Dean, William Michael and Mindaugas, Šiaučiulis and Storr, Thomas E. and Lewis, William and Stockman, Robert A. (2016) Versatile C(sp2)−C(sp3) ligand couplings of sulfoxides for the enantioselective synthesis of diarylalkanes. Angewandte Chemie International Edition, 55 (34). pp. 10013-10016. ISSN 1521-3773

Versatile C(sp2)-C(sp3) 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, traditionally synthesised via transition metal-catalysed cross-couplings, which 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 due to 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 farnesyltransferase inhibitor, lonafarnib (1) and the antihistamines pheniramine (2a), chlorphenamine (2b, Piriton®) and bromphenamine (2c), are of great interest (Figure 1).

While the use of transition metal-catalyzed C(sp2) C(sp3) 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 due to protodemetallation.[4] Furthermore, the stereocontrolled cross coupling of chiral secondary and tertiary C(sp3) units is taxing due to 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.

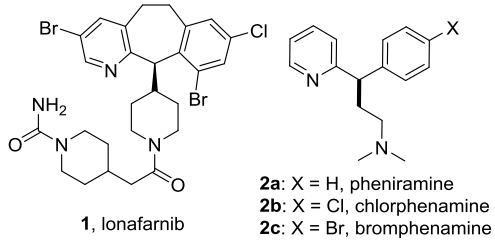


Figure 1. Selected drug targets containing di(hetero)arylalkanes.

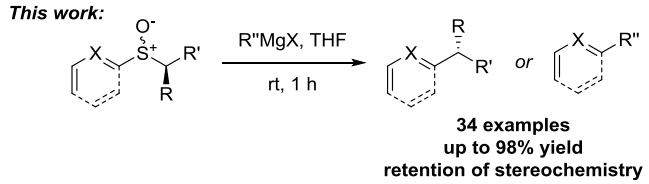
Research into transition metal-free carbon-carbon bond forming reactions promoted by main group elements has emerged at the forefront of synthetic technologies in recent years, driven by some excellent advances in the chemistries of boron and iodine.[7] However, analogous reactions of other p-block elements, 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 centre forms a metastable disphenoidal σ sulfurane intermediate 4 (Scheme 1).[12] Sulfurane 4 may decompose through a reductive extrusion

of two ligands, in an axial and an equatorial position, to form cross-coupled product 5 and magnesium sulfenate 6.[12i]

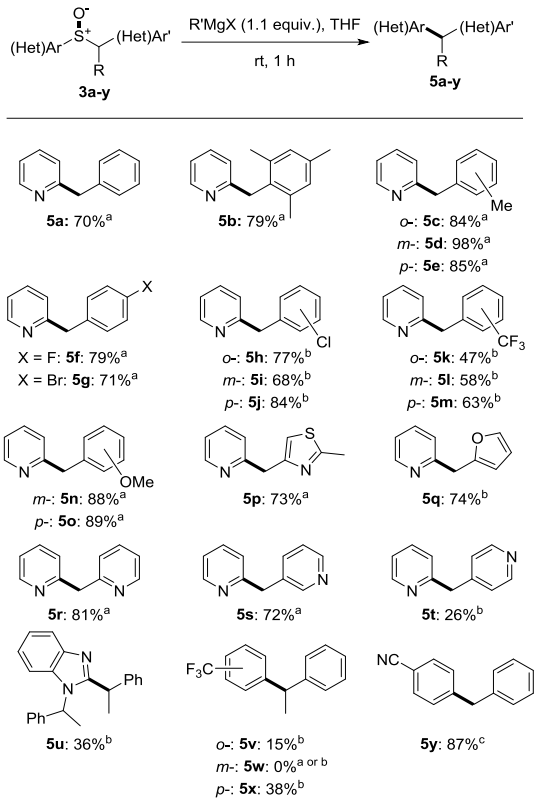
Scheme 1. Proposed mechanistic pathway.

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).



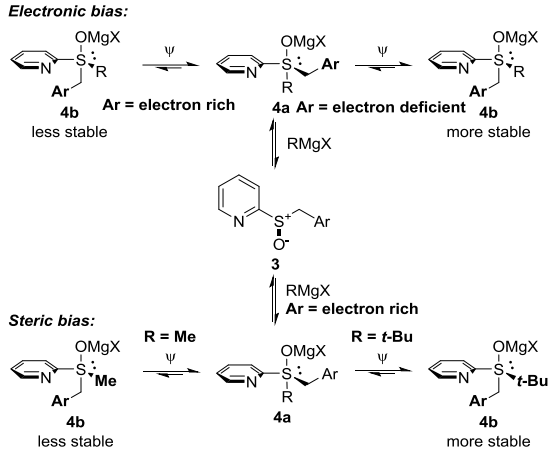
Scheme 2. Summary of ligand coupling reactions developed.

Substitution of benzylic halides or 2-pyridyl chloride by a range of thiols and oxidation provided a range of sulfoxides 3a-y for examination.[13] A simple optimisation 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 t-butylmagnesium 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, producing the corresponding di(hetero)arylmethanes 5p-t in moderate to excellent yields. In the case of 5y, benzyl Grignard gave the best yields, as in this case, two benzyl ligands are on the sulfur, either one of which can migrate.



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.

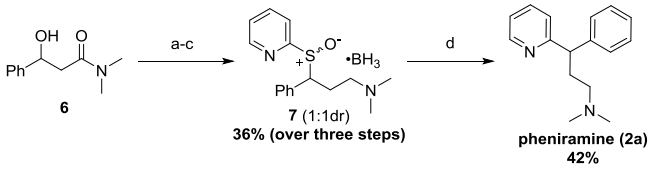
A general trend was observed where t-BuMgCl provided best yields with electron-rich substrates, while MeMgBr was most efficient for electron-deficient substrates. This can be attributed to the relative electronic and steric biases of the equatorial and axial positions of a σ-sulfurane 4 (Scheme 4). Grignard reagents are known to attack a sulfoxide 3 opposite to the sulfinyl oxygen, yielding sulfurane 4a, where the newly incorporated ligand is in an axial position. Reversable pseudorotation processes (denoted as ψ) isomerise sulfurane 4a into sulfurane 4b, the required conformation to undergo ligand coupling. 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, leading to lower yields of these ligand coupling products when MeMgBr is used due to competing magnesium-sulfoxide exchange reactions. The use of t BuMgCl introduces a steric bias on the conformation of sulfuranes 4, since the t-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.



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

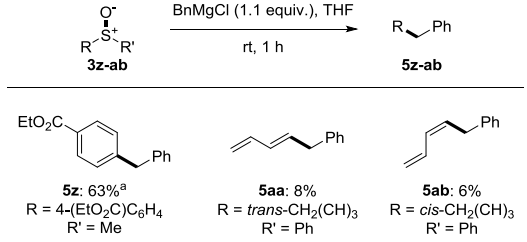
We have also examined the use of electron deficient (hetero)aromatic rings in ligand coupling reactions. Benzimidazole was found to be a viable coupling partner providing 5u in a 36% yield. With electron deficient arylsulfoxides bearing trifluoromethyl and nitrile groups the formation of the desired diarylmethane was also observed (5v-5y). Interestingly, only the ortho and para trifluoromethyl substrates were effective in the ligand coupling reaction (5v-x). Formation of nitrile 5y provides significant scope for further functionalisation 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.



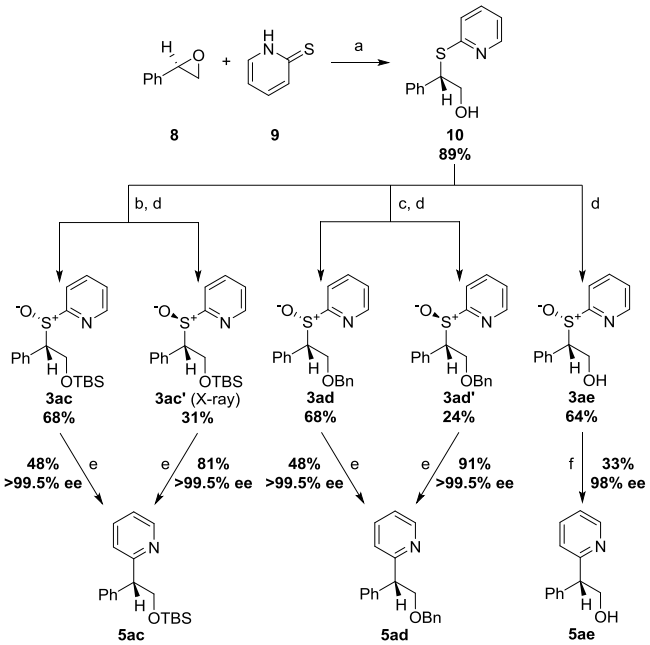
Scheme 5. Synthesis of pheniramine 2a. Conditions: a) MsCl, NEt3, CH2Cl2, rt then 2-mercaptopyridine, rt; b) BH3.DMS, THF, 60 °C; c) mCPBA, CH2Cl2, rt; d) MeMgBr (1.1 equiv.), THF, rt.

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-3ab) (Scheme 6). In all cases the cross coupled products (5z-5ab) 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 be down to lack of an electron-withdrawing ligand on the sulfur, and thus Grignard exchange becomes a more prevalent reaction pathway.



Scheme 6. Cross-coupling reactions of sulfoxides 3z-ab. a) reaction performed at 0 °C.

To elucidate the retention of stereochemistry exhibited by ligand coupling reactions, we set about the synthesis of enantiomerically pure sulfoxides 3ac-3ae (Scheme 7). Erbium(III)-catalysed alkylation of 2 mercaptopyridine (9) with (R) styrene oxide (8) followed by protection and oxidation, provided the required substrates 3ac-3ae. 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-5ae in moderate to very good yield and, importantly, excellent enantiomeric excess. Stereoretention was confirmed by the radical deoxygenation of 5ae and comparison of the optical rotation of the product with literature values (See supplementary information). The higher yields of diarylmethanes 5 produced by substrates with (R)-sulfinyl centres are attributed to steric differences between each diastereomer. It may be possible to employ this insight to produce optimal yields of diarylmethanes which are functionalised at the benzylic centre.



Scheme 7. Synthesis of enantiomerically enriched diarylmethanes 5ac-5ae. Conditions: a) Er(OTf)3, MeCN, rt; b) TBSCl, imidazole, CH2Cl2, rt; c) NaH, BnBr, THF, rt; d) mCPBA, CH2Cl2, rt; e) MeMgBr (1.1 equiv.), THF, rt; f) MeMgBr (2.2 equiv.), THF, rt.

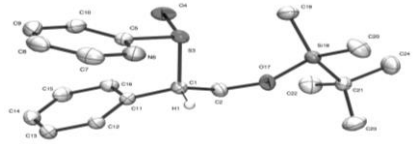


Figure 2. XRD structure of sulfoxide 3ac' (CCDC 1457851)

In summary, using two generalised protocols we have demonstrated the potential for ligand coupling reactions as a complimentary approach to cross-coupling reactions in the formation of C(sp2)-C(sp3) bonds. 34 Examples with electronic and steric diversity have been explored, 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.

Acknowledgements

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

Keywords: sp2-sp3 coupling • sulfoxide • ligand coupling • diarylmethane • sulfurane

[1] a) C. P. Ting, T. J. Maimone, Angew. Chemie Int. Ed. 2014, 53, 3115–3119; 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., Sci. 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. Calimsiz, 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 (Stuttg). 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. – A 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, 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. Chemie Int. Ed. 2010, 49, 5142–5145; d) R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott, V. K. Aggarwal, Angew. Chemie Int. Ed. 2011, 50, 3760–3763; 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. Chemie Int. Ed. 2013, 52, 7018–7022; 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. Chemie Int. Ed. 2005, 44, 5516–5519; 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. Carreno, G. Hernndez-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 sulinamines 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.

– A 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. Sola, 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.
[10] a) Y. Kita, Phosphorus, Sulfur Silicon Relat. Elem. 1997, 120 & 121, 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. Chemie Int. Ed. 2010, 49, 5832–5844; 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. Chemie Int. Ed. 2005, 44, 452–455; f) A. J. Eberhart, D. J. Procter, Angew. Chemie Int. Ed. 2013, 52, 4008–4011; g) L. H. S. Smith, T. T. Nguyen, H. F. Sneddon, D. J. Procter, Chem. Commun. 2011, 47, 10821–10823; h) R. Pummerer, Berichte der Dtsch. Chem. Gesellschaft 1909, 42, 2282–2291; i) A. J. Eberhart, H. J. Shrives, E. Álvarez, A. Carrër, Y. Zhang, D. J. Procter, Chem. – A 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. – A 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. Chemie Int. Ed. 2000, 39, 3072–3074; 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, 0, 405–411; b) Y. H. Khim, S. Oae, Bull. Chem. Soc. Jpn. 1969, 42, 1968–1971; c) S. Oae, Phosphorous Sulfur Relat. Elem. 1986, 27, 13–29; d) S. Oae, T. Takeda, T. Kawai, N. Furukawa, Phosphorous Sulfur Relat. Elem. 1987, 34, 133–137; e) T. Kawai, Y. Kodera, S. Oae, M. Ishida, T. Takeda, S. Wakabayashi, N. Furukawa, Phosphorous 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, 0, 273–276; h) S. Oae, T. Kawai, N. Furukawa, F. Iwasaki, J. Chem. Soc., Perkin Trans. 2 1987, 405–411; i) S. Oae, T. Takeda, J. Uenishi, S. Wakabayashi, Phosphorus. Sulfur. Silicon Relat. Elem. 1996, 115, 179–182; j) S. Oae, T. Kawai, N. Furukawa, Phosphorous Sulfur Relat. Elem. 1987, 34, 123–132; k) S. Oae, T. Kawai, N. Furukawa, Tetrahedron Lett. 1984, 25, 69–72; l) S. Oae, Pure Appl. Chem. 1996, 68, 805–812; m) S. Wakabayashi, M. Ishida, T. Takeda, S. Oae, Tetrahedron Lett. 1988, 29, 4441–4444; n) 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 supporting information for a full optimisation table.