ChemComm

Copper-catalyzed silylation of *p*-quinone methides: new entry to dibenzylic silanes†

Aurora López, Alejandro Parra, Carlos Jarava-Barrera and Mariola Tortosa*

An efficient and general copper(I)-catalyzed silylation of *p*-quinone-methides is described. Non-symmetric dibenzylic silanes are obtained in high yields under mild reaction conditions. These compounds can be used as bench-stable benzylic carbanion precursors.
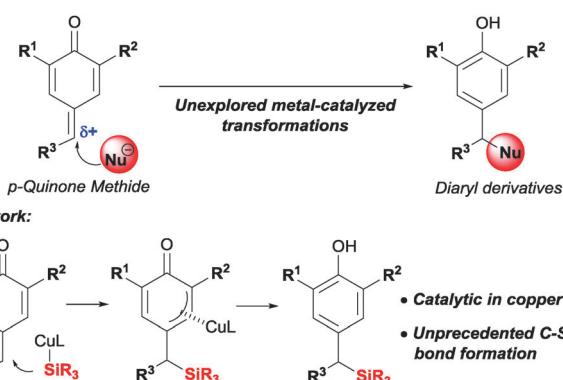
para-Quinone methides are reactive intermediates formed by a cyclohexadiene moiety in *para*-conjugation with a carbonyl group and an *exo*-methylene component. They are neutral entities with a zwitterionic resonance structure that enhances the electrophilic character at the δ-position.[1] Carbanions, aromatic rings, alcohols and amines are typical nucleophiles that quickly react with *p*-quinone methides to afford a variety of diaryl derivatives (Scheme 1).[2] The use of transition metals could allow the formation of C–C and C–X bonds complementary to those formed by direct addition of a typical nucleophile. Surprisingly, the use of metal-catalyzed transformations to functionalize the exocyclic double bond of *p*-quinone methides remains largely unexplored.[3]

We became interested in probing this approach using a silyl copper(I) complex as a formal silicon nucleophile (Scheme 1). To the best of our knowledge, the addition of nucleophilic silicon species to *ortho*- or *para*-quinone methides has not been studied to date. Silicon-containing molecules are valuable synthetic intermediates which can be converted into useful compounds through a number of transformations.[4] Recently, copper-catalyzed silylation reactions have emerged as a powerful tool for C–Si bond formation.[5] We envisioned that insertion of the exocyclic double bond into the Cu–Si bond followed by aromatization would afford non-symmetric benzylic silanes.

The most common way to synthesize benzylic silanes involves the reaction between an *in situ* generated benzylic carbanion and a silyl chloride.[6] Our method would offer a milder alternative to this classic approach, avoiding the use of stoichiometric amounts of

Departamento de Química Orgánica, Universidad Autónoma de Madrid
Cantoblanco, 28049 Madrid, Spain. E-mail: mariola.tortosa@uam.es

† Electronic supplementary information (ESI) available: Experimental details, characterization and crystallographic data. CCDC 1414585. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc06653k

Scheme 1 *p*-Quinone methides as diaryl derivatives precursors.

strong bases. Herein, we describe a copper(I)-catalyzed protocol for the silylation–aromatization of *p*-quinone-methides. The reactions proceed in high yields using only 10% of an inexpensive copper(I) salt and a commercially available silaborane reagent.[7]
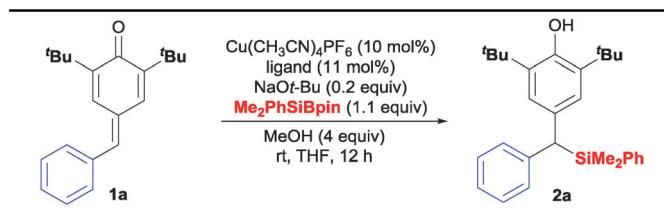
We started our study with *p*-quinone methide **1a**, containing removable *t*-Bu groups at the α-positions (Table 1).[8] A series of ligands were screened (Table 1, entries 1–6) using Cu(CH$_3$CN)$_4$PF$_6$ (10 mol%), Me$_2$PhSiBpin (1.1 equiv.), NaO*t*-Bu (0.2 equiv.) and MeOH (4 equiv.). We found that NHC ligands (entries 5 and 6) were superior to monodentate or bidentate phosphines (entries 1–4). SIMes gave the best results, affording dibenzylic silane **2a** with 86% isolated yield (entry 6, ≥98% conversion). The use of other bases (entries 7–9) or different copper salts (entries 10 and 11) gave poorer results. Lowering the catalyst loading to 5 mol% also resulted in a significantly lowered yield (entry 12). In the absence of MeOH (entry 13) or with only two equivalents (entry 14) compound **2a** was obtained in 46% and 57% yield respectively. Finally, to check the role of the NHC–Cu(I) catalyst we carried out the reaction in the absence of copper salt and ligand (entry 15). Under those conditions, a very complex mixture was observed in the ¹H NMR spectrum of the crude product. From this mixture, we could identify the product of 1,6-addition of methoxide to **1a** as the main compound, unreacted **1a**, and a small amount of **2a**.

Table 1 Optimization of the reaction conditions

Entry[a]	Copper salt	Base	Ligand	2a (%)
1	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	Ph$_3$P	64[b]
2	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	JohnPhos	64[b]
3	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	Xantphos	50[b]
4	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	(±)-BINAP	45[b]
5	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	IMes	87[b]
6	**$Cu(CH_3CN)_4PF_6$**	**NaOt-Bu**	**SIMes**	**≥98[b] (86)[c]**
7	$Cu(CH_3CN)_4PF_6$	KOt-Bu	SIMes	60[c]
8	$Cu(CH_3CN)_4PF_6$	LiOt-Bu	SIMes	68[c]
9	$Cu(CH_3CN)_4PF_6$	CsF	SIMes	61[c]
10	CuCl	NaOt-Bu	SIMes	55[c]
11	Cu$_2$O	NaOt-Bu	SIMes	20[c]
12[d]	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	SIMes	35[c]
13[e]	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	SIMes	46[c]
14[f]	$Cu(CH_3CN)_4PF_6$	NaOt-Bu	SIMes	57[c]
15[g]	—	NaOt-Bu		—
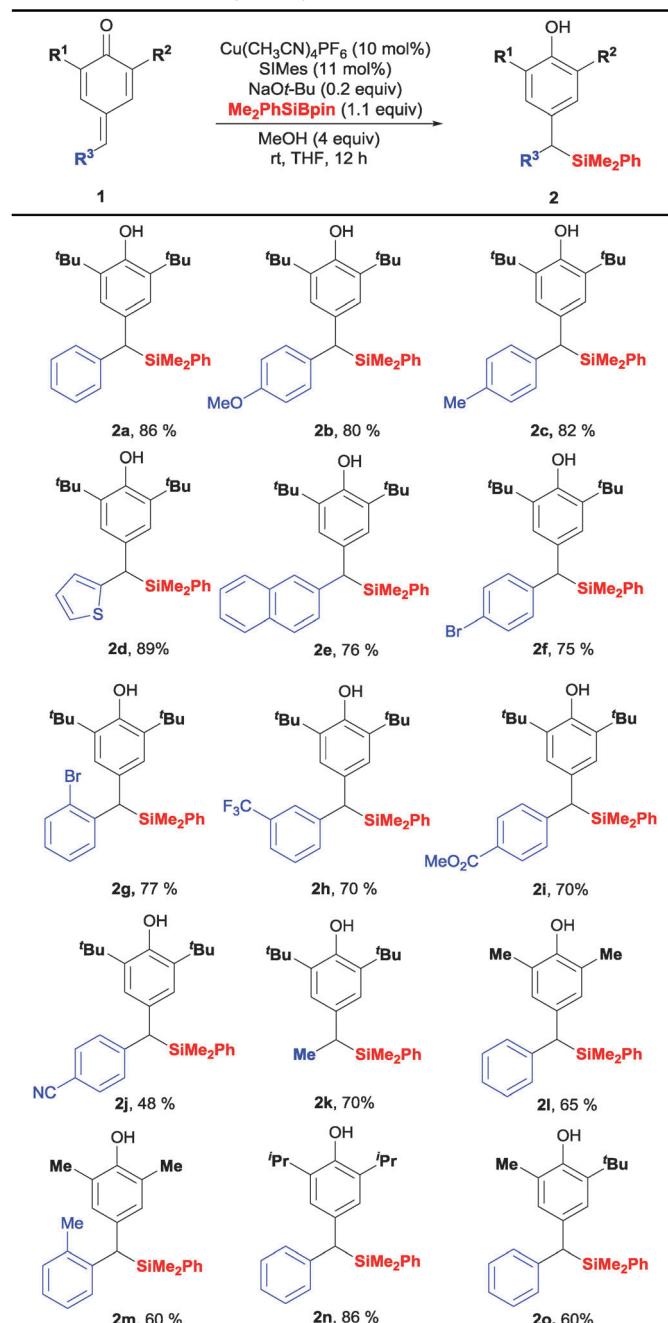
[a] Reaction conditions: **1a** (0.2 mmol), Me$_2$PhSiBpin (0.22 mmol), base (20 mol%), Cu(CH$_3$CN)$_4$PF$_6$ (10 mol%), ligand (11 mol%), MeOH (0.8 mmol), THF (0.1 M). [b] Conversion determined by ^{1}H NMR analysis of the crude mixture. [c] Yield of isolated **2a**. [d] Reaction conditions: **1a** (0.2 mmol), Me$_2$PhSiBpin (0.22 mmol), NaOt-Bu (20 mol%), Cu(CH$_3$CN)$_4$PF$_6$ (5 mol%), ligand (11 mol%), MeOH (0.8 mmol), THF (0.1 M). [e] The reaction was carried out in the absence of MeOH. [f] 0.4 mmol of MeOH were used. [g] Reaction conditions: **1a** (0.2 mmol), Me$_2$PhSiBpin (0.22 mmol), NaOt-Bu (20 mol%), MeOH (0.8 mmol), THF (0.1 M).

The formation of **2a** under these conditions could be explained by alkoxide activation of the silaborane in the absence of the copper catalyst.[9]

With these optimal conditions in hand, we proceeded to study the scope of the silylation–aromatization process (Table 2). We first modified the stereoelectronic properties of the exomethylene substituent (R^3). Dibenzylic silanes with electron donating groups (compounds **2b**–**2c**), heterocycles (compound **2d**), and a larger naphthyl group (compound **2e**) were prepared in high yields. The conditions also worked for p-quinone methides with electron withdrawing groups in *para* (compounds **2f, 2i, 2j**), *ortho* (compound **2g**) and *meta* (compound **2h**) positions. It should be pointed out that our method allows for the synthesis of compounds with halogen substituents (**2f, 2g**) and an ester group (**2i**), which would be difficult to obtain by the reaction of a dibenzylic carbanion and a silyl chloride. Interestingly, monobenzylic silane **2k**, in which R^3 is an alkyl group, was also obtained using the optimized conditions.

Additionally, we modified the R^1 and R^2 substituents. Compounds **2l** and **2m**, with two methyl groups, and compound **2n**, with two isopropyl groups, were obtained in good yields. It is also possible to introduce two different alkyl groups in the α-position (compound **2o**) starting from a non-symmetrical p-quinone methide. Finally, the structure of compound **2g** was confirmed by single crystal X-ray crystallography (Fig. 1).
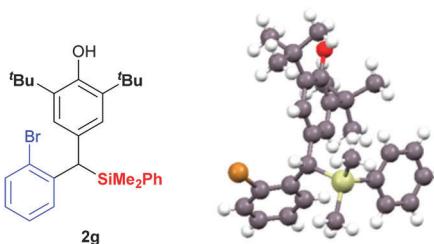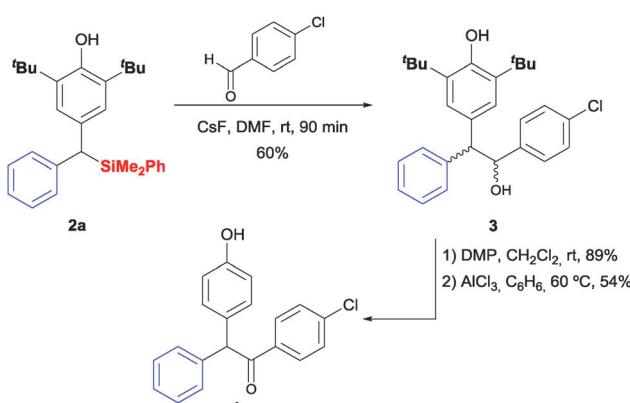
One interesting feature of benzylic silanes is their ability to be used as bench-stable benzylic anion equivalents under mild reaction conditions.[10] However, most known examples of these

**Table 2** Copper(ı)-catalyzed silylation of p-quinone methides[a,b]

[a] Reaction conditions: **1a** (0.2 mmol), Me$_2$PhSiBpin (0.22 mmol), NaOt-Bu (20 mol%), Cu(CH$_3$CN)$_4$PF$_6$ (10 mol%), SIMes (11 mol%), MeOH (0.8 mmol), THF (0.1 M). [b] Yield of isolated **2**.

transformations have been performed with monobenzylic trimethyl-silane derivatives. Therefore, our method provided an opportunity to check if dibenzylic dimethylphenyl silanes such as **2** could be also used as carbanion precursors. To the best of our knowledge, the generation of dibenzylic carbanions from silanes has not previously been reported. Gratifyingly, treatment of silane **2a** with cesium fluoride in DMF, followed by addition of p-chloro benzaldehyde, provided the desired compound **3** as a 1:1 mixture of diastereomers (Scheme 2). Oxidation followed by removal of the t-butyl groups[8] using AlCl$_3$ afforded α,α-diaryl ketone **4** in a good overall yield.

Fig. 1 X-ray structure of compound **2g**.

Scheme 2 Functionalization of the C–Si bond and de-*tert*-butylation.

A possible mechanism for the silylation–aromatization reaction of *p*-quinone methides is shown in Scheme 3. First, a silyl-Cu(ɪ)–NHC complex **B** is formed by reaction of a copper alkoxide **A** and the silaborane reagent. Insertion of the exocyclic double bond of the

Scheme 3 Plausible mechanism for the silylation–aromatization.
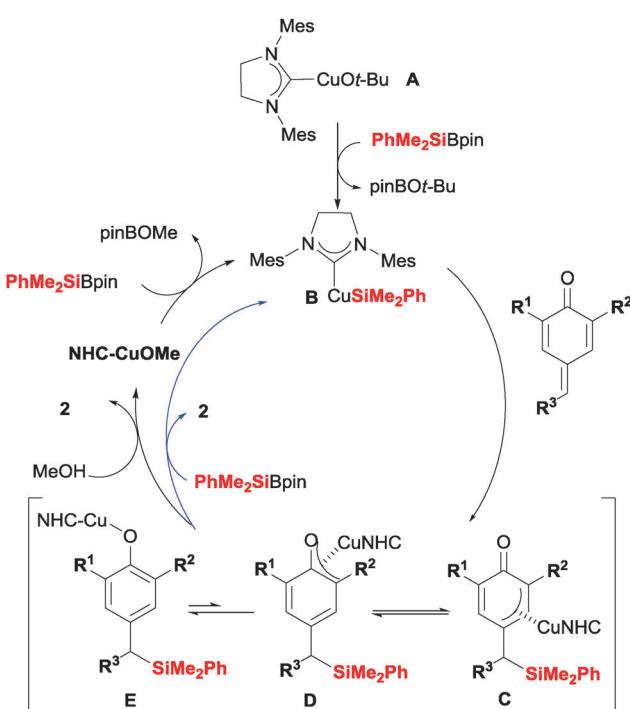
p-quinone methide into the Cu–Si bond affords a π-allyl-copper intermediate (**C**) that could isomerize to copper phenoxide **E**. At this point two pathways are possible. Protonolysis in the presence of MeOH would provide silane **2** with release of NHC–CuOMe to restart the catalytic cycle. On the other hand, copper phenoxide **E** could react directly with the silaborane to provide **2** and silyl-copper complex **B**.

In conclusion, we have found that copper(ɪ) salts can catalyze the silylation–aromatization process of *p*-quinone methides. This study represents the first silicon addition to a quinone methide and provides new insight for the development of novel metal-catalyzed transformations. Mono- and dibenzylic silanes can be prepared in high yields under mild reaction conditions. We have also demonstrated that dibenzylic silanes can be used as stable dibenzylic carbanion equivalents. The development of asymmetric versions of this and related transformations is underway.

Notes and references

1 For reviews and highlights of *p*-quinone methides: (*a*) H.-U. Wagner and R. Gompper, in *The Chemistry of the Quinonoid Compounds*, ed. S. Patai, Wiley, New York, 1974, ch. 18, vol. 2, p. 1145; (*b*) M. M. Toteva and J. P. Richard, *Adv. Phys. Org. Chem.*, 2011, **45**, 39; (*c*) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524; (*d*) L. Caruana, M. Fochi and L. Bernardi, *Molecules*, 2015, **20**, 11733.
2 For selected examples: (*a*) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, 1960, **25**, 9; (*b*) D. J. Hart, P. A. Cain and D. A. Evans, *J. Am. Chem. Soc.*, 1978, **100**, 1548; (*c*) S. R. Angle and K. D. Turnbull, *J. Am. Chem. Soc.*, 1989, **111**, 1136; (*d*) R. Lucius, R. Loos and H. Mayr, *Angew. Chem., Int. Ed.*, 2002, **41**, 92; (*e*) T. Bug and H. Mayr, *J. Am. Chem. Soc.*, 2003, **125**, 12980; (*f*) S. T. A. Berger, A. R. Ofial and H. Mayr, *J. Am. Chem. Soc.*, 2007, **129**, 9753; (*g*) D. Richter, N. Hampel, T. Singer, A. R. Ofial and H. Mayr, *Eur. J. Org. Chem.*, 2009, 3203; (*h*) R. Appel, R. Loos and H. Mayr, *J. Am. Chem. Soc.*, 2009, **131**, 704; (*i*) T. A. Nigst, A. Antipova and H. Mayr, *J. Org. Chem.*, 2012, **77**, 8142; (*j*) D. S. Allgäuer, P. Mayer and H. Mayr, *J. Am. Chem. Soc.*, 2013, **135**, 15216; (*k*) W.-D. Chu, L.-F. Zhang, X. Bao, X.-H. Zhao, C. Zeng, J.-Y. Du, G.- B. Zhang, F.-X. Wang, X.-Y. Ma and C.-A. Fan, *Angew. Chem., Int. Ed.*, 2013, **52**, 9229; (*l*) L. Caruana, F. Kniep, T. K. Johasen, P. H. Poulsen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2014, **136**, 15929; (*m*) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin and J. Sun, *J. Am. Chem. Soc.*, 2015, **137**, 383.
3 For the stabilization of *p*-quinone methides by complexation with transition-metals, see: (*a*) A. Vigalok, L. J. W. Shimon and D. Milstein, *J. Am. Chem. Soc.*, 1998, **120**, 477; (*b*) O. Rabin, A. Vigalok and D. Milstein, *Chem. – Eur. J.*, 2000, **6**, 454.
4 (*a*) E. W. Colvin, *Silicon Reagents in Organic Synthesis*, Academic Press, London, 1988; (*b*) *Chemistry of Organosilicon Compounds*, ed. Z. Rappoport and Y. Apeloig, Wiley-VCH, New York, vol. 3, 2001; (*c*) W. Bains and R. Tacke, *Curr. Opin. Drug Discovery Dev.*, 2003, **6**, 526; (*d*) G. A. Showwell and J. S. Mills, *Drug Discovery Today*, 2003, **8**, 551; (*e*) M. Mortensen, R. Husmann, E. Veri and C. Bolm, *Chem. Soc. Rev.*, 2009, **38**, 1002.
5 For recent copper-catalyzed reactions using a silaborane reagent: (*a*) K.-S. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 2898; (*b*) D. J. Vyas and M. Oestreich, *Angew. Chem., Int. Ed.*, 2010, **49**, 8513; (*c*) A. Welle, J. Petrignet, B. Tinant, J. Wouters and O. Riant, *Chem. – Eur. J.*, 2010, **16**, 10980; (*d*) C. Kleeberg, E. Feldmann, E. Hartmann, D. J. Vyas and M. Oestreich, *Chem. – Eur. J.*, 2011, **17**, 13538; (*e*) D. J. Vyas, C. K. Hazra and M. Oestreich, *Org. Lett.*, 2011, **13**, 4462; (*f*) D. J. Vyas, R. Fröhlich and M. Oestreich, *Org. Lett.*, 2011, **13**, 2094; (*g*) C. Kleeberg, M. S. Cheung, Z. Lin and T. B. Marder, *J. Am. Chem. Soc.*, 2011, **133**, 19060; (*h*) K.-S. Lee, H. Wu, F. Haeffner and A. H. Hoveyda, *Organometallics*, 2012, **31**, 7823; (*i*) T. Fujihara, Y. Tani, K. Semba, J. Terao and Y. Tsuji, *Angew. Chem., Int. Ed.*, 2012, **51**, 11487; (*j*) F. Meng, H. Jang

and A. H. Hoveyda, *Chem. – Eur. J.*, 2013, **19**, 3204; (*k*) C. K. Hazra, E. Irran and M. Oestreich, *Eur. J. Org. Chem.*, 2013, 4903; (*l*) L. B. Delvos, D. J. Vyas and M. Oestreich, *Angew. Chem., Int. Ed.*, 2013, **52**, 4650; (*m*) V. Pace, J. P. Rae, H. Y. Harb and D. J. Procter, *Chem. Commun.*, 2013, **49**, 5150; (*n*) V. Pace, J. P. Rae and D. J. Procter, *Org. Lett.*, 2013, **15**, 476; (*o*) V. Cirriez, C. Rasson, T. Hermant, J. Petrignet, J. Díaz Álvarez, K. Robeyns and O. Riant, *Angew. Chem., Int. Ed.*, 2013, **52**, 1785; (*p*) S. Vercruysse, L. Cornelissen, F. Nahra, L. Collard and O. Riant, *Chem. – Eur. J.*, 2014, **20**, 1834; (*q*) Y.-H. Xu, L.-H. Wu, J. Wang and T.-P. Loh, *Chem. Commun.*, 2014, **50**, 7195; (*r*) A. Hensel, K. Nagura, L. B. Delvos and M. Oestreich, *Angew. Chem., Int. Ed.*, 2014, **53**, 4964; (*s*) J. Rae, Y. C. Hu and D. J. Procter, *Chem. – Eur. J.*, 2014, **20**, 13143; (*t*) A. García-Rubia, J. A. Romero-Revilla, P. Mauleón, R. Gómez-Arrayás and J. C. Carretero, *J. Am. Chem. Soc.*, 2015, **137**, 6857.

6 (*a*) A. R. Katritzky and M. Qi, *J. Org. Chem.*, 1997, **62**, 4116; (*b*) T. R. van den Ancker, C. L. Raston, B. W. Skelton and A. H. White, *Organometallics*, 2000, **19**, 4437; (*c*) V. Georgakilas, G. P. Perdikomatis, A. S. Triantafyllon, M. G. Siskos and A. K. Zarkadis, *Tetrahedron*, 2002, **58**, 2441; (*d*) M. S. Hill and P. B. Hitchcock, *Organometallics*, 2002, **21**, 220; (*e*) N. S. Mills, C. Tirla, M. A. Benish, A. J. Rakowitz, L. M. Bebell, C. M. M. Hurd and A. L. M. Bria, *J. Org. Chem.*, 2005, **70**, 10709; (*f*) J. A. Wilkinson, S. B. Rossington, S. Ducki, J. Leonardb and N. l. Hussain, *Tetrahedron*, 2006, **62**, 1833; (*g*) Y. S. Park, E. K. Yum, A. Basu and P. Beak, *Org. Lett.*, 2006, **8**, 2667;

for an exception using iridium-catalyzed C–H activation: (*h*) Q. Li, M. Driess and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2014, **53**, 8471; for an exception using Ni/Cu-catalyzed C–O cleavage: (*i*) C. Zarate and R. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 2236.

7 (*a*) T. Ohmura and M. Suginome, *Bull. Chem. Soc. Jpn.*, 2009, **82**, 29; (*b*) M. Suginome and Y. J. Ito, *Organomet. Chem.*, 2003, **680**, 43. For a review on the chemistry of silaboranes, see: (*c*) M. Oestreich, E. Hartmann and M. Mewald, *Chem. Rev.*, 2013, **113**, 402.

8 For a review on the use of the *t*-Bu group as a protecting group in the synthesis of aromatic compounds, see: S. A. Saleh and H. I. Tashtoush, *Tetrahedron*, 1998, **54**, 14157.

9 (*a*) J. M. O'Brien and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 7712; (*b*) H. Ito, Y. Horita and E. Yamamoto, *Chem. Commun.*, 2012, **48**, 8006; (*c*) K. Oshima, T. Ohmura and M. Suginome, *Chem. Commun.*, 2012, **48**, 8571; (*d*) C. Kleeberg and C. Borner, *Eur. J. Inorg. Chem.*, 2013, 2799.

10 (*a*) A. Ricci, A. Degl'innocenti, M. Fiorenza, M. Taddei and M. A. Spartera, *Tetrahedron Lett.*, 1982, **23**, 577; (*b*) B. Bennetau and J. Dunogues, *Tetrahedron Lett.*, 1983, **24**, 4217; (*c*) G. Bartoli, M. Bosco, D. Caretti, R. Dalpozzo and P. E. Todesco, *J. Org. Chem.*, 1987, **52**, 4381; (*d*) A. S. Pilcher and P. DeShong, *J. Org. Chem.*, 1996, **61**, 6901; (*e*) S. Thayumanavan, Y. S. Park, P. Farid and P. Beak, *Tetrahedron Lett.*, 1997, **38**, 5429; (*f*) M. Das and D. F. O'Shea, *Tetrahedron*, 2013, **69**, 6448.