A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

GDCh

Chemie

www.angewandte.org

Accepted Article

Title: Copper-Catalyzed Regio- and Enantioselective Addition of Silicon Grignard Reagents to Alkenes Activated by Azaaryl Groups

Authors: Wenbin Mao, Weichao Xue, Elisabeth Irran, and Martin Oestreich

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201905934
Angew. Chem. 10.1002/ange.201905934

Link to VoR: http://dx.doi.org/10.1002/anie.201905934
http://dx.doi.org/10.1002/ange.201905934

WILEY-VCH

10.1002/anie.201905934

COMMUNICATION

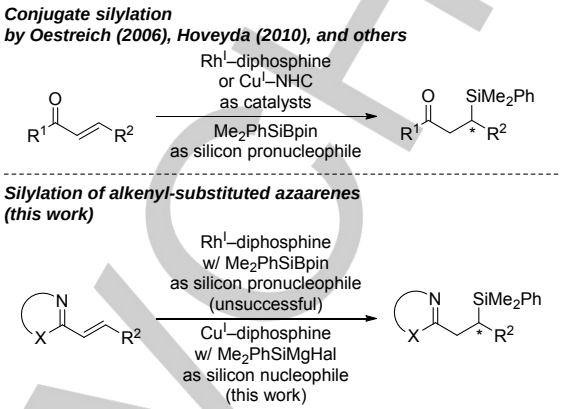
WILEY-VCH

Copper-Catalyzed Regio- and Enantioselective Addition of Silicon Grignard Reagents to Alkenes Activated by Azaaryl Groups

Wenbin Mao[+], Weichao Xue[+], Elisabeth Irran, and Martin Oestreich*

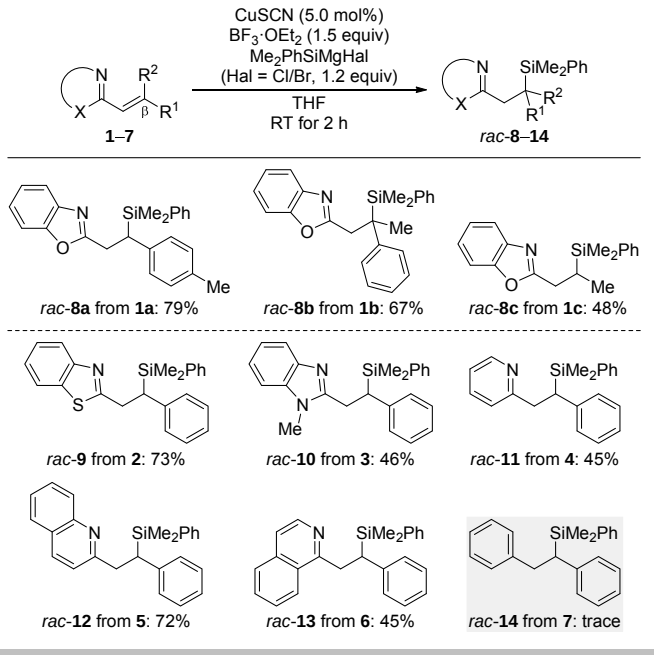
Abstract: A new application of silicon Grignard reagents in C(sp^3)–Si bond formation is reported. With the aid of $BF_3{\cdot}OEt_2$, these silicon nucleophiles add across alkenes activated by various azaaryl groups under copper catalysis. For benzoxazole as the heteroaryl substituent, an enantioselective version employing a Cu^I–josiphos complex has been developed, forming the C(sp^3)–Si bond with good to high enantiomeric ratios (up to 97:3). The method expands the toolbox for 'conjugate-addition'-type C(sp^3)–Si bond formation.

The catalytic enantioselective 1,4-addition of silicon nucleophiles to α,β-unsaturated carbonyl compounds had been a big challenge for decades but can now be considered as a solved problem.[1] Several transition-metal-catalyzed procedures employing either Rh^I–diphosphine[2] or Cu^I–NHC[3] complexes as catalysts are available today, and even NHCs alone have been shown to promote these reactions with high efficacy[4] (Scheme 1, top). All these methods share the use of silylboronic acid esters[5] as silicon pronucleophiles. Early attempts by us to apply our rhodium catalysis[2] to other activated alkenes such as alkenyl-substituted azaarenes to access biologically active molecules[6] had however not been met with success (Scheme 1, bottom).[7] Our efforts had been inspired by the seminal work of Lautens[8] and Lam[9] on the rhodium-catalyzed regioselective addition of arylboronic acids to these acceptors, both in racemic[8,10] and enantioselective[9] fashion. Harutyunyan and co-workers recently advanced this field tremendously with the development of an enantioselective copper catalysis that enables the addition of alkyl Grignard reagents to a broad set of those electron-deficient alkenes.[11] Last year, our laboratory introduced a reliable protocol for the preparation of bench-stable stock solutions of silicon Grignard reagents.[12] These have not been applied in asymmetric catalysis yet, and we have been particularly seeking transformations for which no other method has been reported to date. We disclose here that these silicon Grignard reagents undergo regioselective addition across alkenes activated by various azaaryl groups. Good enantiomeric ratios can be achieved with a chiral Cu^I–diphosphine complex as catalyst (Scheme 1, bottom).[13]



Scheme 1. Transition-metal-catalyzed enantioselective addition of silicon (pro)nucleophiles across electron-deficient alkenes. R^1 = aryl, alkyl, or heteroatom; R^2 = aryl/heteroaryl, alkenyl, or alkyl; X = heteroatom; Hal = Cl and Br. NHC = N-heterocyclic carbene. pin = pinacolato.

We began our study in the racemic series with benzoxazole derivative **1a** and $Me_2PhSiMgHal$[12a] as the silicon nucleophile. With Harutyunyan's catalyst system as a starting point ($CuBr{\cdot}SMe_2$ and $BF_3{\cdot}OEt_2$ in Et_2O),[11a,14] we eventually arrived at CuSCN as catalyst and $BF_3{\cdot}OEt_2$ as additive in THF (see the Supporting Information for the systematic screening of the reaction parameters). Under these reaction conditions, **1a** was regioselectively converted into silylated *rac*-**8a** in 79% yield (Scheme 2, top). Remarkably, a fully substituted β position as in **1b** was tolerated, affording *rac*-**8b** with a quaternary carbon atom in 67% yield. Alkyl-substituted **1c** reacted to *rac*-**8c** in 48% yield. It must be noted that the use of $Me_2PhSiBpin$[5c] as well as $Me_2PhSiZnCl$[15] and $Me_2PhSiLi$ resulted in far less or no conversion (not shown).[16]



[*] W. Mao,[+] W. Xue,[+] E. Irran,[++] Prof. Dr. M. Oestreich
Institut für Chemie, Technische Universität Berlin
Strasse des 17. Juni 115, 10623 Berlin (Germany)
E-mail: martin.oestreich@tu-berlin.de
Homepage: http://www.organometallics.tu-berlin.de

[+] These authors contributed equally to this work.

[++] X-ray crystal-structure analyses.

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

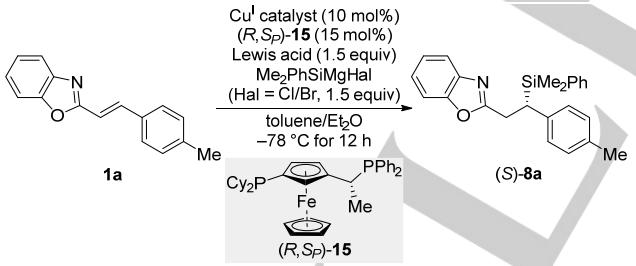
10.1002/anie.201905934

Scheme 2. Copper-catalyzed addition of the silicon Grignard reagent to various alkenyl-substituted azaarenes.

With the optimized setup in hand, we probed its compatibility with representative azaaryl groups (Scheme 2, bottom). Both benzothiazole (**2**→*rac*-**9**) and benzimidazole (**3**→*rac*-**10**) fulfilled the same role as the benzoxazole in substrates **1**. The yields for the pyridine derivatives **4**–**6** were in a similar range. Conversely, *trans*-stilbene (**7**) only furnished trace amounts of *rac*-**14**. This result shows that the electron-deficient azaaryl substituent is essential for the electronic activation the alkene[6] and additionally likely acting as directing or coordinating group. This also explains the exclusive β-selectivity.

We next targeted the enantioselective version (Table 1). Josiphos ligand (*R*,S_p)-**15** emerged from a screening of chiral ligands (see the Supporting Information for details). The model reaction of **1a** and $Me_2PhSiMgHal$ was promoted by the combination of CuBr·SMe_2/(*R*,S_p)-**15** and BF_3·OEt_2 in toluene to afford (*S*)-**8a** in 70% yield and with an enantiometric ratio (e.r.) of 90:10 (entry 1).[17] Several boron Lewis acids as additives were examined[14] but either diminished yield or eroded enantioenrichment were observed (entries 2–5); racemic material was obtained with BBr_3 and BPh_3. We included typical Cu^I salts as precatalysts, and it was only CuCl that led to better enantioselectivity than CuBr·SMe_2 (entries 6–10). Further improvement of the enantiomeric ratio from 92.5:7.5 to 97:3 was achieved by using 2.0 equiv of BF_3·Et_2O (entry 11). It is worth noting here that the use of the more coordinating solvent THF employed in the racemic series (cf. Scheme 2) resulted in complete loss of enantioinduction (not shown).[18] Application of the optimized procedure to β,β-disubstituted **1b** and alkyl-substituted **1c** failed; both **8b** and **8c** were isolated in moderate yields with little or no enantioselectivity (Figure 1).

Table 1. Selected examples of the optimization of the enantioselective addition.



Entry	Catalyst	Lewis acid	Yield [%][a]	e.r.[b]
1	CuBr·SMe_2	BF_3·OEt_2	70	90:10
2	CuBr·SMe_2	BF_3·OBu_2	65	87.5:12.5
3	CuBr·SMe_2	BF_3·SMe_2	87	80.5:19.5
4	CuBr·SMe_2	BBr_3	53	50:50
5	CuBr·SMe_2	BPh_3	49	50:50
6	CuSCN	BF_3·OEt_2	83	78.5:21.5
7	CuTc	BF_3·OEt_2	72	86.5:13.5
8	CuI	BF_3·OEt_2	92	88.5:11.5
9	CuBr	BF_3·OEt_2	87	82.5:17.5
10	CuCl	BF_3·OEt_2	82	92.5:7.5
11[c]	CuCl	BF_3·OEt_2	81	97:3

[a] All reactions were performed on a 0.10 mmol scale with isolated yield after flash chromatography on silica gel. [b] Determined by HPLC analysis on a chiral stationary phase. [c] 2.0 equiv of BF_3·OEt_2 used.

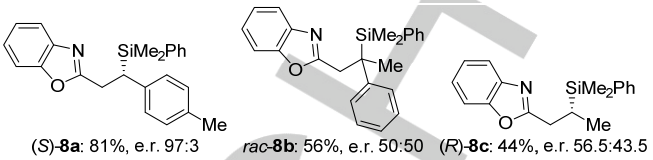


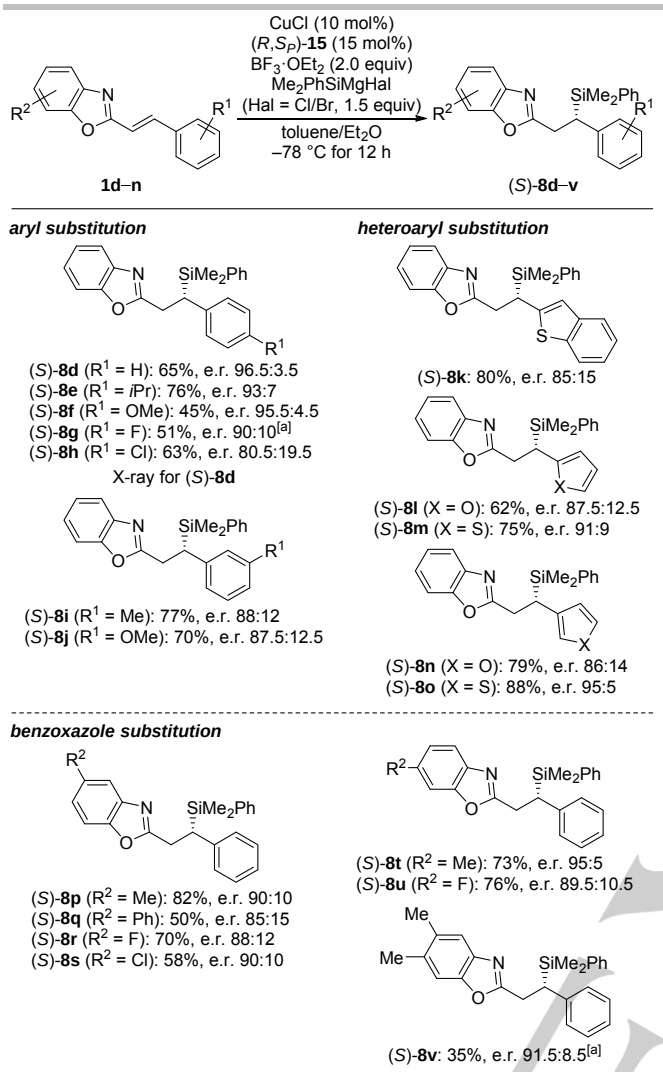
Figure 1. Probing the β substitution in the enantioselective silylation.

In turn, the scope was excellent for aryl-substituted benzoxazole-activated alkenes (Scheme 3). A broad range of substituents at the aryl group was compatible with the standard setup (**1d–j**→(*S*)-**8d–j**, top left). The absolute configuration was established by X-ray diffraction; the molecular structure of **8d** revealed its *S* configuration.[19] Enantioinduction remained at a good level (e.r. ≥ 87.5:12.5) except for a chloro substituent in the *para* position (e.r. 80.5:19.5). The situation did not change with heteroaryl groups at the β carbon atom (**1k–o**→(*S*)-**8k–o**, top right). Interestingly, the regioselectivity was not impaired by the furyl and (benzo)thienyl groups. However, a substrate containing a 4-pyridyl group in the β position did not convert under these reaction conditions (not shown). Likewise, the protocol was also tolerant of monosubstitution at the benzoxazole moiety (**1p–u**→(*S*)-**8p–u**, bottom). The benzoxazole **1v** with two methyl groups participated rather moderately, giving (*S*)-**8v** in low yield but with high enantioselectivity. Other silicon Grignard reagents[12a] were also tested with substrate **1d** but the reaction was highly dependent on the steric demand around the silicon atom: *t*-butyl-substituted *t*$BuPh_2SiMgHal$ and *t*Bu(Me)PhSiMgHal as well as $(Et_2N)Ph_2SiMgHal$ were too bulky; $MePh_2SiMgHal$ (40%, e.r. 65:35) and $Ph_3SiMgHal$ (27%, e.r. 50:50) did react in moderate and low yield, respectively with hardly any enantioinduction (see the Supporting Information for details).

Accepted Manuscript

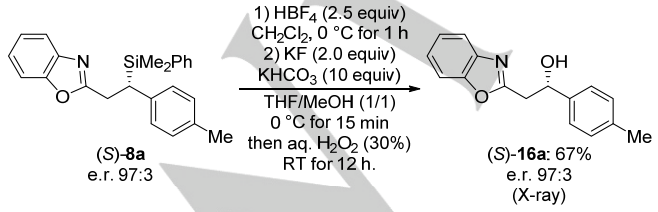
This article is protected by copyright. All rights reserved.

10.1002/anie.201905934



Scheme 3. Copper-catalyzed enantioselective addition of the silicon Grignard reagent to various alkenyl-substituted benzoxazole derivatives. [a] 5.0 equiv of $BF_3{\cdot}OEt_2$ used.

An important synthetic application of the silyl group is that it can be used as an equivalent of the hydroxy group.[1c] Tamao–Fleming oxidation[20] of (*S*)-**8a** yielded alcohol (*S*)-**16a** in 67% yield and with retention of configuration (Scheme 4). The absolute configuration of **16** was assigned as *S* by X-ray diffraction.[19]



Scheme 4. Enantiospecific oxidative degradation of the C(sp^3)–Si bond.

To conclude, we accomplished a copper-catalyzed, highly β-selective addition of silicon Grignard reagents to alkenes activated by azaaryl groups. An enantioselective version was developed for benzoxazole-derived substrates with a Josiphos chiral ligand.[11,21] Enantiomeric ratios as high 97:3 have been achieved for this enantioselective C(sp^3)–Si bond formation.

Acknowledgements

This research was supported by the China Scholarship Council through predoctoral fellowships to W.M. (2017–2021) and W.X. (2015–2019). M.O. is indebted to the Einstein Foundation Berlin for an endowed professorship. We thank the Solvias AG for the generous donation of (R,S_p)-**15**.

Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis • conjugate addition • copper • magnesium • silicon

[1] a) A. Hensel, M. Oestreich, *Top. Organomet. Chem.* **2016**, *58*, 135–167; b) M. Sawamura, H. Ito in *Copper-Catalyzed Asymmetric Synthesis* (Eds.: A. Alexakis, N. Krause, S. Woodward), Wiley-VCH, Weinheim, **2014**, pp. 157–177; c) E. Hartmann, D. J. Vyas, M. Oestreich, *Chem. Commun.* **2011**, *47*, 7917–7932.

[2] a) C. Walter, G. Auer, M. Oestreich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5775–5677; *Angew. Chem.* **2006**, *118*, 5803−5805; b) C. Walter, M. Oestreich, *Angew. Chem. Int. Ed.* **2008**, *47*, 3818–3820; *Angew. Chem.* **2008**, *120*, 3878−3820; c) C. Walter, R. Fröhlich, M. Oestreich, *Tetrahedron* **2009**, *65*, 5513–5520; d) E. Hartmann, M. Oestreich, *Angew. Chem. Int. Ed.* **2010**, *49*, 6195–6198; *Angew. Chem.* **2010**, *122*, 6331–6334; e) E. Hartmann, M. Oestreich, *Org. Lett.* **2012**, *14*, 2406–2409.

[3] a) K-s. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900; b) H. Y. Harb, K. D. Collins, J. V. Garcia Altur, S. Bowker, L. Campbell, D. J. Procter, *Org. Lett.* **2010**, *12*, 5446–5449; c) K.-s. Lee, H. Wu, F. Haeffner, A. H. Hoveyda, *Organometallics* **2012**, *31*, 7823–7826; d) V. Pace, J. P. Rae, H. Y. Harb, D. J. Procter, *Chem. Commun.* **2013**, *49*, 5150–5152; e) V. Pace, J. P. Rae, D. J. Procter, *Org. Lett.* **2014**, *16*, 476–479; see also: f) I. Ibrahem, S. Santoro, F. Himo, A. Córdova, *Adv. Synth. Catal.* **2011**, *353*, 245–252 (iminium-ion catalysis); g) T. Kitanosono, L. Zhu, C. Liu, P. Xu, S. Kobayashi, *J. Am. Chem. Soc.* **2015**, *137*, 15422–15425 (Cu^{II}–bipyridine complex).

[4] J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712–7715.

[5] a) L. B. Delvos, M. Oestreich in *Science of Synthesis Knowledge Update 2017/1* (Ed.: M. Oestreich), Thieme, Stuttgart, **2017**, pp. 65–176; b) M. Oestreich, E. Hartmann, M. Mewald, *Chem. Rev.* **2013**, *113*, 402–441; for the preparation of Si–B reagents, see: M. Suginome, T. Matsuda, Y.Ito, *Organometallics* **2000**, *19*, 4647–4649.

[6] For an authoritative perspective, see: D. Best, H. W. Lam, *J. Org. Chem.* **2014**, *79*, 831–845.

[7] A. Hensel, *Master Thesis*, Westfälische Wilhelms-Universität Münster (Germany), **2012**.

[8] M. Lautens, A. Roy, K. Fukuoka, K. Fagnou, B. Martín-Matute, *J. Am. Chem. Soc.* **2001**, *123*, 5358–5359.

[9] a) G. Pattison, G. Piraux, H. W. Lam, *J. Am. Chem. Soc.* **2010**, *132*, 14373–14375; b) I. D. Roy, A. R. Burns, G. Pattison, B. Michel, A. J. Parker, H. W. Lam, *Chem. Commun.* **2014**, *50*, 2865–2868.

[10] See also: R. Amengual, V. Michelet, J.-P. Genêt, *Tetrahedron Lett.* **2002**, *43*, 5905–5908.

[11] a) R. P. Jumde, F. Lanza, M. J. Veenstra, S. R. Harutyunyan, *Science* **2016**, *352*, 433–437; b) R. P. Jumde, F. Lanza, T. Pellegrini, S. R. Harutyunyan, *Nat. Commun.* **2017**, *8*, 2058.

[12] a) W. Xue, R. Shishido, M. Oestreich, *Angew. Chem. Int. Ed.* **2018**, *57*, 12141–12145; *Angew. Chem*. **2018**, *130*, 12318–12322; these silicon Grignard reagents have already been applied to allylic substitution and

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201905934

ring opening of aziridines, respectively: b) W. Xue, M. Oestreich, *Synthesis* **2019**, *51*, 233–239; c) H. Yi, M. Oestreich, *Chem. Eur. J.* **2019**, *25*, 6505–6507.

[13] Meng and co-workers recently reported a broadly applicable borylation using $B_2(pin)_2$ as the boron pronucleophile and a Cu^I–1,2-bis[(2*R*,5*R*)-2,5-diphenylphospholan-1-yl]ethane [(*R*,*R*)-Ph-BPE] complex as catalyst. Subsequent oxidation established a hydroxy group β to the heteroaryl group. L. Wen, Z. Yue, H. Zhang, Q. Chong, F. Meng, *Org. Lett.* **2017**, *19*, 6610–6613. Our approach with silicon as a placeholder for oxygen is related to this work (cf. Ref. [1c].)

[14] According to Harutyunyan, Lewis acid additives are thought to further activate the azaaryl group (see Ref. [11]).

[15] A. Weickgenannt, M. Oestreich, *Chem. Eur. J.* **2010**, *16*, 402–412 and cited references.

[16] The role of magnesium cations in related copper-catalyzed conjugate addition reactions was studied by Minnaard, Feringa, and co-workers, and their model has been adopted by Harutyunyan (Ref. [11a]). S. R. Harutyunyan, F. López, W. R. Browne, A. Correa, D. Peña, R. Badorrey, A. Meetsma, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.

[17] Aside from benzoxazole-containing **1**, all other alkenyl-substituted azaarenes **3**–**6** with the exception of **2** did not react (< 5% yield). Acceptor **2** activated by a benzothiazole furnished 29% yield but with low enantioinduction (e.r. 60:40).

[18] T. Robert, J. Velder, H. G. Schmalz, *Angew. Chem. Int. Ed*. **2008**, *47*, 7718–7721; *Angew. Chem*. **2008**, *120*, 7832–7835.

[19] CCDC 1913584 [(*S*)-**8d**] and CCDC 1913585 [(*S*)-**16a**] contain the supplementary crystallographic data for this paper. These data can be obained free of charge from The Cambridge Crystallographic Data Centre.

[20] R. Shintani, K. Okamoto, T. Hayashi, *Org. Lett.* **2005**, *7*, 4757–4759.

[21] L. Rupnicki, A. Saxena, H. W. Lam, *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201905934

WILEY-VCH

Suggestion for the Entry for the Table of Contents

COMMUNICATION

New kid on the block. An example of an enantioselective catalysis with silicon Grignard reagents is reported. With the assistance of $BF_3{\cdot}OEt_2$, a Cu^I–josiphos complex promotes the highly regioselective addition of silicon Grignard reagents to alkenyl-substituted heteroarenes (see scheme). The new method expands the scope of 'conjugate-addition'-type $C(sp^3)$–Si bond-forming reactions.

*W. Mao, W. Xue, E. Irran, M. Oestreich**

Page No. – Page No.

Copper-Catalyzed Regio- and Enantioselective Addition of Silicon Grignard Reagents to Alkenes Activated by Azaaryl Groups

WILEY-VCH

Accepted Manuscript

This article is protected by copyright. All rights reserved.