionone derivative **12** and *ar*-turmerone **13**.

2n in good yield, excellent 1,4-selectivity and high enantioselectivity (93 % *ee*). A two-step regeneration of the aldehyde functionality finally furnished **12** (with no erosion of the enantioselectivity), which is a novel ionone derivative with a pleasant fruity/floral smell. In a second synthetic application, *ar*-turmerone **13**^[22] was efficiently synthesized from *p*-tolualdehyde in a few steps. The addition of the methyl group to unsaturated **1o** (obtained in two steps from *p*-tolualdehyde) led to **2o** in high selectivity and finally the imidazole moiety was successfully transformed, thus affording (+)-*ar*-turmerone **13**.^[23]

In conclusion, a catalytic system through the combination of copper/chiral-NHC complex was proposed to mediate enantioselective conjugate addition of dimethylzinc to unsaturated acyl-*N*-methylimidazole systems, a still underexplored class of Michael acceptors to date. The advantages of using such flexible substrates could be underscored with 1) the synthesis of several 1,4-adducts in high regio- and enantioselectivities (up to 95 % *ee*), 2) the derivatization into versatile building blocks such as aldehydes, esters, ketones, and amines, and 3) the use as key intermediates during the asymmetric syntheses of both ionone derivative and *ar*-turmerone. Besides, the powerful catalytic system proposed herein, in which the high levels of selectivity might be correlated with the chirality of the chelating side arm (e.g., the amino alcohol side chain) of the NHC ligand used, could pave the way to an enantioselective iterative process as illustrated with the synthesis of a 1,3-desoxypropionate unit. Currently, further applications of this expedient methodology on asymmetric transformations are under investigation, and the results will be reported in due course. DFT studies are currently underway to determine the role of the *N*-methylimidazole and ligand moieties in the observed selectivities.

Acknowledgements

This work was supported by the Agence Nationale de la Recherche (project SCATE, number ANR-12-B507-0009-01 granted to M.S.T.M. and S.D.A.). R.M.F., M.M., and O.B. also thank the CNRS. We thank Takasago for a generous gift of citronellal and V. Vidal for a loan of DIFLUORPHOS.

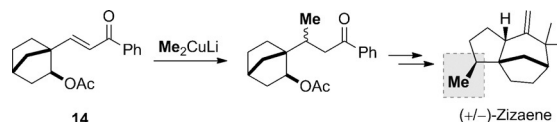
Keywords: acyl-*N*-methylimidazoles · asymmetric catalysis · *N*-heterocyclic carbenes · conjugate addition · iterative processes

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 11830–11834
Angew. Chem. **2015**, *127*, 11996–12000

- [1] For recent books and review in asymmetric conjugate addition, see: a) M. Mauduit, O. Baslé, H. Clavier, C. Crévisy, A. Denicourt-Nowicki in *Comprehensive Organic Synthesis II*, Vol. 4 (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, pp. 186; b) *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley, Hoboken, **2014**; c) C. Hawner, A. Alexakis, *Chem. Commun.* **2010**, *46*, 7295; d) A. Alexakis, J. E. Backvall, N. Krause, O. Pamies, M. Dieguez, *Chem. Rev.* **2008**, *108*, 2796; e) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard, B. L. Feringa, *Chem. Rev.* **2008**, *108*, 2824.

- [2] For instance, see: a) K. S. Lee, M. K. Brown, A. W. Hird, A. H. Hoveyda, *J. Am. Chem. Soc.* **2006**, *128*, 7182; b) M. K. Brown, T. L. May, C. A. Baxter, A. H. Hoveyda, *Angew. Chem. Int. Ed.* **2007**, *46*, 1097; *Angew. Chem.* **2007**, *119*, 1115; c) D. Martin, S. Kehrli, M. D'Augustin, H. Clavier, M. Mauduit, A. Alexakis, *J. Am. Chem. Soc.* **2006**, *128*, 8416; d) S. Kehrli, D. Martin, D. Rix, M. Mauduit, A. Alexakis, *Chem. Eur. J.* **2010**, *16*, 9890; e) N. Germain, M. Magrez, S. Kehrli, M. Mauduit, A. Alexakis, *Eur. J. Org. Chem.* **2012**, 5301.
- [3] For instance, see: a) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem. Int. Ed.* **2008**, *47*, 9122; *Angew. Chem.* **2008**, *120*, 9262; b) M. Tissot, D. Poggiali, H. Hénon, D. Müller, L. Guénée, M. Mauduit, A. Alexakis, *Chem. Eur. J.* **2012**, *18*, 8731; c) E. Fillion, A. Wilsily, E. T. Liao, *Tetrahedron: Asymmetry* **2006**, *17*, 2957; d) R. R. Cesati, J. de Armas, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 96–101; e) T. Nishimura, A. Noishiki, T. Hayashi, *Chem. Commun.* **2012**, *48*, 973; f) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2008**, *47*, 398; *Angew. Chem.* **2008**, *120*, 404; g) T. den Hartog, D. J. van Dijken, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2010**, *21*, 1574; For recent reviews dealing with 1,6-conjugate additions: h) A. G. Csáky, G. de La Herran, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080; i) E. M. P. Silva, A. M. S. Silva, *Synthesis* **2012**, 3109.
- [4] a) T. den Hartog, D. J. van Dijken, A. J. Minnaard, B. L. Feringa, *Tetrahedron: Asymmetry* **2010**, *21*, 1574; b) M. Magrez-Chiquet, M. S. T. Morin, J. Wencel-Delord, S. Drissi Amraoui, O. Baslé, A. Alexakis, C. Crévisy, M. Mauduit, *Chem. Eur. J.* **2013**, *19*, 13663.
- [5] “Applications to the synthesis of natural products”: B. C. Calvo, J. Buter, A. J. Minnaard in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley, Hoboken, **2014**, chap. 14, pp. 373–447.
- [6] For recent examples highlighting this challenge, see: a) S. Goncalves-Contal, L. Gremaud, A. Alexakis, *Angew. Chem. Int. Ed.* **2013**, *52*, 12701; *Angew. Chem.* **2013**, *125*, 12933; b) K. Endo, D. Hamada, S. Yakeishi, T. Shibata, *Angew. Chem. Int. Ed.* **2013**, *52*, 606; *Angew. Chem.* **2013**, *125*, 634; c) L. Palais, L. Babel, A. Quintard, S. Belot, A. Alexakis, *Org. Lett.* **2010**, *12*, 1988; d) M. Fañanás-Mastral, B. L. Feringa, *J. Am. Chem. Soc.* **2010**, *132*, 13152; e) A. De Roma, F. Ruffo, S. Woodward, *Chem. Commun.* **2008**, 5384; f) S.-Y. Wang, S.-J. Ji, T.-P. Loh, *J. Am. Chem. Soc.* **2007**, *129*, 276; g) H.-C. Guo, J.-A. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354; *Angew. Chem.* **2006**, *118*, 362.
- [7] R. Des Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 9966; see also Ref. [4a].
- [8] For examples of the transformation of the 2-acylimidazole moiety to other functional groups such as esters, amides, ketone derivatives, carboxylic acids, see: a) S. Otha, S. Hayakawa, K. Nishimura, M. Okamoto, *Chem. Pharm. Bull.* **1987**, *35*, 1058; b) D. A. Evans, K. R. Fandrick, H.-J. Song, *Org. Lett.* **2006**, *8*, 351.
- [9] α,β -Unsaturated 2-acyl-*N*-methylimidazoles have been successfully used in metal-catalyzed ECA (i.e., Friedel–Crafts alkylation) involving non-organometallic nucleophiles. With indoles: a) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942; b) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029; With malonates: c) D. Coquière, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.* **2007**, *46*, 9308; *Angew. Chem.* **2007**, *119*, 9468; d) D. Coquière, J. Bos, J. Beld, G. Roelfes, *Angew. Chem. Int. Ed.* **2009**, *48*, 5159; *Angew. Chem.* **2009**, *121*, 5261; e) J. Wang, E. Benedetti, L. Bethge, S. Vonhoff, S. Klusmann, J.-J. Vasseur, J. Cossy, M. Smietana, S. Arseniyadis, *Angew. Chem. Int. Ed.* **2013**,

- 52, 11546; *Angew. Chem.* **2013**, *125*, 11760; With malonitriles: f) C. Wang, L.-A. Chen, H. Huo, X. Shen, K. Harms, L. Gong, E. Meggers, *Chem. Sci.* **2015**, *6*, 1094.
- [10] M. Yoshida, H. Ohmiya, M. Sawamura, *J. Am. Chem. Soc.* **2012**, *134*, 11896.
- [11] For previous use of BINAP and tol-BINAP in Cu-ECA, see for instance: a) T. den Hartog, A. Rudolph, B. Macia, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2010**, *132*, 14349; b) L. Grimaud, A. Alexakis, *Angew. Chem. Int. Ed.* **2012**, *51*, 794; *Angew. Chem.* **2012**, *124*, 818; c) M. S. T. Morin, T. Vives, O. Baslé, C. Crévisy, V. Ratovelomanana-Vidal, M. Mauduit, *Synthesis*, **2015**, DOI: 10.1055/s-0034-1378813.
- [12] During a seminal study dealing with the Cu-ECA of Grignard reagents to extended Michael acceptors, the acyl-*N*-methylimidazole function has been considered with BnCH_2MgBr leading to the 1,4-adduct in low yield (34%) and negligible enantioselectivity (2%): T. den Hartog, Y. Huang, M. Fananas-Mastral, A. Meuwese, A. Rudolph, M. Perez, A. J. Minnaard, B. L. Feringa, *ACS Catal.* **2015**, *5*, 560.
- [13] For previous use of SEGPHOS in ECA, see for instance: G. Chen, N. Tokunaga, T. Hayashi, *Org. Lett.* **2005**, *7*, 2285.
- [14] For previous use of DIFLUORPHOS in Cu-ECA, see Ref. [11c].
- [15] For phosphoramidite-type ligands in Cu-ECA, see: J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486; *Angew. Chem.* **2010**, *122*, 2538.
- [16] For ferrocenyl-type ligands in Cu-ECA, see for instance: B. L. Feringa, R. Badorrey, D. Pena, S. R. Harutyunyan, A. J. Minnaard, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5834.
- [17] For a recent review and book on NHC-TM and applications in catalysis, see: a) S. Díez-González, *N-Heterocyclic Carbenes*, RSC Catalysis series, RSC Publishing, Cambridge, **2011**; b) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.
- [18] For a review dealing with chiral hydroxyalkyl-NHCs in Cu-ECA, see: J. Wencel, H. Hénon, S. Kehrli, M. Mauduit, A. Alexakis, *Aldrichimica Acta* **2009**, *42*, 43.
- [19] For the NHC precursor **8**, see: a) H. Clavier, L. Coutable, J.-C. Guillemin, M. Mauduit, *Tetrahedron: Asymmetry* **2005**, *16*, 921; b) H. Clavier, L. Coutable, L. Toupet, J.-C. Guillemin, M. Mauduit, *J. Organomet. Chem.* **2005**, *690*, 5237; c) D. Rix, S. Labat, L. Toupet, C. Crévisy, M. Mauduit, *Eur. J. Inorg. Chem.* **2009**, 1989; For L3 a,b, see ref. [2e].
- [20] The copper-catalyzed addition of diethylzinc has been reported on the β -substituted *tert*-butyl α -phenylenone with 74% *ee* and 5% yield, see: Y. Takahashi, Y. Yamamoto, K. Katagari, H. Danjo, K. Yamaguchi, T. Imamoto, *J. Org. Chem.* **2005**, *70*, 9009.
- [21] The conjugate addition of Me_2CuLi to the bridgehead-norcamphor β -substituted enone **14** was used as key step in the total racemic synthesis of sesquiterpene ($\pm$)-zizaene, see: R. M. Coates, R. L. Sowerby, *J. Am. Chem. Soc.* **1972**, *94*, 5386.



- [22] a) C. Fuganti, S. Serra, A. Dulio, *J. Chem. Soc. Perkin Trans. I* **1999**, 279. The (*S*)-(+)-*ar*-turmerone has been recently synthesized through the ECA of trimethylaluminum to *N*-acetylpyrrole derivatives: Ref. [6b].
- [23] The enantiomeric excess of (+)-*ar*-turmerone has been determined by chiral HPLC and rotation ($[\alpha]_{\text{D}}^{20} = +52.4$) is in good agreement with previously reported data $[\alpha]_{\text{D}}^{20} = +50.6$ (Ref. [6b]).

Received: July 6, 2015

Published online: August 18, 2015