Asymmetric Hydrogenation

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Asymmetric Hydrogenation of Vinylthioethers: Access to Optically Active 1,5-Benzothiazepine Derivatives

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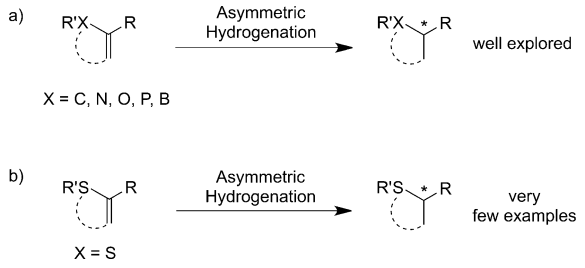
Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: *A novel asymmetric hydrogenation of vinylthioethers was developed using a ruthenium(II) NHC complex. This method provides an efficient approach to optically active 1,5-benzothiazepines featuring stereocenters with C–S bonds. Excellent enantioselectivities (up to 95 % ee) and high yields (up to 99 %) were obtained for a variety of substrates bearing a range of useful functional groups. Moreover, this methodology could be directly applied to the synthesis of the antidepressant drug R-(−)-thiazesim.*

Asymmetric hydrogenation of functionalized olefins is a reliable and powerful method to access useful chiral molecules and has been widely applied in both academia and industry.[1] Compounds containing vinyl groups directly connected to C, N, O, P, or B substituents such as α-dehydroamino acids, acrylates, enamides, enamines, enols, vinylphosphonates, or vinylboronates have been broadly used as substrates in the construction of stereocenters bearing C–X bonds (Scheme 1 a).[2] In stark contrast, much less success has been achieved in the asymmetric hydrogenation of vinylthioethers or other sulfur-functionalized alkenes, even though this method would provide a straightforward approach to access stereocenters bearing a C–S bond which commonly exists in natural products and synthetic molecules (Scheme 1 b).[3] Particularly, organosulfur compounds make up an important fraction (ca. 20 %) of marketed pharmaceuticals, with many of the top-selling drugs in 2012 containing at least one C–S bond.[4] In 2007, Feringa and co-workers reported the first enantioselective hydrogenation of alkyl-(vinyl)thioethers although *ee* values of only up to 60 % were obtained.[5] In 2008, the Pfaltz group reported the hydrogenation of 2-phenyl-4*H*-thiochromene giving 73 % conversion and 91 % *ee*.[6] Our group previously realized the hydrogenation of thiophenes and benzothiophenes to the corresponding reduced heterocycles with 32–99 % yields and up to 98 % *ee*.[7] One challenge observed during the reduction of these sulfur-containing molecules is the catalyst deactivation by coordination of the sulfur atom to the transition metal.[2,5] Considering the widespread application of asymmetric hydrogenation and the significance of organosulfur compounds, the development of efficient and divergent asymmetric hydrogenation processes applicable to vinylthioethers and other sulfur-substituted alkenes to access chiral organosulfur compounds is highly valuable.

Optically active 1,5-benzothiazepine, which contains a seven-membered ring bearing a sulfur-substituted stereocenter, is a versatile pharmacophore in the field of pharmaceutical research.[8] Thiazesim and diltiazem are representative drugs featuring this motif (Scheme 2 a).[9] Although much effort has been devoted to access this building block, methods using asymmetric catalysis are quite limited. Typically multistep strategies are employed with an initial addition of a sulfur nucleophile to a Michael acceptor or an epoxide constructing the stereogenic center being followed by a cyclization to afford the ring structure.[10] Recently, Matsubara and co-



Scheme 1. Construction of chiral X-substituted carbons by asymmetric hydrogenation.

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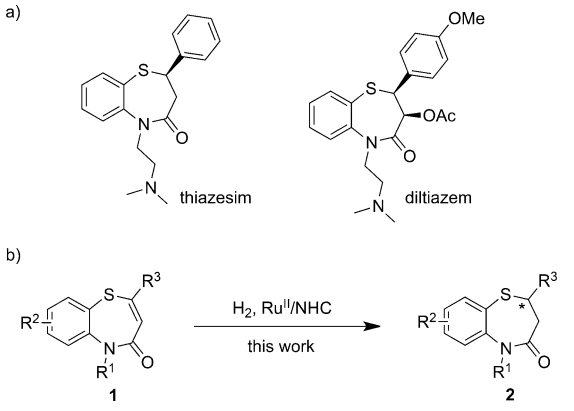


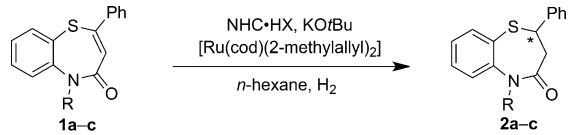
Scheme 2. a) Selected examples of drug molecules featuring the 2,3-dihydro-1,5-benzothiazepinone core. b) $Ru(NHC)_2$-catalyzed asymmetric hydrogenation of 1,5-benzothiazepinones.

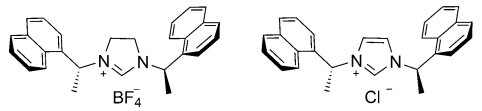
workers reported a facile formal cycloaddition approach to produce chiral 2,3-dihydro-1,5-benzothiazepinones catalyzed by a benzotetramisole catalyst.[11] Undoubtedly, the exploration of new catalytic strategies to construct diverse optically active 1,5-benzothiazepine derivatives would be highly desirable for drug discovery. Based on our previous studies in the field of asymmetric hydrogenation of heterocycles,[7,12] we envisioned that an asymmetric hydrogenation of the vinylthioether motif in 1,5-benzothiazepinones may provide a direct method to access these important compounds through the construction of a stereocenter possessing a C–S bond (Scheme 2b). In addition to employing hitherto seldom sulfur-containing compounds, this process would also represent a rare example of asymmetric hydrogenation of seven-membered heterocycles.[2]

After a preliminary investigation, we found a straightforward route to rapidly access unsaturated 1,5-benzothiazepinone **1a** from commercially available 2-aminothiophenol and phenylpropiolic acid (see the Supporting Information for details). An initial test reaction was then conducted with this unprotected substrate (**1a**) under 100 bar H_2 in *n*-hexane at room temperature using our previously developed ruthenium N-heterocyclic carbene (NHC) catalyst prepared in situ from [Ru(cod)(2-methylallyl)$_2$] (cod = cycloocta-1,5-diene), (*R*,*R*)-SINpEt·HBF$_4$, and KO*t*Bu.[13] Unfortunately, no reduced product was observed, presumably due to catalyst deactivation arising from the free amide group in **1a** (Table 1, entry 1). The *N*-Boc-protected substrate **1b** (Boc = *tert*-butoxycarbonyl) was then submitted to the same hydrogenation conditions but was still unreactive, possibly due to detrimental electronic bias (entry 2). We were, however, pleased to find that when the *N*-methyl-protected substrate **1c** was used, the corresponding 2,3-dihydro-1,5-benzothiazepinone **2c** could be isolated in 70% yield with 92% *ee* (entry 3). The use of the unsaturated NHC derivative (*R*,*R*)-INpEt·HCl resulted in a similar yield but a lower enantioinduction (entry 4). Reaction at a higher temperature (35 °C) led to both lower yield and lower enantioselectivity, possibly due to the enhanced poisoning propensity of sulfur-containing compounds (entry 5). A reaction conducted at the lower temperature of 10 °C afforded the product with a slightly better *ee* but with lower conversion (entry 6). Other solvents such as toluene and *t*-amyl alcohol led to lower enantioselectivities, while ethereal solvents such as THF, Et_2O, and DME led to decomposition of the starting material. Better conversion was observed when the reaction mixture was diluted (entry 7). Finally, prolonging the reaction time could increase the yield of the product to 99% while maintaining an *ee* value of 93% (entry 8).

With the optimized conditions in hand (Table 1, entry 8), we examined the substrate scope of the reaction as shown in Schemes 3 and 4. Hydrogenation of the *N*-4-methoxybenzyl-protected substrate **1d** gave the corresponding product in 70% yield with 93% *ee* (Scheme 3). The influence of electronic nature of the substituents on the aminothiophenol

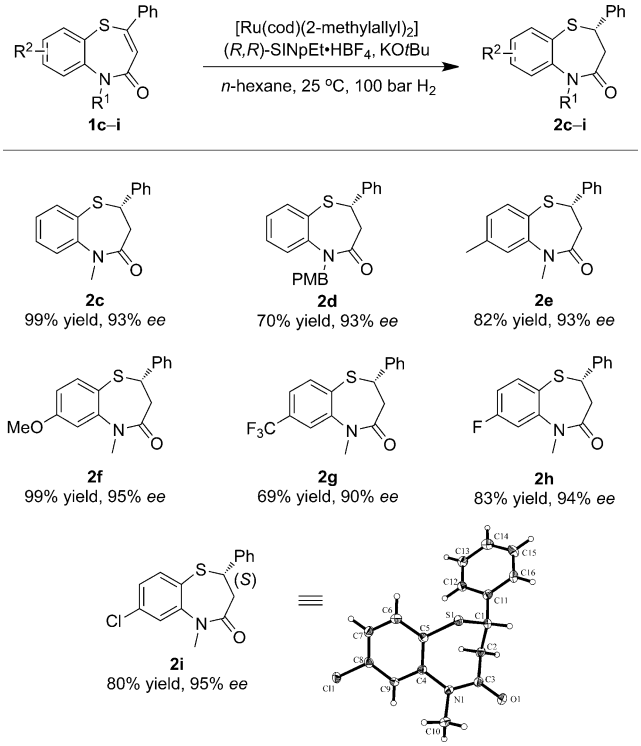
Table 1: Optimization of the reaction conditions.[a]



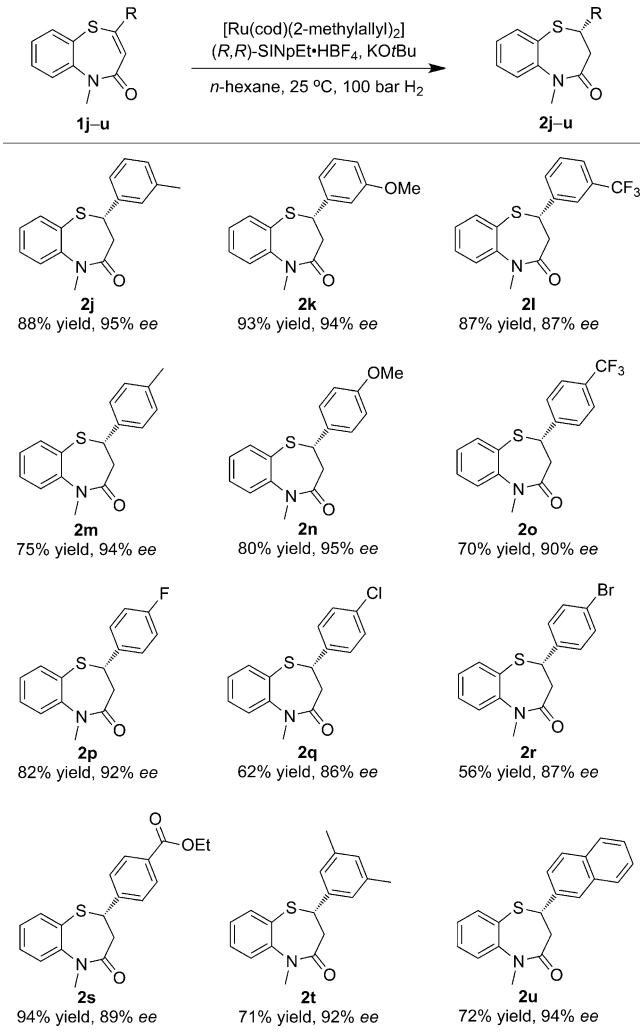


Entry	NHC·HX	R	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	(*R*,*R*)-SINpEt·HBF$_4$	H (**1a**)	25	0	–
2	(*R*,*R*)-SINpEt·HBF$_4$	Boc (**1b**)	25	0	–
3	(*R*,*R*)-SINpEt·HBF$_4$	Me (**1c**)	25	70	92
4	(*R*,*R*)-INpEt·HCl	Me (**1c**)	25	73	85
5	(*R*,*R*)-SINpEt·HBF$_4$	Me (**1c**)	35	60	85
6	(*R*,*R*)-SINpEt·HBF$_4$	Me (**1c**)	10	45	95
7[d]	(*R*,*R*)-SINpEt·HBF$_4$	Me (**1c**)	25	93	93
8[d,e]	(*R*,*R*)-SINpEt·HBF$_4$	Me (**1c**)	25	99	93

[a] General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.01 mmol), KO*t*Bu (0.025 mmol), and NHC·HX (0.02 mmol) were stirred at 70 °C in *n*-hexane (0.5 mL) for 16 h, after which the mixture was added to **1a–c** (0.10 mmol) in *n*-hexane (1.5 mL), and hydrogenation was performed at 100 bar H_2 for 24 h. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] *n*-hexane (3.0 mL). [e] The reaction time was prolonged to 36 h.



Scheme 3. Substrate scope of unsaturated 1,5-benzothiazepinones **1c–i**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.02 mmol), KO*t*Bu (0.05 mmol), and (*R*,*R*)-SINpEt·HBF$_4$ (0.04 mmol) were stirred at 70 °C in *n*-hexane for 16 h, after which the mixture was added to **1c–i** (0.20 mmol) in *n*-hexane, and hydrogenation was then performed under 100 bar H_2 at 25 °C for 24–48 h. Yields of isolated products are given. *ee* values were determined by HPLC analysis on a chiral stationary phase. PMB = 4-methoxybenzyl.

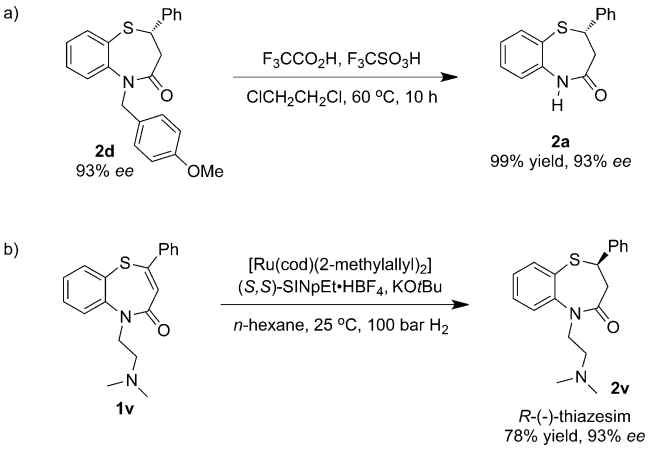


Scheme 4. Substrate scope of unsaturated 1,5-benzothiazepinones **1j–u**. General conditions: [Ru(cod)(2-methylallyl)$_2$] (0.02 mmol), KO*t*Bu (0.05 mmol), and (*R*,*R*)-SINpEt·HBF$_4$ (0.04 mmol) were stirred at 70 °C in *n*-hexane for 16 h, after which the mixture was added to **1j–u** (0.20 mmol) in *n*-hexane, and hydrogenation was performed under 100 bar H_2 at 25 °C for 24–48 h. Yields of isolated products are given. *ee* values were determined by HPLC analysis on a chiral stationary phase.

ring was investigated. Electron-rich substrates provided the corresponding 2,3-dihydro-1,5-benzothiazepinones with excellent enantioselectivities and yields (Scheme 3, **2e**,**f**), while the electron-poor substrate **1g** provided **2g** in comparatively lower *ee* of 90 % and 69 % yield. Notably, fluoro- (**1h**) and chloro-substituted substrates (**1i**) were also tolerated under these conditions providing the corresponding products with excellent enantioselectivities and good yields. In addition, the absolute configuration of **2i** was determined to be *S* by X-ray crystallographic analysis.[14] The configurations of the other products were assigned by analogy.

We then further explored substrates derived from various substituted propiolic acids as shown in Scheme 4. Introducing electron-donating groups and electron-withdrawing groups at the *meta*- or *para*-positions of the phenyl group had minimal influence on the reactivity and selectivity, providing the desired 2,3-dihydro-1,5-benzothiazepinones **2j–o** with excellent enantioselectivities (87–95 % *ee*) and in good yields (70–93 %). The halogenated substrates **1p–r** were tolerated, giving the corresponding products **2p–r** in 86–92 % *ee* and 56–82 % yield. Only trace amounts of dehalogenated products were detected by NMR analysis for both substrates **1q** and **1r**. Furthermore, the ester functionality in substrate **1s** presented no problems in this hydrogenation process, and the corresponding product was produced in 94 % yield and 89 % *ee*. These functional groups (OMe, F, Cl, Br, and ester groups) provide an excellent opportunity for further modification of the 1,5-benzothiazepinone products. The disubstituted substrate **1t** was successfully reduced to give **2t** in 92 % *ee* and 71 % yield. Moreover, 2-naphthyl-substituted substrate **1u** was hydrogenated with excellent enantioselectivity and good yield. We also tested several 1,5-benzothiazepinones derived from aliphatic propiolic acids; however, poor results were obtained under the current catalytic conditions.

To demonstrate the synthetic utility of this process, further derivatization and application were carried out (Scheme 5). Firstly, **2d** was conveniently deprotected under strongly Brønsted acidic conditions, affording the unprotected 2,3-dihydro-1,5-benzothiazepinone **2a** in almost quantitative yield without any loss of enantiomeric excess (Scheme 5 a).[15]



Scheme 5. Applications of the asymmetric hydrogenation reaction.

The remarkable functional group tolerance of this hydrogenation methodology allowed us to directly apply the unsaturated 1,5-benzothiazepinone **1v** containing a tertiary amine moiety, affording the seven-membered heterocyclic antidepressant drug (*R*)-(−)-thiazesim **2v** with 93 % *ee* and 78 % yield using (*S*,*S*)-SINpEt·HBF$_4$ as the ligand precursor (Scheme 5 b). The absolute configuration of thiazesim **2v** was confirmed by comparing the optical rotation with the known literature value (see the Supporting Information for details). As far as we know, the present methodology provides the most straightforward process for the asymmetric synthesis of thiazesim to date.[10,11]

In summary, we have described a novel enantioselective hydrogenation of cyclic vinylthioethers to access optically active 2,3-dihydro-1,5-benzothiazepinones. Using a ruthenium(II) NHC catalyst, a series of unsaturated 1,5-benzothi-

azepinones were smoothly hydrogenated, producing the desired products with excellent *ee* values (up to 95%), high yields (up to 99%) and good functional group tolerance.

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Keywords: 1,5-benzothiazepine · asymmetric hydrogenation · N-heterocyclic carbenes · ruthenium · vinylthioethers

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[1] a) *Catalysis in Asymmetric Synthesis* (Eds.: V. Caprio, J. M. J. Williams), Wiley VCH, Chichester, **2009**; b) *Modern Reduction Methods* (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**; c) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **2004**; d) *Asymmetric Catalysis on Industrial Scale* (Eds.: H. U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**.

[2] For selected reviews, see: a) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; b) X. Cui, K. Burgess, *Chem. Rev.* **2005**, *105*, 3272; c) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; d) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557; e) Z. Yu, W. Jin, Q. Jiang, *Angew. Chem. Int. Ed.* **2012**, *51*, 6060; *Angew. Chem.* **2012**, *124*, 6164; f) B. Zhao, Z. Han, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 4744; *Angew. Chem.* **2013**, *125*, 4844; g) J. J. Verendel, O. Pamies, M. Dieguez, P. G. Andersson, *Chem. Rev.* **2014**, *114*, 2130.

[3] a) A. Nudelman, *The Chemistry of Optically Active Sulfur Compounds*, Gordon and Breach, New York, **1984**; b) *Sulphur-Containing Drugs and Related Organic Compounds* (Ed.: L. A. Damani), Wiley, New York, **1989**; c) *Organosulfur Chemistry in Asymmetric Synthesis* (Eds.: T. Toru, C. Bolm), Wiley-VCH, Weinheim, **2008**; d) J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582; e) P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807.

[4] a) V. Tyagi, R. B. Bonn, R. Fasan, *Chem. Sci.* **2015**, *6*, 2488; b) http://www.genengnews.com/insight-and-intelligenceand153/top-20-best-selling-drugs-of-2012/77899775/?page=2.

[5] A. F. Meindertsma, M. M. Pollard, B. L. Feringa, J. G. de Vries, A. J. Minnaard, *Tetrahedron: Asymmetry* **2007**, *18*, 2849.

[6] A. Pfaltz, C. Valla, A. Baeza, F. Menges, *Synlett* **2008**, 3167.

[7] S. Urban, B. Beiring, N. Ortega, D. Paul, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 15241.

[8] For reviews on synthesis and applications of 1,5-benzothiazepine derivatives, see: a) A. Lévai, *J. Heterocycl. Chem.* **2000**, *37*, 199; b) A. Lévai, A. Kiss-Szikszai, *ARKIVOC* **2008**, 65; c) J. B. Bariwal, K. D. Upadhyay, A. T. Manvar, J. C. Trivedi, J. S. Singh, K. S. Jain, A. K. Shah, *Eur. J. Med. Chem.* **2008**, *43*, 2279.

[9] Thiazesim, an antidepressant drug: a) J. Krapcho, E. R. Spitzmiller, C. F. Turk, *J. Med. Chem.* **1963**, *6*, 544; b) J. Krapcho, C. F. Turk, *J. Med. Chem.* **1966**, *9*, 191; c) J. Krapcho, C. F. Turk, J. J. Piala, *J. Med. Chem.* **1968**, *11*, 361. Diltiazem, used as Ca^{2+} channel blocker for the treatment of hypertension: d) T. Nagao, M. Sato, H. Nakajima, A. Kiyomoto, *Chem. Pharm. Bull.* **1973**, *21*, 92; e) H. Inoue, S. Takeo, M. Kawazu, H. Kugita, *Yakugaku Zasshi* **1973**, *93*, 729.

[10] a) Q.-L. Pei, H.-W. Sun, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem.* **2011**, *76*, 7849; b) T. Ogawa, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2012**, *51*, 8551; *Angew. Chem.* **2012**, *124*, 8679; c) X. Fang, J. Li, C.-J. Wang, *Org. Lett.* **2013**, *15*, 3448; d) E. N. Jacobsen, L. Deng, Y. Furukawa, L. E. Martínez, *Tetrahedron* **1994**, *50*, 4323.

[11] Y. Fukata, K. Asano, S. Matsubara, *J. Am. Chem. Soc.* **2015**, *137*, 5320.

[12] a) S. Urban, N. Ortega, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 3803; *Angew. Chem.* **2011**, *123*, 3887; b) N. Ortega, S. Urban, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 1710; *Angew. Chem.* **2012**, *124*, 1742; c) D. Zhao, B. Beiring, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 8454; *Angew. Chem.* **2013**, *125*, 8612; d) N. Ortega, D.-T. D. Tang, S. Urban, D. Zhao, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 9500; *Angew. Chem.* **2013**, *125*, 9678; e) J. Wysocki, N. Ortega, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 8751; *Angew. Chem.* **2014**, *126*, 8896.

[13] For the use of NHCs as ligands in transition-metal catalysis, see: a) S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, Weinheim, **2006**; b) F. Glorius, *N-Heterocyclic Carbenes in Transition Metal Catalysis*, Springer, Berlin, **2007**; c) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem. Int. Ed.* **2007**, *46*, 2768; *Angew. Chem.* **2007**, *119*, 2824; d) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612; e) S. Bellemin-Laponnaz, S. Dagorne, *Chem. Rev.* **2014**, *114*, 8747; f) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485. For reviews on the physicochemical properties of NHCs, see: g) T. Dröge, F. Glorius, *Angew. Chem. Int. Ed.* **2010**, *49*, 6940; *Angew. Chem.* **2010**, *122*, 7094; h) D. J. Nelson, S. P. Nolan, *Chem. Sco. Rev.* **2013**, *42*, 6723.

[14] CCDC 1441631 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] F. Hoffmann-Emery, R. Jakob-Roetne, A. Flohr, F. Bliss, R. Reents, *Tetrahedron Lett.* **2009**, *50*, 6380.

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