



Copper-catalyzed asymmetric silyl addition to alkenyl-substituted *N*-heteroarenes†

 Cite this: *Chem. Commun.*, 2020, 56, 1693

 Received 14th November 2019,
 Accepted 6th January 2020

DOI: 10.1039/c9cc08910a

rsc.li/chemcomm

Asymmetric conjugate addition of PhMe₂SiBPin to a wide range of *N*-heteroaryl alkenes proceeded in the presence of a copper catalyst coordinated with an easily accessible chiral phosphoramidite ligand to afford useful β-silyl *N*-heteroarenes in high yields (up to 96%) and excellent enantioselectivities (up to 97% ee).

N-Containing heteroarenes are very important structural units, which are commonly found in a wide variety of natural products and pharmaceutically active compounds. Although elaboration of the *N*-containing heteroarenes continues to be the main approach to access functionalized heterocyclic aromatic compounds, exploration of asymmetric conjugate addition of nucleophiles to alkenes activated by adjacent *N*-containing heteroarenes has gained prominence in the last decade (Scheme 1a).¹ Key contributions in the area include transition metal-catalyzed asymmetric arylation and hydrogenation of alkenyl azaarenes, reported by Lam and co-workers.² In addition, other groups presented elegant, highly enantioselective conjugate additions to *N*-heteroaryl alkenes using pyrazoles,^{3c} Grignard reagents,^{3d,e} B₂(pin)₂,^{3f} and thiols^{3h} as nucleophiles, respectively. However, contrary to common Michael acceptors, such as α,β-unsaturated carbonyl, nitro, nitrile and sulfonyl compounds, which have been widely studied in asymmetric conjugate addition,⁴ alkenyl azaarenes have received little attention.³ The scarcity of available asymmetric approaches is attributed to the low activation from the *N*-heteroaryl group and the generation of unfavorable intermediates through a transient dearomatization step.



Scheme 1 Catalytic asymmetric nucleophilic addition to alkenyl azaarenes.

Chiral silanes are versatile intermediates in organic synthesis.⁵ The silicon motif is widely used as a masked hydroxyl group,⁶ and the C–Si bond can also be readily transformed into C–C bonds.⁷ Accordingly, the vital objective in this area of research is to develop efficient and practical routes to chiral silanes. Among the available approaches to provide chiral organosilicon compounds, asymmetric silyl conjugate addition to electron-deficient alkenes is one of the most reliable ways.^{8–13} In 1988, Hayashi and Ito's group pioneered the development of enantioselective disilylation of enones using palladium catalysis.⁸ Subsequently, the reaction scope and catalytic systems were expanded by Oestreich,⁹ Hoveyda,¹⁰ Córdova,¹¹ Procter¹² and Kobayashi.¹³ Although significant progress has been achieved with regard to asymmetric silylation of a wide range of cyclic and acyclic α,β-unsaturated carbonyl systems, a few studies on silyl transfer to alkenes conjugated to weaker electron-withdrawing groups, and in particular alkenyl-substituted *N*-heterocycles, have been described. The topic still represents a challenge. Very recently, Oestreich reported the first Cu(I)-catalyzed asymmetric conjugate addition of silicon Grignard reagents to poorly reactive alkenyl heteroarenes with Lewis acid activation (Scheme 1b).¹⁴ Because of the high activity of the silicon Grignard reagents, the reactions must

^a Chemical Synthesis and Pollution Control, Key Laboratory of Sichuan Province, College of Chemistry and Chemical Engineering, China West Normal University, No. 1, Shida Road, Nanchong 637002, China. E-mail: chuwendanpo@126.com, quanzhongliu@cwnu.edu.cn

^b College of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong 252059, China

^c College of Chemistry and Materials Engineering, Guiyang University, Guiyang 550005, China

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data, and copies of NMR and HPLC spectra, including X-ray crystal structures of **2b**. CCDC 1955733. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc08910a

be carried out at very low temperature.^{14,15} Although this work marks a significant breakthrough, the enantioselective reaction is limited to benzoxazole-derived substrates and the ee values are moderate in most cases. Thus, further development of catalytic highly enantioselective silyl addition to alkenes activated by other azaaryl groups with an easily obtained catalyst is urgently demanded. Herein, we describe an operationally simple, highly chemo- and enantioselective silylation protocol of a wide range of *N*-heteroaryl-substituted alkenes using PhMe₂SiBpin^{16,17} as the nucleophile and chiral phosphoramidite/Cu(I) as the catalyst (Scheme 1c). PhMe₂SiBpin is readily available, bench-stable, and easy-to-handle. Since Suginome and Ito first introduced it in the Pd-catalyzed silaboration of alkynes,¹⁶ the development of PhMe₂SiBpin chemistry has been the subject of intense research in recent years.¹⁷

Initially, we selected 2-alkenylquinoline **1a** and PhMe₂SiBpin as model substrates to study the silylation reaction (Table 1).¹⁸ Racemic product **2a** was produced in low yields in the presence of Cu(MeCN)₄PF₆, the bidentate chiral phosphine ligand (**L1** or **L2**) and NaOtBu in THF at room temperature (entries 1 and 2). To our delight, the chiral phosphoramidite ligand **L3** was found to be effective in asymmetric induction, presenting 57% enantioselectivity and 19% yield (entry 3). Encouraged by this result, the substituents on the nitrogen atom were examined.

Table 1 Optimization of the reaction conditions^a



Entry	Ligand	Solvent	Yield ^b (%)	ee ^c (%)
1 ^d	L1	THF	44	0
2 ^d	L2	THF	39	5
3	L3	THF	19	57
4	L4	THF	48	83
5	L5	THF	32	85
6	L6	THF	22	85
7	L7	THF	64	89
8	L8	THF	49	91
9	L9	THF	86	93
10	L9	Et ₂ O	69	93
11	L9	Hexane	66	90
12	L9	Toluene	58	93
13	L9	DMF	48	89

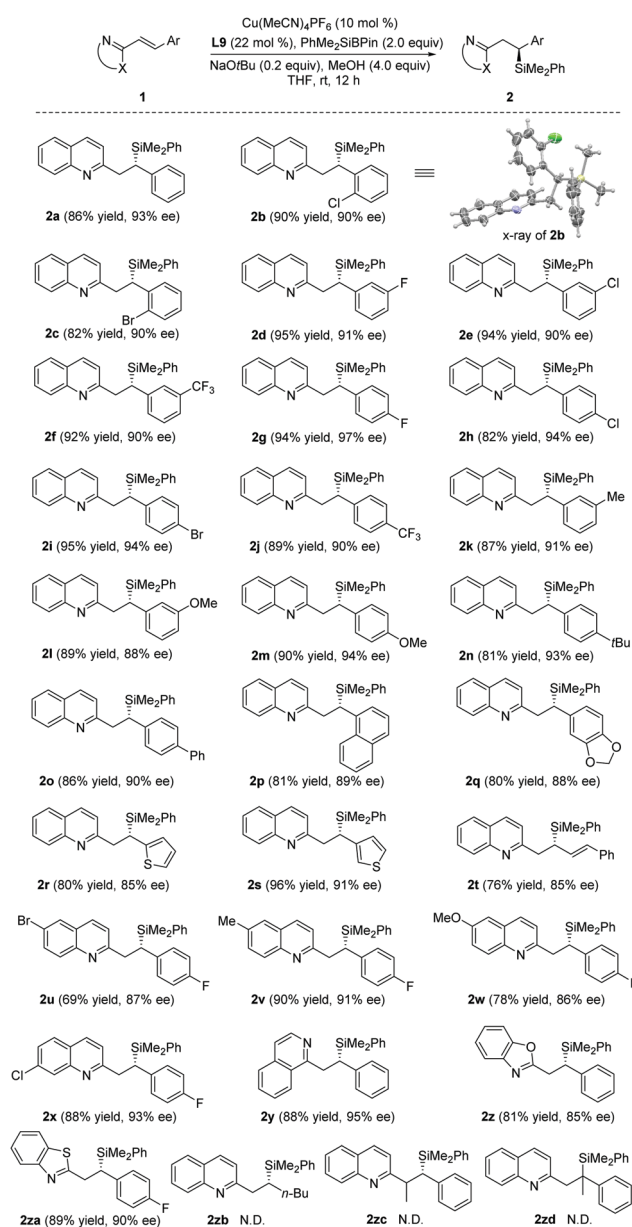
^a Reaction conditions: **1a** (0.1 mmol), PhMe₂SiBpin (0.2 mmol), NaOtBu (0.2 equiv.), Cu(MeCN)₄PF₆ (10 mol%), ligand (22 mol%), MeOH (4.0 equiv.), and the solvent (0.05 M). ^b Isolated yields. ^c Determined by chiral HPLC. ^d 0.11 equiv. of ligand was employed.



The morpholine moiety (**L9**) was superior to others, such as other acyclic amines (**L4–L6**), pyrrolidine (**L7**) and indoline (**L8**), affording **2a** in 86% yield with 93% ee (entries 4–9). In addition, we evaluated the effect of the solvent on the reaction. It was found that the reactions in Et₂O, hexane, toluene and DMF all provided the product **2a** with similarly high ee, but the yields varied greatly and the reaction in THF gave the highest yield (entries 9–13).

With the optimal conditions in hand, the substrate scope was then examined (Table 2). A wide range of alkenyl quinolines bearing electron-neutral, -deficient or -rich β-aromatic substituents

Table 2 Substrate scope^a



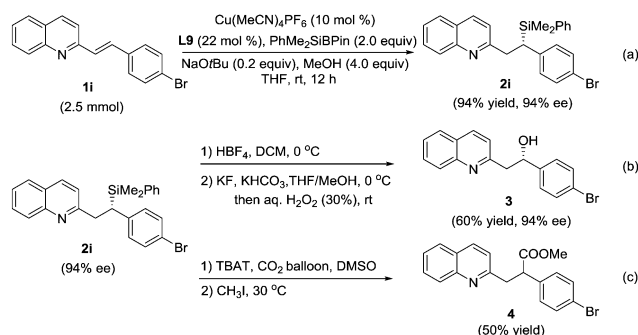
^a Reaction conditions: **1** (0.1 mmol), PhMe₂SiBpin (0.2 mmol), NaOtBu (0.2 equiv.), Cu(MeCN)₄PF₆ (10 mol%), **L9** (22 mol%), MeOH (4.0 equiv.), and THF (0.05 M). Yields of the isolated product **2**. ee determined by HPLC analysis. N.D. = not detected.

reacted efficiently with $\text{PhMe}_2\text{SiBpin}$ to afford the corresponding products **2a–q** in 80–95% yields and 88–97% ee. The absolute configuration of **2b** was unambiguously established by X-ray crystallographic analysis.¹⁹ Substrates with 2- and 3-thienyl groups were also amenable to this protocol to produce the corresponding products **2r–s** with high yields and enantioselectivities. Interestingly, when the silylation of the conjugate divinyl quinoline **1t** was investigated, there was only 1,4-addition and the corresponding adduct **2t** was isolated in 76% yield with 85% ee. The substituents (such as Br, Me, OMe or Cl) on the quinoline ring of **1** did not compromise the enantioselectivities of **2u–x**. Other heteroaromatic substrates, such as isoquinoline (**1y**), benzoxazole (**1z**) and benzothiazole (**1za**), were also suitable for the reaction and the corresponding silylated products **2y–2za** were obtained with excellent results (81–89% yields, 85–95% ee). Finally, the reactions between $\text{PhMe}_2\text{SiBpin}$ and alkyl-substituted **1zb**, α,β -disubstituted **1zc** or β,β -disubstituted **1zd** were also attempted, but they were unsuccessful.

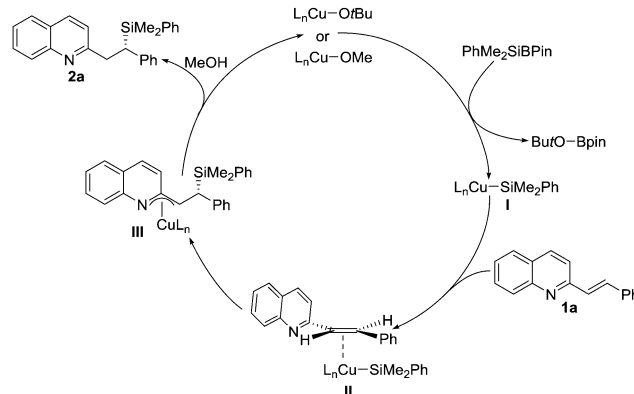
The reaction on a gram scale (2.5 mmol of **1i**) was also performed to obtain the 1,4-adduct **2i** with 94% ee and 94% yield (Scheme 2a). A key synthetic transformation of the silicon motif is that it can be used as a masked hydroxyl group.⁶ Compound **2i** could be transformed into alcohol **3** through Tamao–Fleming oxidation²⁰ without the erosion of stereoselectivity (Scheme 2b). Furthermore, the treatment of **2i** in the presence of TBAT and CO_2 could provide the desired ester **4** in 50% yield.^{17k} Unfortunately, no transformation in chirality was observed in this reaction (Scheme 2c).

A possible mechanism for the reactions is illustrated in Scheme 3. L_nCu -alkoxides react with $\text{PhMe}_2\text{SiBpin}$ to produce the derived $\text{L}_n\text{Cu-SiMe}_2\text{Ph}$ **I**, which can undergo an asymmetric conjugate addition reaction with alkenyl-substituted quinoline **1a** to obtain intermediate **III** through transition state **II**. The resulting aza- π -allylcopper intermediate **III** reacts with methanol to afford the desired product **2a** and regenerate the active copper catalysts for the next catalytic cycle.

In conclusion, we have developed an operationally simple and highly enantioselective Cu(I)-catalyzed conjugate addition of $\text{PhMe}_2\text{SiBpin}$ to a wide range of alkenyl *N*-heteroarenes with easily accessible chiral phosphoramidite as the ligand. A series of useful β -silyl *N*-heteroarenes were achieved in high yields and ees. Moreover, the reaction can be effectively performed at room temperature on a gram scale.



Scheme 2 Scale-up experiment and synthetic applications of compound **2i**.



Scheme 3 Proposed catalytic cycle.

We gratefully acknowledge the Department of Science and Technology of Sichuan Province (2019YJ0339) and the NSFC (21572183, 21772158, and 21801208) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- Reviews: (a) D. Best and H. W. Lam, *J. Org. Chem.*, 2014, **79**, 831; (b) D. A. Klumpp, *Synlett*, 2012, 1590.
- (a) L. Rupnick, A. Saxena and H. W. Lam, *J. Am. Chem. Soc.*, 2009, **131**, 10386; (b) G. Pattison, G. Piroux and H. W. Lam, *J. Am. Chem. Soc.*, 2010, **132**, 14373; (c) A. Saxena and H. W. Lam, *Chem. Sci.*, 2011, **2**, 2326; (d) A. Saxena, B. Choi and H. W. Lam, *J. Am. Chem. Soc.*, 2012, **134**, 8428; (e) I. D. Roy, A. R. Burns, G. Pattison, B. Michel, A. J. Parker and H. W. Lam, *Chem. Commun.*, 2014, **50**, 2865; (f) B. Choi, A. Saxena, J. J. Smith, G. H. Churchill and H. W. Lam, *Synlett*, 2015, 350; (g) J. J. Smith, D. Best and H. W. Lam, *Chem. Commun.*, 2016, **52**, 3770.
- (a) A. A. Friedman, J. Panteleev, J. Tsoung, V. Huynh and M. Lautens, *Angew. Chem., Int. Ed.*, 2013, **52**, 9755; (b) S. Wang, X. Li, H. Liu, L. Xu, J. Zhuang, J. Li, H. Li and W. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 2303; (c) Y.-Y. Wang, K. Kanomata, T. Korenaga and M. Terada, *Angew. Chem., Int. Ed.*, 2016, **55**, 927; (d) R. P. Jumde, F. Lanza, M. J. Veenstra and S. R. Harutyunyan, *Science*, 2016, **352**, 433; (e) R. P. Jumde, F. Lanza, T. Pellegrini and S. R. Harutyunyan, *Nat. Commun.*, 2017, **8**, 2058; (f) L. Wen, Z. Yue, H. Zhang, Q. Chong and F. Meng, *Org. Lett.*, 2017, **19**, 6610; (g) Y. Yin, Y. Dai, H. Jia, J. Li, L. Bu, B. Qiao, X. Zhao and Z. Jiang, *J. Am. Chem. Soc.*, 2018, **140**, 6083; (h) M. Formica, G. Sorin, A. J. M. Farley, J. Díaz, R. S. Paton and D. J. Dixon, *Chem. Sci.*, 2018, **9**, 6969.
- For selected recent reviews, see: (a) G. J. Reyes-Rodríguez, N. M. Rezayee, A. Vidal-Albalat and K. A. Jørgensen, *Chem. Rev.*, 2019, **119**, 4221; (b) L. Wu, J. Shen, G. Yang and W. Zhang, *Tetrahedron Lett.*, 2018, **59**, 4055; (c) K. Zheng, X. Liu and X. Feng, *Chem. Rev.*, 2018, **118**, 7586; (d) T. Jia, P. Cao and J. Liao, *Chem. Sci.*, 2018, **9**, 546; (e) B. Mao, M. Fañanás-Mastral and B. L. Feringa, *Chem. Rev.*, 2017, **117**, 10502; (f) C. Hui, F. Pu and J. Xu, *Chem. – Eur. J.*, 2017, **23**, 4023; (g) M. Hayashi and R. Matsubara, *Tetrahedron Lett.*, 2017, **58**, 1793; (h) T. N. Nguyen and J. A. May, *Tetrahedron Lett.*, 2017, **58**, 1535; (i) A. Mondal, S. Bhowmick, A. Ghosh, T. Chanda and K. C. Bhowmick, *Tetrahedron: Asymmetry*, 2017, **28**, 849; (j) D. A. Alonso, A. Baeza, R. Chinchilla, C. Gómez, G. Guillena, I. M. Pastor and D. J. Ramón, *Molecules*, 2017, **22**, 895; (k) M. M. Heravi, M. Dehghani and V. Zadsirjan, *Tetrahedron: Asymmetry*, 2016, **27**, 513.
- Reviews: (a) J. R. Wilkinson, C. E. Nuyen, T. S. Carpenter, S. R. Harruff and R. Van Hoveln, *ACS Catal.*, 2019, **9**, 8961; (b) S. Bähr, W. Xue and M. Oestreich, *ACS Catal.*, 2019, **9**, 16; (c) M. Sugimoto and Y. Ito, *Chem. Rev.*, 2000, **100**, 3221.

- 6 (a) D. J. Ager and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 1978, 177; (b) K. Tamao, N. Ishida, T. Tanaka and M. Kumada, *Organometallics*, 1983, 2, 1694; (c) I. Fleming, R. Henning and H. Plaut, *J. Chem. Soc., Chem. Commun.*, 1984, 29; (d) K. Tamao, T. Tanaka, T. Nakajima, R. Sumiya, H. Arai and Y. Ito, *Tetrahedron Lett.*, 1986, 27, 3377; (e) I. Fleming and P. E. J. Sanderson, *Tetrahedron Lett.*, 1987, 28, 4229; For selected reviews, see: (f) I. Fleming, A. Barbero and D. Walter, *Chem. Rev.*, 1997, 97, 2063; (g) I. Fleming, in *Science of Synthesis*, ed. I. Fleming, Thieme, Stuttgart, 2002, vol. 4, pp. 927–946.
- 7 (a) L.-W. Xu, L. Li, G.-Q. Lai and J.-X. Jiang, *Chem. Soc. Rev.*, 2011, 40, 1777; (b) T. Komiyama, Y. Minami and T. Hiyama, *ACS Catal.*, 2017, 7, 631.
- 8 T. Hayashi, Y. Matsumoto and Y. Ito, *J. Am. Chem. Soc.*, 1988, 110, 5579.
- 9 (a) C. Walter, G. Auer and M. Oestreich, *Angew. Chem., Int. Ed.*, 2006, 45, 5675; (b) C. Walter and M. Oestreich, *Angew. Chem., Int. Ed.*, 2008, 47, 3818; (c) E. Hartmann and M. Oestreich, *Angew. Chem., Int. Ed.*, 2010, 49, 6195; (d) E. Hartmann and M. Oestreich, *Org. Lett.*, 2012, 14, 2406.
- 10 (a) K.-s. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, 132, 2898; (b) J. M. O'Brien and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, 133, 7712; (c) K.-s. Lee, H. Wu, F. Haefner and A. H. Hoveyda, *Organometallics*, 2012, 31, 7823.
- 11 I. Ibrahim, S. Santoro, F. Himo and A. Córdova, *Adv. Synth. Catal.*, 2011, 353, 245.
- 12 (a) V. Pace, J. P. Rae, H. Y. Harb and D. J. Procter, *Chem. Commun.*, 2013, 49, 5150; (b) V. Pace, J. P. Rae and D. J. Procter, *Org. Lett.*, 2014, 16, 476.
- 13 T. Kitanosono, L. Zhu, C. Liu, P. Xu and S. Kobayashi, *J. Am. Chem. Soc.*, 2015, 137, 15422.
- 14 W. Mao, W. Xue, E. Irran and M. Oestreich, *Angew. Chem., Int. Ed.*, 2019, 58, 10723.
- 15 (a) W. Xue, R. Shishido and M. Oestreich, *Angew. Chem., Int. Ed.*, 2018, 57, 12141; (b) W. Xue and M. Oestreich, *Synthesis*, 2019, 233; (c) H. Yi and M. Oestreich, *Chem. – Eur. J.*, 2019, 25, 6505.
- 16 M. Suginome, H. Nakamura and Y. Ito, *Chem. Commun.*, 1996, 2777.
- 17 For reviews on the utility of silylborane reagents in chemical synthesis, see: (a) T. Ohmura and M. Suginome, *Bull. Chem. Soc. Jpn.*, 2009, 82, 29; (b) E. Hartmann and M. Oestreich, *Chim. Oggi*, 2011, 29, 34; (c) E. Hartmann, D. J. Vyas and M. Oestreich, *Chem. Commun.*, 2011, 47, 7917; (d) M. Oestreich, E. Hartmann and M. Mewald, *Chem. Rev.*, 2013, 113, 402, and recent asymmetric examples see: (e) Z.-L. Liu, C. Yang, Q.-Y. Xue, M. Zhao, C.-C. Shan, Y.-H. Xu and T. Loh, *Angew. Chem., Int. Ed.*, 2019, 58, 16538; (f) C.-Y. He, L.-B. Xie, R. Ding, P. Tian and G.-Q. Lin, *Tetrahedron*, 2019, 75, 1682; (g) L. Zhang and M. Oestreich, *Chem. – Eur. J.*, 2019, 25, 14304; (h) K. Yabushita, A. Yuasa, K. Nagao and H. Ohmiya, *J. Am. Chem. Soc.*, 2019, 141, 113; (i) Y. Shi, Q. Gao and S. Xu, *J. Org. Chem.*, 2018, 83, 14758; (j) B.-C. Da, Q.-J. Liang, Y.-C. Luo, T. Ahmad, Y.-H. Xu and T.-P. Loh, *ACS Catal.*, 2018, 8, 6239; (k) F.-F. Meng, J.-H. Xie, Y.-H. Xu and T.-P. Loh, *ACS Catal.*, 2018, 8, 5306.
- 18 For screening of bases, additives and copper salts, see the ESI†.
- 19 CCDC 1955733 (2b)† contains the supplementary crystallographic data for this paper.
- 20 R. Shintani, K. Okamoto and T. Hayashi, *Org. Lett.*, 2005, 7, 4757.