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Copper(I)-catalysed asymmetric allylic reductions with hydrosilanes†

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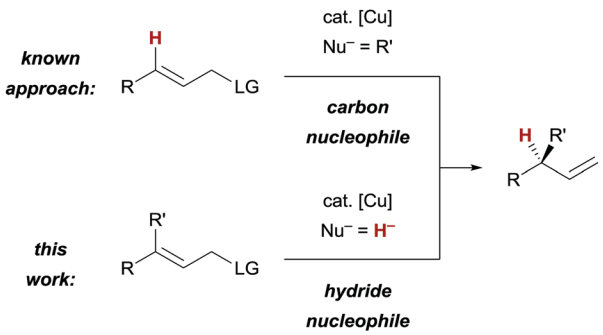
A copper(I)-catalysed asymmetric allylic reduction enables a regio- and stereoselective transfer of a hydride nucleophile in an S_N2'-fashion onto allylic bromides. This transformation represents a conceptually orthogonal approach to allylic substitution reactions with carbon nucleophiles. A copper(I) complex based upon a chiral N-heterocyclic carbene (NHC) ligand allows for stereoselectivity reaching 99% ee. The catalyst enables a stereoconvergent reaction irrespective of the double bond configuration of the starting materials.

The catalytic asymmetric allylic substitution reaction is a hallmark of transition metal catalysis, which enables the generation of terminal alkenes bearing a stereogenic center in the allylic position.[1] Especially for carbon-based nucleophiles, chiral copper(I) complexes are well-established catalysts for asymmetric allylic substitution reactions.[2] However, no generally applicable catalyst is available, and for every nucleophile class to be transferred (bearing either an aryl or alkyl group, from *e.g.* Zn, Mg, B or Al-based reagents) a specialised protocol is required (Scheme 1, top).[3–8] An orthogonal alternative approach would be the stereoselective transfer of a hydride nucleophile to a higher substituted starting material. This approach would ideally be applicable to a wide variety of allylic acceptors, independent of the nature of the substituents R and R′ (Scheme 1, bottom). However, two possible challenges might hamper the development of a successful catalytic protocol: (i) the higher substituted starting materials might be sterically too demanding for effective catalysis and (ii) stereoinduction might be difficult for a relatively small hydride nucleophile.

Even though copper(I) hydride complexes have been successfully employed as hydride nucleophiles in a wide variety of asymmetric transformations,[9] their use in asymmetric allylic substitution reactions has not been described to the best of our knowledge. Such a copper-catalysed allylic hydride transfer – an allylic reduction – has been postulated as a part of a multi-step catalytic transformation,[10,11] but has never been realised as an isolated, catalyst-controlled process.[12,13] We report herein the development of a copper-catalysed enantioselective hydride transfer in an S_N2'-fashion.[14] This asymmetric allylic reduction relies on hydrosilanes as stoichiometric hydride donors.



Scheme 1 Alternative approaches to chiral α-olefins: copper(I)-catalysed asymmetric allylic substitutions with carbon or hydride nucleophiles (LG = leaving group).

Following the precedence of the racemic variant, in orienting experiments we have identified chiral copper(I)/NHC complexes (NHC = N-heterocyclic carbene) as potent catalysts to induce stereoselectivity for the envisaged catalytic transformation. Employing 2-naphthophenone-derived trisubstituted allylic bromide **1** as a non-volatile model substrate with a catalyst derived from the ligand precursor (*S*,*S*)-**4**[15] and heptamethyltrisiloxane as a hydride source, the corresponding terminal alkene **2** was obtained from *E*-**1** in good yield and with an excellent 97% ee (Scheme 2).[16] It was found that also *Z*-**1** gave (*S*)-**2** with a similar ee value (95%), indicating a stereoconvergent process.[17] In both reactions the regioselectivity was high (<5% α-substitution product **3**). This stereoconvergence obviates the need for a stereoselective preparation of the allylic bromide and therefore, *E*/*Z* mixtures of the corresponding allylic bromides can directly be employed without the need for separation of isomers. This feat simplifies the overall process, as the stereoselective synthesis of allylic bromides can be tedious.

With optimised conditions in hand, we sought to explore the substrate scope and limitations of the asymmetric allylic

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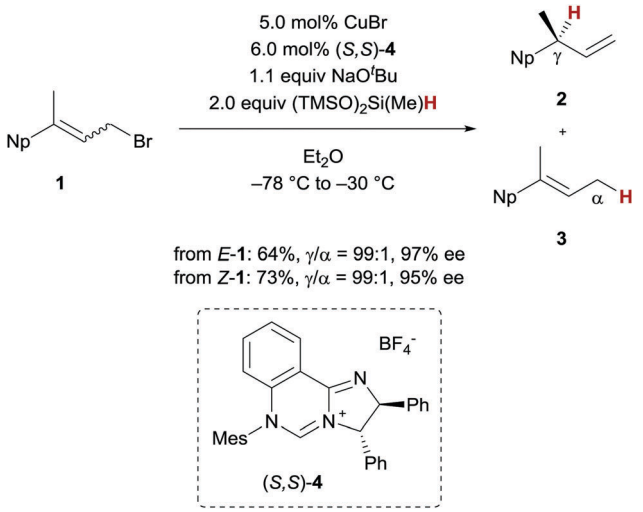
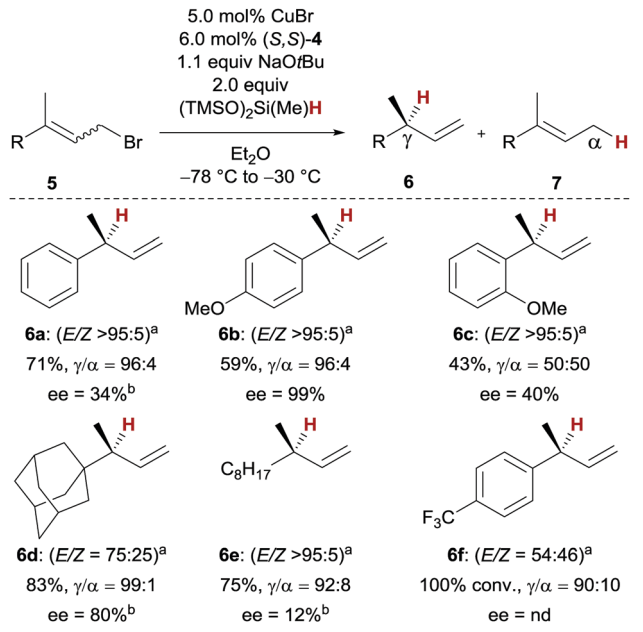
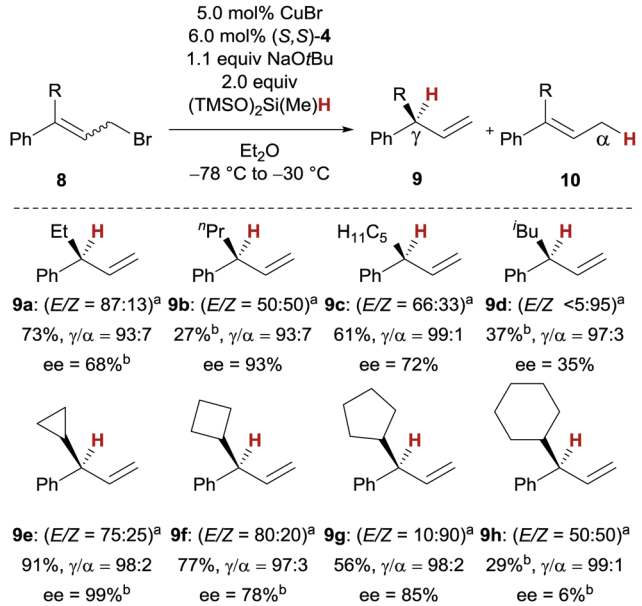


Scheme 2 Optimised conditions for the copper-catalysed allylic reduction and stereoconvergence (Np = 2-naphthyl).

reduction protocol. Generally, the isolated yields and regioselectivity (**6**/**7**) were good to excellent (Schemes 3 and 4). Furthermore, in most cases *E*/*Z*-mixtures of the allylic bromides **5** or **8** were employed. First, we investigated a variety of methyl-substituted allylic bromides **5**, to probe whether the present method could be used to install stereogenic centers bearing a methyl group (Scheme 3). We found that for the successful transfer of the relatively small hydride nucleophile with the optimised catalyst, small electronic and steric variations have a



Scheme 3 Cu-Catalysed allylic reduction and generation of stereocenters bearing a methyl group. (Yield is given as combined yield of **6** and **7**. The **6**/**7** ratio was determined by GC analysis. Determination of ee values by GC or HPLC analysis employing chiral stationary phases. [a] The *Z*/*E* ratio of the starting material **5**. [b] Determined *via* NMR analysis of the Mosher ester derivative (obtained from hydroboration/oxidation and transformation to the Mosher ester); see the ESI† for details.)



Scheme 4 Cu-Catalysed allylic reduction and generation of stereocenters bearing alkyl substituents. (Yield is given as combined yield of **9** and **10**. The **9**/**10** ratio was determined by GC analysis. Determination of ee values by GC or HPLC analysis employing chiral stationary phases. [a] The *Z*/*E* ratio of the starting material **8**. [b] Determined *via* NMR analysis of the Mosher ester derivative (obtained from hydroboration/oxidation and transformation to the Mosher ester); see the ESI† for details. [c] Product is volatile.)

large impact on the stereoselectivity of the overall reaction: while moving from the 2-naphthyl-substituent in **1** (Scheme 2) to the phenyl group in **5a**, a significant drop in stereoselectivity was observed (34% ee). In contrast, the electron-rich anisole-derived terminal alkene **6b** could be isolated with excellent 99% ee. *ortho*-Substituents on the aromatic ring seem to interfere with the catalyst, as can be seen from the diminished regio- and stereoselectivity in the generation of terminal alkene **6c** with 40% ee and an S_N2' to S_N2 ratio of 50 : 50. While the sterically demanding adamantyl-derived allylic bromide **5d** was converted with acceptable 80% ee, the present method finds limitations with undecenyl-derived compound **6e** (12% ee). This last example, however, represents a particularly challenging substrate, as (i) a relatively small hydride nucleophile has to be transferred and (ii) the catalyst has to differentiate between a primary (methyl-) and a secondary alkyl carbon atom (*n*-octyl) for stereodiscrimination. Allylic bromides bearing electron-withdrawing groups such as **5f** gave full conversion (γ/α = 90 : 10), but rapidly decomposed during workup.

We investigated allylic bromides substituted by other alkyl groups in the γ-position next. Compared to the results of terminal alkene **6a** in terms of stereoselectivity (Scheme 3), the corresponding longer alkyl chains give rise to significantly higher ee values (Scheme 4): terminal alkenes **9a**–**9c** bearing ethyl, *n*-propyl and *n*-pentyl chains can be isolated with 68%, 93% and 72% enantiomeric excesses, respectively. A branched substituent such as in the iso-butyl-derivative **9d** seemed to interfere with the stereoinduction (35% ee). We found that the present asymmetric allylic reduction protocol is especially suited for allylic bromides bearing small rings in the γ position: the cyclopropyl- to

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cyclopentyl-substituted terminal alkenes **9e–9g** can be furnished with high enantiomeric excesses (78–99% ee). It should be noted that there is no general approach to this substrate class in the literature.[18] The cyclohexyl derivative **9h** gave only negligible values of enantioselectivity (6% ee) which serves as an indication for the mode of stereodiscrimination (see below).

To explain the stereoselectivity and -convergence found for the allylic reduction protocol, we resort to a previously developed model for similar allylic borylations.[15] Following this precedent, we hypothesise that the stereoselectivity of the present allylic reduction is governed solely by the two substituents in the γ-position of the allylic bromide when approaching the copper(I) hydride NHC complex (hydride attack from the *Re* face). This leads to a stereoconvergent process independent of the double bond configuration (Fig. 1). Indeed, comparing the absolute configuration obtained in the present asymmetric allylic reduction with the literature precedents of borylations[15] and silylations[19] shows that all the nucleophiles are delivered from the same face to the corresponding allylic acceptors when employing (*S*,*S*)-**4**.[20] Following this model, the difference in size of the two γ-substituents is essential for high stereoinduction, which explains the low ee value found for the cyclohexyl-derivative **9h** (Scheme 4). Here, the steric demands of the cyclohexyl and phenyl groups seem to be relatively similar, leading to little enantioinduction.

With regards to the catalytic cycle, the fact that for most of the allylic reduction experiments a small amount (generally $<5\%$) of the corresponding α-substituted internal alkenes **7** or **10** is detected serves as an indication that during the catalytic cycle a π-allyl-copper complex should be accessible. This is also backed up by our findings from the racemic variant, where minute changes of the electronic properties of the NHC ligand led to a drastic reversal of the regioselectivity of the reaction.[14] Therefore, a plausible mechanism is presented in Scheme 5: after initial salt metathesis to yield the active copper(I)-*tert*-butoxide complex **A**, the copper(I) hydride complex **B** is formed through σ bond metathesis.[21] Subsequent oxidative addition leads to a σ-allyl complex which most likely is in equilibrium with the corresponding π-allyl complex **C**.[22] Reductive elimination then leads to the allylic reduction product and copper(I) bromide complex **D**, which can re-enter the catalytic cycle *via* the reaction with another equivalent of NaO^{t}Bu.

In conclusion, we have developed a hitherto unknown copper(I)-catalysed asymmetric transfer of a hydride nucleophile stemming from a hydrosilane to allylic bromides. The resulting asymmetric allylic reduction delivers the corresponding terminal alkenes bearing a stereocenter with high regioselectivity and up to excellent ee values, and therefore represents a conceptually orthogonal approach to the well-established asymmetric allylic substitutions with carbon-based nucleophiles. Particularly, substrates bearing small rings previously unavailable through other asymmetric syntheses deliver very good results in terms of stereoselectivity. These ee values are remarkable considering the size of the hydride nucleophile being transferred. The present catalyst allows for the application of both double bond isomers of the starting materials through a stereoconvergent catalytic process, which circumvents the need for a laborious stereoselective preparation of the allylic bromides.

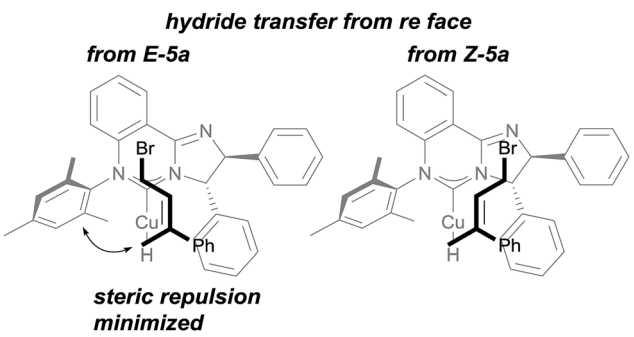
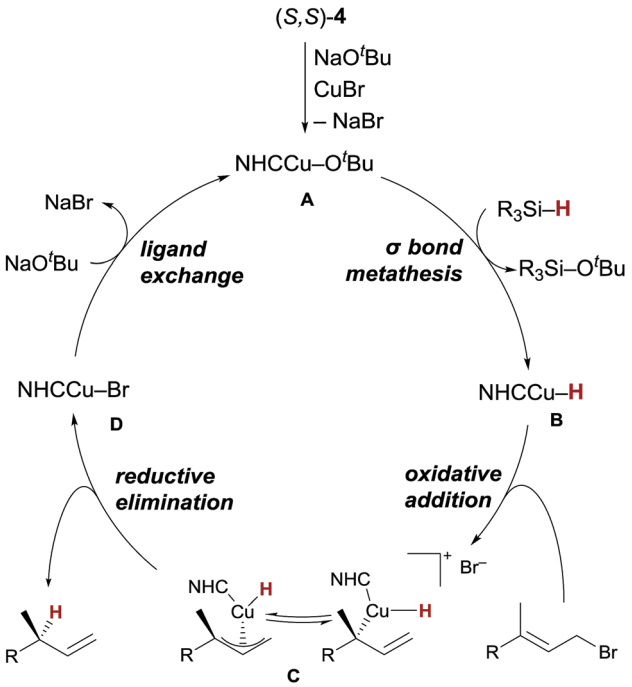


Fig. 1 Proposed model for stereoinduction (adapted from ref. 15*b*).



Scheme 5 Plausible catalytic cycle.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For a general overview on asymmetric allylic substitution reactions, see: ed. U. Kazmaier, *Topics in Organometallic Chemistry*, Springer, Berlin, 2012, vol. 38.
2 For reviews, see: (*a*) A. Alexakis, J.-E. Bäckvall, N. Krause, O. Pàmies and M. Diéguez, *Chem. Rev.*, 2008, **108**, 2796; (*b*) S. R. Harutyunyan, T. den Hartog, K. Geurts, A. J. Minnaard and B. L. Feringa, *Chem. Rev.*, 2008, **108**, 2824; (*c*) J.-B. Langlois and A. Alexakis, Transition Metal Catalysed Allylic Substitution in Organic Synthesis, in *Topics in Organometallic Chemistry*, ed. U. Kazmaier, Springer, Berlin, 2012, vol. 38, p. 235.
3 Zn-Based nucleophiles, selected examples: (*a*) F. Dübner and P. Knochel, *Tetrahedron Lett.*, 2000, **41**, 9233; (*b*) C. Börner, P. J.

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Goldsmith, S. Woodward, J. Gimeno, S. Gladiali and D. Ramazzotti, *Chem. Commun.*, 2000, 2433; (*c*) K. E. Murphy and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2003, **125**, 4690; (*d*) H. Malda, A. W. van Zijl, L. A. Arnold and B. L. Feringa, *Org. Lett.*, 2001, **3**, 1169; (*e*) A. O. Larsen, W. Leu, C. N. Oberhuber, J. E. Campbell and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2004, **126**, 11130; (*f*) P. J. Goldsmith, S. J. Teat and S. Woodward, *Angew. Chem., Int. Ed.*, 2005, **44**, 2235.

4 Mg-Based nucleophiles, selected examples: (*a*) M. van Klaveren, E. S. Persson, A. del Villar, D. M. Grove, J.-E. Bäckvall and G. van Koten, *Tetrahedron Lett.*, 1995, **36**, 3059; (*b*) K. Tissot-Croset, D. Polet and A. Alexakis, *Angew. Chem., Int. Ed.*, 2004, **43**, 2426; (*c*) S. Tominaga, Y. Oi, T. Kato, D. K. An and S. Okamoto, *Tetrahedron Lett.*, 2004, **45**, 5585; (*d*) F. López, A. W. van Zijl, A. J. Minnaard and B. L. Feringa, *Chem. Commun.*, 2006, 409; (*e*) K. B. Selim, Y. Matsumoto, K.-I. Yamada and K. Tomioka, *Angew. Chem., Int. Ed.*, 2009, **48**, 8733.

5 Al-Based nucleophiles, selected examples: (*a*) Y. Lee, K. Akiyama, D. G. Gillingham, M. K. Brown and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2008, **130**, 446; (*b*) J. A. Dabrowski, F. Gao and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 4778.

6 B-Based nucleophiles, review: (*a*) R. Shintani, *Synthesis*, 2016, 1087; selected examples: (*b*) H. Ohmiya, U. Yokobori, Y. Makida and M. Sawamura, *J. Am. Chem. Soc.*, 2010, **132**, 2895; (*c*) H. Ohmiya, N. Yokokawa and M. Sawamura, *Org. Lett.*, 2010, **12**, 2438; (*d*) A. M. Whittaker, R. P. Rucker and G. Lalic, *Org. Lett.*, 2010, **12**, 3216; (*e*) R. Shintani, K. Takatsu, M. Takeda and T. Hayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 8656; (*f*) Y. Shido, M. Yoshida, M. Tanabe, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc.*, 2012, **134**, 18573; (*g*) K. Hojoh, Y. Shido, H. Ohmiya and M. Sawamura, *Angew. Chem., Int. Ed.*, 2014, **53**, 4954.

7 Li-Based nucleophiles, selected examples: (*a*) M. Pérez, M. Fañanás-Mastral, P. H. Bos, A. Rudolph, S. R. Harutyunyan and B. L. Feringa, *Nat. Chem.*, 2011, **3**, 377; (*b*) M. Fañanás-Mastral, M. Pérez, P. H. Bos, A. Rudolph, S. R. Harutyunyan and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2012, **51**, 1922; (*c*) S. Guduguntla, V. Hornillos, R. Tessier, M. Fañanás-Mastral and B. L. Feringa, *Org. Lett.*, 2016, **18**, 252.

8 Zr-Based nucleophiles, selected examples: (*a*) H. Zhou, E. Rideau, M. Sidera and S. P. Fletcher, *Nature*, 2015, **517**, 351; (*b*) M. Sidera and S. P. Fletcher, *Chem. Commun.*, 2015, **51**, 5044.

9 For reviews on copper hydride chemistry, see: (*a*) A. Jordan, G. Lalic and J. P. Sadighi, *Chem. Rev.*, 2016, **116**, 8318; (*b*) B. H. Lipshutz, in *Copper-Catalysed Asymmetric Synthesis*, ed. A. Alexakis, N. Krause and S. Woodward, Wiley-VCH, Weinheim, 2014; (*c*) C. Deutsch, N. Krause and B. H. Lipshutz, *Chem. Rev.*, 2008, **108**, 2916; (*d*) S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, 2007, **46**, 498.

10 For a proposed asymmetric allylic reduction as an elementary step of a hydroamination protocol, see: S. Zhu, N. Niljianskul and S. L. Buchwald, *Nat. Chem.*, 2016, **8**, 144.

11 For a proposed racemic allylic reduction as a part of a reduction of Morita–Baylis–Hillman adducts, see: R. T. H. Linstadt, C. A. Peterson, C. I. Jette, Z. V. Boskovic and B. H. Lipshutz, *Org. Lett.*, 2017, **19**, 328.

12 For the related Cu-catalysed hydride transfer to chiral propargylic acceptors under substrate control, see: (*a*) C. Deutsch, B. H. Lipshutz and N. Krause, *Angew. Chem., Int. Ed.*, 2007, **46**, 1650; (*b*) C. Zhong, Y. Sasaki, H. Ito and M. Sawamura, *Chem. Commun.*, 2009, 5850; (*c*) C. Deutsch, B. H. Lipshutz and N. Krause, *Org. Lett.*, 2009, **11**, 5010.

13 The only other known asymmetric allylic reduction protocol is a palladium-catalysed hydride transfer from ammonium formate: (*a*) T. Hayashi, H. Iwamura, M. Naito, Y. Matsumoto, Y. Uozumi, M. Miki and K. Yanagi, *J. Am. Chem. Soc.*, 1994, **116**, 775; (*b*) T. Hayashi, M. Kawatsura, H. Iwamura, Y. Yamaura and Y. Uozumi, *Chem. Commun.*, 1996, 1767; (*c*) K. Fuji, M. Sakurai, T. Kinoshita and T. Kawabata, *Tetrahedron Lett.*, 1998, **39**, 6323; (*d*) M. Kawatsura, Y. Uozumi, M. Ogasawara and T. Hayashi, *Tetrahedron*, 2000, **56**, 2247.

14 For the racemic variant of this process, see: T. N. T. Nguyen, N. O. Thiel, F. Pape and J. F. Teichert, *Org. Lett.*, 2016, **18**, 2455.

15 (*a*) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk and D. T. McQuade, *Org. Lett.*, 2010, **12**, 5008; (*b*) J. K. Park, H. H. Lackey, B. A. Ondrusek and D. T. McQuade, *J. Am. Chem. Soc.*, 2011, **133**, 2410; (*c*) J. K. Park and D. T. McQuade, *Synthesis*, 2012, 1485.

16 For full details, see the ESI†.

17 The absolute configuration of (*S*)-**2** was established by comparison of the sign of the specific rotation with the value reported in the literature: H. Kiuchi, D. Takahashi, K. Funaki, T. Sato and S. Oi, *Org. Lett.*, 2012, **14**, 4502. The same absolute configuration could be established for a variety of other substrates; see the ESI† for details.

18 Cyclopentyl-derived alkene **9g** has been prepared *via* allylic substitution in the presence (80% ee) and absence (88% ee) of copper catalysts, see: D. Grassi and A. Alexakis, *Adv. Synth. Catal.*, 2015, **357**, 3171.

19 (*a*) L. B. Delvos, D. J. Vyas and M. Oestreich, *Angew. Chem., Int. Ed.*, 2013, **52**, 4650; (*b*) L. B. Delvos, A. Hensel and M. Oestreich, *Synthesis*, 2014, 2957; (*c*) L. B. Delvos and M. Oestreich, *Synthesis*, 2015, 924; (*d*) A. Hensel and M. Oestreich, *Chem. – Eur. J.*, 2015, **21**, 9062.

20 For related copper-catalysed stereoconvergent processes *via* different mechanisms, see for example: (*a*) C. A. Falciola and A. Alexakis, *Angew. Chem., Int. Ed.*, 2007, **46**, 2619; (*b*) H. Ito, S. Kunii and M. Sawamura, *Nat. Chem.*, 2010, **2**, 972; (*c*) J.-B. Langlois, D. Emery, J. Mareda and A. Alexakis, *Chem. Sci.*, 2012, **3**, 1062; (*d*) J. K. Park and D. T. McQuade, *Angew. Chem., Int. Ed.*, 2012, **51**, 2717; (*e*) Y. Shido, M. Yoshida, M. Tanabe, H. Ohmiya and M. Sawamura, *J. Am. Chem. Soc.*, 2012, **134**, 18573; (*f*) M. Takeda, K. Takatsu, R. Shintani and T. Hayashi, *J. Org. Chem.*, 2014, **79**, 2354.

21 (*a*) S. Rendler, O. Plefka, B. Karatas, G. Auer, R. Fröhlich, C. Mück-Lichtenfeld, S. Grimme and M. Oestreich, *Chem. – Eur. J.*, 2008, **14**, 11512; (*b*) T. Gathy, D. Peeters and T. Leyssens, *J. Organomet. Chem.*, 2009, **694**, 3943; (*c*) T. Vergote, F. Nahra, A. Merschaert, O. Riant, D. Peeters and T. Leyssens, *Organometallics*, 2014, **33**, 1953.

22 At this stage, a stereoconvergent process *via* a σ–π–σ allylic rearrangement cannot be ruled out.

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