Cross-Coupling

International Edition: DOI: 10.1002/anie.201602264
German Edition: DOI: 10.1002/ange.201602264

Versatile C(sp^2)–C(sp^3) Ligand Couplings of Sulfoxides for the Enantioselective Synthesis of Diarylalkanes

*William M. Dean, Mindaugas Šiaučiulis, Thomas E. Storr, William Lewis, and Robert A. Stockman**

Abstract: *The reaction of chiral (hetero)aryl benzyl sulfoxides with Grignard reagents affords enantiomerically pure diarylalkanes in up to 98% yield and greater than 99.5% enantiomeric excess. This ligand coupling reaction is tolerant to multiple substitution patterns and provides access to diverse areas of chemical space in three operationally simple steps from commercially available reagents. This strategy provides orthogonal access to electron-deficient heteroaromatic compounds, which are traditionally synthesized by transition metal catalyzed cross-couplings, and circumvents common issues associated with proto-demetalation and β-hydride elimination.*

Syntheses of both enantiomerically pure and racemic diarylalkanes have been become a topic of intense research because of the presence of these moieties in a multitude of biologically active molecules,[1] with the diarylmethane motif being described as a privileged structure.[2] In particular, 2-benzylpyridines such as the farnesyltransferase inhibitor, lonafarnib (**1**), and the antihistamines pheniramine (**2a**), chlorphenamine (**2b**; Piriton®) and bromphenamine (**2c**), are of great interest (Figure 1).

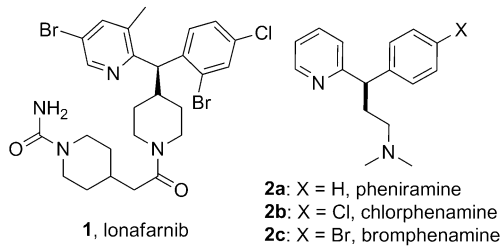
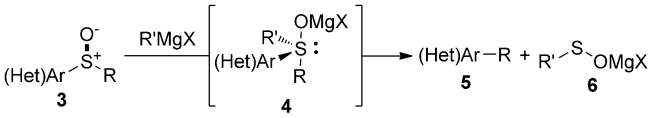


Figure 1. Selected drug targets containing di(hetero)arylalkanes.

While the use of transition metal catalyzed C(sp^2)–C(sp^3) reactions in the synthesis of diarylmethanes has become common place,[3] such methodologies suffer from several competing processes. First, the coupling of electron-deficient heteroaromatics is widely known to be troublesome because of protodemetallation.[4] Furthermore, the stereocontrolled cross-coupling of chiral secondary and tertiary C(sp^3) units is taxing because of the loss of stereochemical integrity[5] as well as issues associated with β-hydride elimination.[6] Whilst both complications have been overcome independently, to the best of our knowledge they have never been resolved simultaneously.

Research into transition-metal-free carbon–carbon bond-forming reactions promoted by main-group elements has emerged at the forefront of synthetic technologies in recent years, driven by significant advances in the development of boron and iodine reagents.[7] However, analogous reactions of other *p*-block elements, such as sulfur, remain overlooked by comparison despite promising initial results published in the field over half a century ago.[8]

The ability of sulfur(IV) auxiliaries and reagents to impart chiral information in the formation diastereomerically enriched compounds is well known.[9] Furthermore, reactions such as the Pummerer rearrangement[10] and magnesium sulfoxide exchange[11] have received significant attention of late. The ligand coupling reaction of sulfoxides has, by comparison, been remarkably underexploited. Pioneering work by Oae and co-workers proposed that attack of a Grignard reagent at a sulfinyl center forms a metastable disphenoidal σ-sulfurane intermediate (**4**; Scheme 1).[12] The sulfurane **4** may decompose through a reductive extrusion of two ligands, from an axial and equatorial position, to form the cross-coupled product **5** and the magnesium sulfenate **6**.[12i]



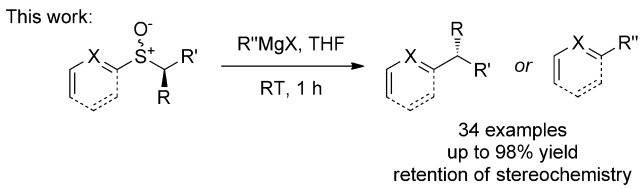
Scheme 1. Proposed mechanistic pathway.

Despite initial mechanistic investigations into the ligand coupling reactions of sulfoxides, few accounts on the synthetic utility of this reaction have been described. Herein, we report the results of our investigation into the scope and application of the ligand coupling reaction (Scheme 2).

Substitution of benzylic halides or 2-pyridyl chloride by a range of thiols and oxidation provided a range of sulfoxides (**3a–y**; see Scheme 3) for examination.[13] A simple optimization of reaction conditions was performed to enhance the steric and electronic effects of the Grignard reagent used to promote the ligand coupling reaction. Two optimal protocols were identified which use readily available Grignard reagents, either methylmagnesium bromide or *tert*-butylmagnesium

[*] W. M. Dean, M. Šiaučiulis, Dr. T. E. Storr, Dr. W. Lewis, Prof. R. A. Stockman
School of Chemistry, University of Nottingham
University Park, Nottingham, NG7 2RD (UK)
E-mail: robert.stockman@nottingham.ac.uk

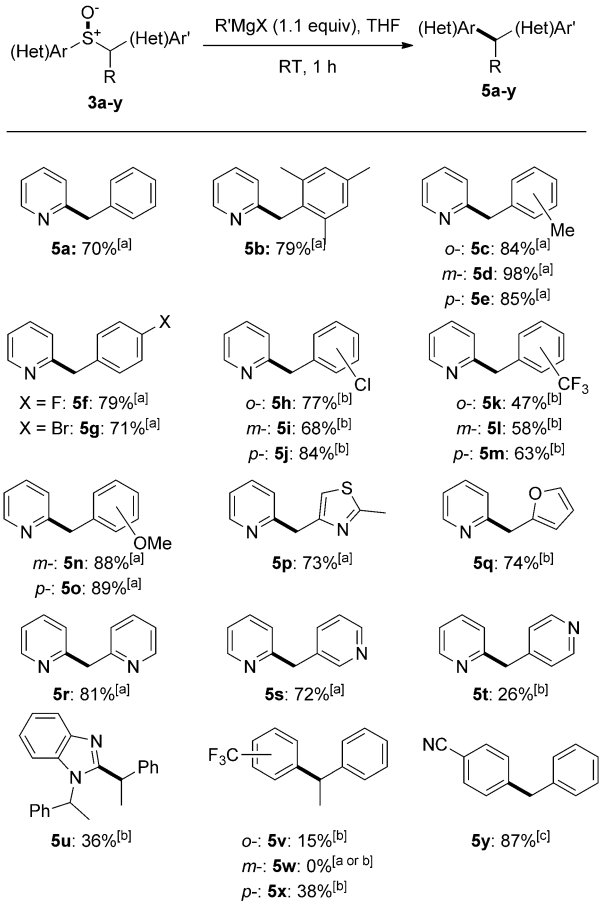
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201602264.



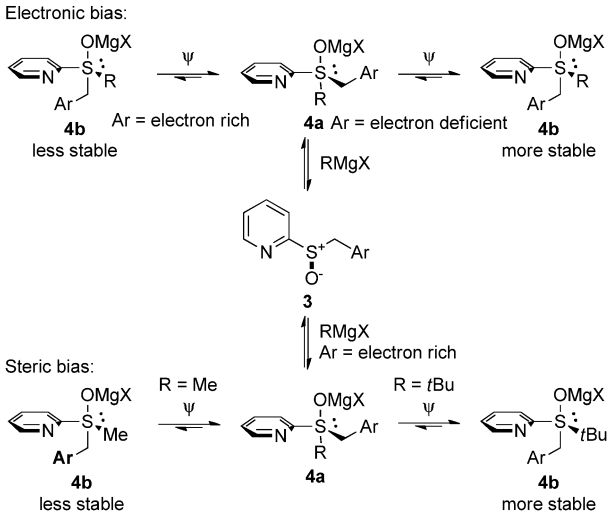
Scheme 2. Summary of ligand coupling reactions developed. THF = tetrahydrofuran.

chloride, as the promoter.[13] The results from the subjection of the sulfoxide substrates **3a–y** to the Grignard reagents in THF are presented in Scheme 3. In general, substitution around the aromatic ring is well tolerated for unactivated (**5a–e**), electron-deficient (**5f–m**), and electron-rich functionalities (**5n,o**). It is important to note that sterically encumbered groups, such as mesityl sulfoxide **5b**, were also tolerated well. Pleasingly, methylene units bearing heteroaromatics were also found amenable to the reaction conditions, thus producing the corresponding di(hetero)arylmethanes **5p–t** in moderate to excellent yields.

A general trend was observed where *t*BuMgCl provided best yields with electron-rich substrates, while MeMgBr was most efficient for electron-deficient substrates. This trend can be attributed to the relative electronic and steric biases of the equatorial and axial positions of **4** (Scheme 4). Grignard



Scheme 3. Ligand coupling reactions of benzyl sulfoxides **3a–y**. [a] R′ = *t*Bu, X = Cl; [b] R′ = Me, X = Br; [c] R′ = Bn, X = Cl.

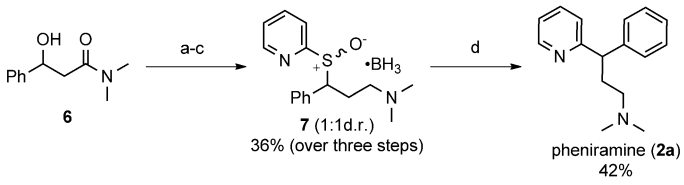


Scheme 4. Electronic and steric biases on the σ-sulfuranes **4**.

reagents are known to attack a sulfoxide (**3**) opposite to the sulfinyl oxygen atom, thus yielding the sulfurane **4a**, where the newly incorporated ligand is in an axial position. Reversible pseudorotation processes (denoted as ψ) isomerize **4a** into the sulfurane **4b**, the required conformation to undergo ligand coupling. The sulfurane **4b** is more stable with electron-deficient benzylic ligands, which undergo reductive extrusion readily. Electron-rich benzylic ligands are less stable in the axial position, thus leading to lower yields of these ligand coupling products when MeMgBr is used, because of competing magnesium-sulfoxide exchange reactions. The use of *t*BuMgCl introduces a steric bias on the conformation of the sulfuranes **4**, since the *tert*-butyl ligand is more easily accommodated in an equatorial position than in a confined axial position. This lowers the energy of the required conformation **4b** relative to its isomer **4a**. Thus higher yields are observed in the ligand coupling reactions of electron-rich benzylic ligands when *t*BuMgCl is used.

We have also examined the use of electron-deficient (hetero)aromatic rings in ligand coupling reactions. Benzimidazole was found to be a viable coupling partner, thus providing **5u** in a 36% yield (Scheme 3). With electron-deficient arylsulfoxides bearing trifluoromethyl and nitrile groups the formation of the desired diarylmethane was also observed (**5v–y**). Interestingly, only the *ortho*- and *para*-trifluoromethyl substrates were effective in the ligand coupling reaction (**5v–x**). In the case of **5y**, benzyl Grignard gave the best yields, as in this case two benzyl ligands are on the sulfur atom and either can migrate. Formation of the nitrile **5y** provides significant scope for further functionalization following ligand coupling reaction.

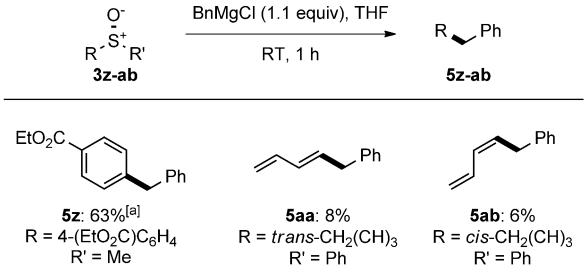
To exemplify the potential for more complex substitution at the benzylic position, we embarked on a synthesis of the antihistamine pheniramine (**2a**; Scheme 5). Synthesis of the required sulfoxide **7** was efficiently achieved in three steps from commercially available alcohol **6**. Treatment of **7** with methylmagnesium bromide followed by an acidic workup afforded pheniramine (**2a**) in 42% yield.



Scheme 5. Synthesis of pheniramine (**2a**). Reaction conditions: a) MsCl, NEt_3, CH_2Cl_2, RT then 2-mercaptopyridine, RT; b) BH_3·DMS, THF, 60 °C; c) *m*CPBA, CH_2Cl_2, RT; d) MeMgBr (1.1 equiv), THF, RT. DMS = dimethylsulfide, *m*CPBA = *m*-chloroperbenzoic acid, Ms = methanesulfonyl.

With the intramolecular ligand coupling explored, our attention was turned to the possibility for the cross-coupling of a substituted sulfoxide with a Grignard reagent. Benzylmagnesium chloride was reacted with sulfoxides furnished with ethyl 4-benzoate (**3z**) and butadiene (both *cis* and *trans*, **3aa**,**ab**; Scheme 6). In all cases the cross-coupled products (**5z**–**ab**) were obtained, albeit in low yield, with retention of alkene geometry in the synthesis of **5aa** and **5ab**. We attribute the low yields in the latter two cases to result from the lack of an electron-withdrawing ligand on the sulfur, and thus Grignard exchange becomes a more prevalent reaction pathway.

To elucidate the retention of stereochemistry exhibited by ligand coupling reactions, we set about the synthesis of enantiomerically pure sulfoxides (**3ac**–**ae**; Scheme 7). Erbium(III)-catalyzed alkylation of 2-mercaptopyridine (**9**) with (*R*)-styrene oxide (**8**), followed by protection and oxidation, provided the required substrates **3ac**–**ae**. The structure and absolute stereochemistry of **3ac′** was determined by X-ray crystallography (Figure 2). Subjection to MeMgBr afforded the corresponding 1,1-di(hetero)arylethanes **5ac**–**ae** in moderate to very good yield and, importantly, excellent enantiomeric excess. Stereoretention was confirmed by the



Scheme 6. Cross-coupling reactions of the sulfoxides **3z**–**ab**. [a] reaction performed at 0 °C.

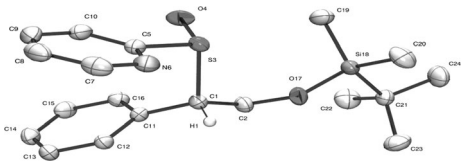
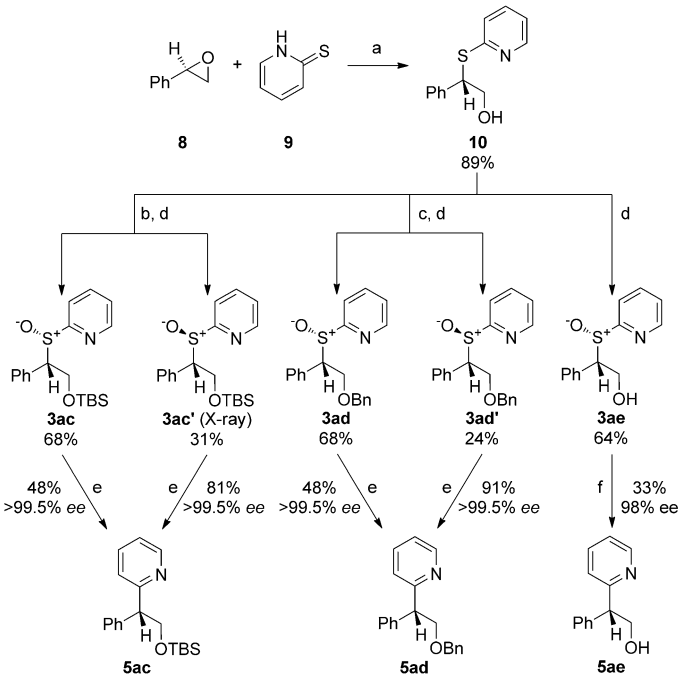


Figure 2. XRD structure of sulfoxide **3ac′** (CCDC 1457851). Thermal ellipsoids shown at 50% probability.

radical deoxygenation of **5ae** and comparison of the optical rotation of the product with literature values (see the Supporting Information). The higher yields of the diarylmethanes **5**, produced by substrates with *R*-sulfinyl centers, are attributed to steric differences between each diastereomer. It may be possible to employ this insight to produce optimal yields of diarylmethanes which are functionalized at the benzylic center.

In summary, by using two generalized protocols we have demonstrated the potential for ligand coupling reactions as a complimentary approach to cross-coupling



Scheme 7. Synthesis of enantiomerically enriched diarylmethanes **5ac**–**ae**. Reaction conditions: a) $Er(OTf)_3$, MeCN, RT; b) TBSCl, imidazole, CH_2Cl_2, RT; c) NaH, BnBr, THF, RT; d) *m*CPBA, CH_2Cl_2, RT; e) MeMgBr (1.1 equiv), THF, RT; f) MeMgBr (2.2 equiv), THF, RT. TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

reactions in the formation of $C(sp^2)$–$C(sp^3)$ bonds. We have studied 34 examples with electronic and steric diversity, thus providing diarylmethanes in up to 98% chemical yield. This work has been extended into cross-coupling reactions and enantioretentive synthesis as well as being employed in the synthesis of a drug molecule. Work within our group is currently directed towards the further expansion of scope and application of this reaction methodology.

Acknowledgments

The authors acknowledge the EPSRC (EP/I038489) for financial support.

Keywords: arenes · cross-coupling · magnesium · reaction mechanisms · sulfur

[1] a) C. P. Ting, T. J. Maimone, *Angew. Chem. Int. Ed.* **2014**, *53*, 3115 – 3119; *Angew. Chem.* **2014**, *126*, 3179 – 3183; b) F. Schmidt, R. T. Stemmler, J. Rudolph, C. Bolm, *Chem. Soc. Rev.* **2006**, *35*, 454 – 470; c) K. Andries, P. Verhasselt, J. Guillemont, H. W. H. Göhlmann, J.-M. Neefs, H. Winkler, J. Van Gestel, P. Timmerman, M. Zhu, E. Lee, et al., *Science* **2005**, *307*, 223 – 227; d) S. A. Snyder, A. Gollner, M. I. Chiriac, *Nature* **2011**, *474*, 461 – 466; e) P. Tolstoy, M. Engman, A. Paptchikhine, J. Bergquist, T. L. Church, A. W.-M. Leung, P. G. Andersson, *J. Am. Chem. Soc.* **2009**, *131*, 8855 – 8860.

[2] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, *J. Med. Chem.* **1988**, *31*, 2235 – 2246; b) L. Costantino, D. Barlocco, *Curr. Med. Chem.* **2006**, *13*, 65 – 85.

[3] a) R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 14391 – 14393; b) B. M. Trost, D. A. Thaisrivongs, *J. Am. Chem. Soc.* **2009**, *131*, 12056 – 12057; c) J. B. Gianino, B. L. Ashfeld, *J. Am. Chem. Soc.* **2012**, *134*, 18217 – 18220; d) M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal, R. J. K. Taylor, *Org. Lett.* **2007**, *9*, 5397 – 5400.

[4] a) J. Lozada, Z. Liu, D. M. Perrin, *J. Org. Chem.* **2014**, *79*, 5365 – 5368; b) A. J. J. Lennox, G. C. Lloyd-Jones, *Chem. Soc. Rev.* **2014**, *43*, 412 – 443.

[5] a) L. Li, C.-Y. Wang, R. Huang, M. R. Biscoe, *Nat. Chem.* **2013**, *5*, 607 – 612; b) S. Çalimsiz, M. G. Organ, *Chem. Commun.* **2011**, *47*, 5181 – 5183; c) C. M. Crudden, B. W. Glasspoole, C. J. Lata, *Chem. Commun.* **2009**, 6704 – 6716; d) B. W. Glasspoole, M. S. Oderinde, B. D. Moore, A. Antoft-Finch, C. M. Crudden, *Synthesis* **2013**, *45*, 1759 – 1763; e) B. W. Glasspoole, K. Ghozati, J. W. Moir, C. M. Crudden, *Chem. Commun.* **2012**, *48*, 1230 – 1232; f) L. Chausset-Boissarie, K. Ghozati, E. LaBine, J. L.-Y. Chen, V. K. Aggarwal, C. M. Crudden, *Chem. Eur. J.* **2013**, *19*, 17698 – 17701; g) S. C. Matthew, B. W. Glasspoole, P. Eisenberger, C. M. Crudden, *J. Am. Chem. Soc.* **2014**, *136*, 5828 – 5831.

[6] a) J. F. Hartwig, *Organotransition Metal Chemistry*, University Science Books, Sausalito, **2010**; b) C. Han, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 7532 – 7533.

[7] a) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature* **2014**, *513*, 183 – 188; b) C. G. Watson, V. K. Aggarwal, *Org. Lett.* **2013**, *15*, 1346 – 1349; c) V. Bagutski, R. M. French, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2010**, *49*, 5142 – 5145; *Angew. Chem.* **2010**, *122*, 5268 – 5271; d) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2011**, *50*, 3760 – 3763; *Angew. Chem.* **2011**, *123*, 3844 – 3847; e) J. L. Stymiest, V. Bagutski, R. M. French, V. K. Aggarwal, *Nature* **2008**, *456*, 778 – 782; f) S. Roesner, D. J. Blair, V. K. Aggarwal, *Chem. Sci.* **2015**, *6*, 3718 – 3723; g) U. Farid, F. Malmedy, R. Claveau, L. Albers, T. Wirth, *Angew. Chem. Int. Ed.* **2013**, *52*, 7018 – 7022; *Angew. Chem.* **2013**, *125*, 7156 – 7160; h) H. Tohma, Y. Harayama, M. Hashizume, M. Iwata, Y. Kiyono, M. Egi, Y. Kita, *J. Am. Chem. Soc.* **2003**, *125*, 11235 – 11240; i) V. K. Aggarwal, B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516 – 5519; *Angew. Chem.* **2005**, *117*, 5652 – 5655; j) R. M. Moriarty, *J. Org. Chem.* **2005**, *70*, 2893 – 2903.

[8] G. Wittig, H. Fritz, *Justus Liebigs Ann. Chem.* **1952**, *577*, 39 – 46.

[9] For reviews on the use of sulfoxides as chiral auxiliaries, see: a) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129 – 6144; b) B. Delouvrié, L. Festerbank, F. Nájera, M. Malacria, *Eur. J. Org. Chem.* **2002**, 3507 – 3525; for uses of sulfinimines as chiral auxiliaries see: c) Y.-W. Zhong, Y.-Z. Dong, K. Fang, K. Izumi, M.-H. Xu, G.-Q. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 11956 – 11957; d) G. Liu, D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913 – 9914; e) C. Roe, T. M. Sola, L. Sasraku-Neequaye, H. Hobbs, I. Churcher, D. MacPherson, R. A. Stockman, *Chem. Commun.* **2011**, *47*, 7491 – 7493; f) C. Roe, H. Hobbs, R. A. Stockman, *J. Org. Chem.* **2011**, *76*, 9452 – 9459; g) C. Roe, H. Hobbs, R. A. Stockman, *Chem. Eur. J.* **2011**, *17*, 2704 – 2708; h) E. M. Rochette, W. Lewis, A. G. Dossetter, R. A. Stockman, *Chem. Commun.* **2013**, *49*, 9395 – 9397; i) T. M. Solá, I. Churcher, W. Lewis, R. A. Stockman, *Org. Biomol. Chem.* **2011**, *9*, 5034 – 5035; j) G. Procopiou, W. Lewis, G. Harbottle, R. A. Stockman, *Org. Lett.* **2013**, *15*, 2030 – 2033; k) T. Moragas, I. Churcher, W. Lewis, R. A. Stockman, *Org. Lett.* **2014**, *16*, 6290 – 6293; l) M. T. Robak, M. A. Herbage, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 3600 – 3740.

[10] a) Y. Kita, *Phosphorus Sulfur Silicon Relat. Elem.* **1997**, *120*, 145 – 164; b) M. Miller, J. C. Vogel, W. Tsang, A. Merrit, D. J. Procter, *Org. Biomol. Chem.* **2009**, *7*, 589 – 597; c) L. H. S. Smith, S. C. Coote, H. F. Sneddon, D. J. Procter, *Angew. Chem. Int. Ed.* **2010**, *49*, 5832 – 5844; *Angew. Chem.* **2010**, *122*, 5968 – 5980; d) L. A. McAllister, S. Brand, R. de Gentile, D. J. Procter, *Chem. Commun.* **2003**, 2380 – 2381; e) L. A. McAllister, R. A. McCormick, S. Brand, D. J. Procter, *Angew. Chem. Int. Ed.* **2005**, *44*, 452 – 455; *Angew. Chem.* **2005**, *117*, 456 – 459; f) A. J. Eberhart, D. J. Procter, *Angew. Chem. Int. Ed.* **2013**, *52*, 4008 – 4011; *Angew. Chem.* **2013**, *125*, 4100 – 4103; g) L. H. S. Smith, T. T. Nguyen, H. F. Sneddon, D. J. Procter, *Chem. Commun.* **2011**, *47*, 10821 – 10823; h) R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282 – 2291; i) A. J. Eberhart, H. J. Shrives, E. Álvarez, A. Carrër, Y. Zhang, D. J. Procter, *Chem. Eur. J.* **2015**, *21*, 7428 – 7434; j) A. J. Eberhart, J. E. Imbriglio, D. J. Procter, *Org. Lett.* **2011**, *13*, 5882 – 5885.

[11] a) M. A. M. Capozzi, C. Cardellicchio, F. Naso, G. Spina, P. Tortorella, *J. Org. Chem.* **2001**, *66*, 5933 – 5936; b) L. Melzig, C. B. Rauhut, N. Naredi-Rainer, P. Knochel, *Chem. Eur. J.* **2011**, *17*, 5362 – 5372; c) S. Yoshida, F. Karaki, K. Uchida, T. Hosoya, *Chem. Commun.* **2015**, *51*, 8745 – 8748; d) R. W. Hoffmann, B. Hölzer, O. Knopff, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 3072 – 3074; *Angew. Chem.* **2000**, *112*, 3206 – 3207; e) F. Kopp, G. Sklute, K. Polborn, I. Marek, P. Knochel, *Org. Lett.* **2005**, *7*, 3789 – 3791.

[12] a) S. Oae, T. Kawai, N. Furukawa, F. Iwasaki, *J. Chem. Soc. Perkin Trans. 2* **1987**, 405 – 411; b) Y. H. Khim, S. Oae, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 1968 – 1971; c) S. Oae, *Phosphorus Sulfur Relat. Elem.* **1986**, *27*, 13 – 29; d) S. Oae, T. Takeda, T. Kawai, N. Furukawa, *Phosphorus Sulfur Relat. Elem.* **1987**, *34*, 133 – 137; e) T. Kawai, Y. Kodera, S. Oae, M. Ishida, T. Takeda, S. Wakabayashi, N. Furukawa, *Phosphorus Sulfur Relat. Elem.* **1987**, *34*, 139 – 148; f) S. Oae, Y. Uchida, *Acc. Chem. Res.* **1991**, *24*, 202 – 208; g) S. Oae, T. Takeda, S. Wakabayashi, F. Iwasaki, N. Yamazaki, Y. Katsube, *J. Chem. Soc. Perkin Trans. 2* **1990**, 273 – 276; h) S. Oae, T. Takeda, J. Uenishi, S. Wakabayashi, *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *115*, 179 – 182; i) S. Oae, T. Kawai, N. Furukawa, *Phosphorus Sulfur Relat. Elem.* **1987**, *34*, 123 – 132; j) S. Oae, T. Kawai, N. Furukawa, *Tetrahedron Lett.* **1984**, *25*, 69 – 72; k) S. Oae, *Pure Appl. Chem.* **1996**, *68*, 805 – 812; l) S. Wakabayashi, M. Ishida, T. Takeda, S. Oae, *Tetrahedron Lett.* **1988**, *29*, 4441 – 4444; m) B. Trost, R. LaRochelle, R. Atkins, *J. Am. Chem. Soc.* **1969**, *91*, 2175 – 2177.

[13] Sub-optimal yields were generally accompanied by an increase in the yield of 2,2′-bipyridine. See the Supporting Information for a full optimization table.

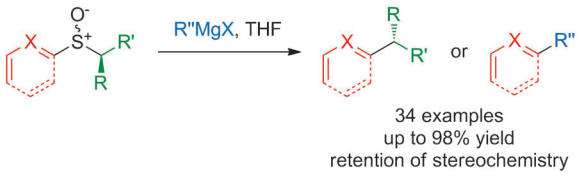
Received: March 4, 2016
Revised: April 29, 2016
Published online: ■■ ■■, ■■■■

Communications

Cross-Coupling

W. M. Dean, M. Šiaučiulis, T. E. Storr, W. Lewis, R. A. Stockman* _____ ■■■■–■■■■

Versatile C(sp^2)–C(sp^3) Ligand Couplings of Sulfoxides for the Enantioselective Synthesis of Diarylalkanes



On three: The reaction of chiral (hetero)aryl benzyl sulfoxides with Grignard reagents affords diarylalkanes with greater than 99.5% enantiomeric excess. The reaction is tolerant to multiple substitution patterns and proceeds in three operationally simple steps from commercially available reagents. This strategy provides orthogonal access to electron-deficient heteroaromatic compounds.