Enantioselective Cu-Catalyzed Arylation of Secondary Phosphine Oxides with Diaryliodonium Salts toward the Synthesis of P-Chiral Phosphines

Rodolphe Beaud, Robert J. Phipps, and Matthew J. Gaunt

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

Supporting Information

ABSTRACT: Catalytic synthesis of nonracemic P-chiral phosphine derivatives remains a significant challenge. Here we report Cu-catalyzed enantioselective arylation of secondary phosphine oxides with diaryliodonium salts for the synthesis of tertiary phosphine oxides with high enantiomeric excess. The new process is demonstrated on a wide range of substrates and leads to products that are well-established P-chiral catalysts and ligands.

Chiral phosphines are essential ligands for enantioselective metal-catalyzed reactions. Most of the chiral phosphines commonly used today display planar or point chirality where the asymmetric feature is presented in the carbon framework of the ligand. Although P-stereogenic phosphines have been known as effective ligands for enantioselective catalysis for over 40 years, they are less frequently utilized compared with more readily available planar- and point-chiral phosphines. Classical methods for the synthesis of P-stereogenic phosphines usually rely on auxiliary-based or resolution processes. Recently, however, advances in asymmetric catalysis have provided alternative methods to access these chiral phosphorus compounds via methods based on alkene phosphination, arylation or alkylation of secondary phosphines, and C(sp²)–H activation of aryl phosphate derivatives. Despite these advances, the development of distinct strategies that provide convenient access to a broad range of P-stereogenic phosphines remains an ongoing challenge in chemical synthesis. Herein we report a new method to form P-stereogenic organophosphorous compounds via enantioselective Cu-catalyzed arylation of secondary phosphine oxides (SPOs) using diaryliodonium salts (DAISs).

Over the past 8 years, our laboratory has developed a new reactivity platform based on the combination of DAISs and Cu catalysts to generate an aromatic electrophile equivalent in the form of a putative Cu(III)–aryl intermediate (Scheme 1a). As a result, the arylation of carbon-centered neutral nucleophiles, including amines, alkenes, and alkynes, has led to the realization of many distinct transformations. Furthermore, we and others have translated this novel activation mode to asymmetric catalysis using chiral bisoxazoline ligands to achieve the enantioselective C-arylation of enol silanes, allylic amides, and tryptamine derivatives. In further expanding the scope of this asymmetric arylation platform, we questioned whether certain heteroatom nucleophiles could engage the catalytically generated aromatic electrophile to form configurationally stable products. To test this, we selected SPOs as suitable nucleophiles, whose arylation would lead to tertiary phosphate oxides (TPOs), precursors to P-chiral phosphines as well as useful asymmetric catalysts in their own right.

An SPO exists in equilibrium with its phosphinous acid form when in solution, with the latter recognized as a competent ligand for a range of transition metals (Scheme 1b). Therefore, we envisioned that a simple SPO would bind to a high-oxidation-state chiral Cu(III)–aryl complex, formed through the action of a DAIS on the starting Cu catalyst, through the P atom, resulting in a square-pyramidal complex (Scheme 1c). The aromatic group would be transferred to the substrate as part of a stereocontrolled reductive elimination process to form the enantioenriched TPO. At the outset of our studies, we were aware of a report by Zhao that racemic arylation of SPOs can be achieved with diaryliodium salts and simple Cu catalysts. By applying the knowledge accrued from our enantioselective arylation studies with C-symmetric bisoxazoline ligands, we began our studies with the straightforward merger of these sets of reaction conditions toward the development of a catalytic enantioselective arylation process (Scheme 1d).

We began by attempting the asymmetric arylation of SPO 1a with substituted DAIS 2a using (S,S)-diphenylbisoxazoline 4a as the chiral ligand, copper(II) triflate as the catalyst, and Et₃N as the base in CH₂Cl₂ solution at room temperature (Table 1).
NaHCO₃ resulted in a significant increase in the yield of ligand and dtbpy as the base resulted in a dramatic increase in the yield. Conditions (entry 1). However, we found that using the hindered tert-butylpyridine (dtbpy) as the limiting reagent in the presence of 10 mol % Cu(OTf)₂, 12 mol % pybox ligand 4d, 2 equiv of K₂HPO₄, and 2 equiv of water in MeCN with stirring for 12 h at room temperature, which gave 3a in 96% yield with 96% ee after purification by silica gel chromatography.

With an optimal process in hand, we next investigated the scope of the SPO component in this transformation (Table 2). Simple SPOs bearing methyl and n-alkyl substituents were arylated to give the desired TPOs 3b–d with excellent ee and yield. SPOs with secondary branched alkyl groups also were excellent substrates for the arylation and gave high yields of 3e and 3f with excellent ee. Substrates with branching adjacent to the P atom gave mixed results. While arylation of t-Bu- and cyclohexyl-derived SPOs resulted in good yields of 3g and 3h, respectively, the enantioselectivities were moderate. However, cyclopropyl- and isopropyl-substituted SPOs underwent arylation in excellent yields to give 3i and 3j, respectively, with high ee using slightly modified conditions. More functionalized substituents, including benzyl and CH₂SiMe₃ groups, also gave the desired products (3k, 3l) in comparably high yields and ee.

We next investigated different DAISs displaying a variety of electronic and steric properties (Table 3). Electron-withdrawing groups at the para position were well-tolerated, and enantioenriched TPOs 3m–o were obtained in excellent yields and ee. Halogenated arenes were also transferred smoothly to afford 3p and 3q in good yields and enantioselectivities. Finally, more electron-rich aryls delivered 3r and 3s with remarkably high enantioselectivity. After recrystallization, 3r was obtained as a single enantiomer, and its X-ray structure confirmed the absolute stereochemistry of the enantioenriched TPOs.

Unfortunately, only traces of 3a were observed under these conditions (entry 1). However, we found that using the hindered base di-tert-butylpyridine (dtbpy) afforded the arylated TPO 3a with low conversion but importantly with modest enantioselective excess (56% ee) (entry 3). A survey of readily available ligands showed that changing substituents on the oxazoline moieties or using the corresponding tridentate pyridinebisoxazoline (pybox) catalysts led to no improvement using dtbpy as the base (entries 4 and 5). However, we were delighted to find that changing the solvent to MeCN while retaining (S,S)-diphenylpybox 4d as the ligand and dtbpy as the base resulted in a dramatic increase in the ee of 3a, but only a modest yield. Moreover, changing the base to NaHCO₃ resulted in a significant increase in conversion, with 3a isolated in 99% yield (with respect to DAIS 2a) and high ee. Further improvement was achieved by changing the base to K₂HPO₄, and we found that the presence of 2 equiv of water was important in securing a reproducible and robust reaction. Thus, the optimal conditions involved treatment of 2 equiv of SPO 1a with DAIS 2a as the limiting reagent in the presence of 10 mol %.

Table 2. Enantioselective Arylation of SPOs: Scope of the SPO Component

| Entry | Ligand | Base | Solvent | Additive | Yield ϵ (ee) |
|-------|--------|------|--------|----------|--------------|
| 1     | 4a     | Et₃N| CH₂Cl₂ | none     | Trace        |
| 2     | 4a     | none | CH₂Cl₂ | none     | No reaction  |
| 3     | 4a     | dtbpy| CH₂Cl₂ | none     | 11% (56)     |
| 4     | 4b     | dtbpy| CH₂Cl₂ | none     | <5% (20)     |
| 5     | 4c     | dtbpy| CH₂Cl₂ | none     | 12% (26)     |
| 6     | 4d     | dtbpy| CH₂Cl₂ | none     | 22% (52)     |
| 7     | 4d     | dtbpy| MeCN   | none     | 20% (84)     |
| 8     | 4d     | NaHCO₃| MeCN | none     | 99% (92)     |
| 9     | 4d     | Na₂PO₄| MeCN | none     | 90% (90)     |
| 10    | 4d     | K₂HPO₄| MeCN | none     | 96% (94)     |
| 11    | 4d     | KHPO₄| MeCN   | H₂O⁵     | 96% (96)     |

“Yields of isolated products based on 2a as the limiting reagent are shown. Average yield over 3 runs.”

DOI: 10.1021/jacs.6b09334 J. Am. Chem. Soc. 2016, 138, 13183–13186
deficient PAMP\textsuperscript{11} analogue \textit{3ag} in excellent yield with very good ee. An o-tolyl iodonium salt reacted in almost quantitative yield to afford \textit{3ah}, again with excellent ee. We were also pleased to find that ortho-halogenated iodonium salts reacted smoothly to produce TPOs with a convenient handle for further functionalization (\textit{3ai}–\textit{3ak}) in high yields and ee.

Reflecting on a possible mechanism for this enantioselective arylation process, our first impressions were that the reaction would operate as an arylative kinetic resolution process. On the basis of the formation of TPO \textit{3a}, its enantioselectivity, and the assumption of first-order kinetics, this arylative kinetic resolution displays a selectivity factor of 148. Although in principle the starting material should be produced with enantiomeric excess, we found that isolating the remaining starting material was not trivial. A deleterious oxidation process transforms the remaining SPO into the corresponding phosphinic acid derivative, which undergoes O-arylation to give the phosphinate. However, it was possible to isolate the small quantities of the remaining SPO, and we were surprised that this material was either racemic or displayed very low enantiomeric excess and hence was not consistent with a classical kinetic resolution. To probe this unusual finding, we conducted a series of control reactions. We tested the stability of enantioenriched SPO (\textit{−}-\textit{1c}) under a number of conditions related to the optimal process and were surprised to find that in all cases the remaining SPO was partially or fully racemized in the presence of any of the reaction components (Scheme 2a) and accompanied by significant amount of the corresponding aryl phosphinate. While this configurational instability of the SPO is contrary to most reports in the literature, we believe that racemization is the result of acid generated as a result of the deleterious oxidation pathway.

We also showed that the reaction of enantioenriched (\textit{−}-\textit{1c}) under standard conditions but without the chiral ligand gave a stereospecific arylation in moderate yield accompanied by oxidative arylation to racemic phosphinate \textit{5a} (Scheme 2b). Reaction of (\textit{−}-\textit{1c}) with (S,S)-4d-Cu(OTf)\textsubscript{2} leads to the productive, matched formation of the arylation product in high er. However, we were surprised to find that the supposed mismatched experiment (with (R,R)-4d-Cu(OTf)\textsubscript{2}) gave a similar yield and high er of the opposite enantiomer of the product, accompanied by the corresponding arylated phosphinate in low yield and enantioselectivity (Scheme 2c). We rationalize this observation on the basis that the starting enantioenriched SPO must be racemizing during the reaction\textsuperscript{11} to form quantities of the enantiomer that is matched to the catalyst being used, resulting in arylation to give the observed TPO enantiomer. Taken together, these experiments hinted at the opportunity for a dynamic kinetic resolution arylation of a racemic SPO, but all attempts to secure such a transformation have failed; clearly, the mechanism of this enantioselective arylation process is more complex than simply a kinetic resolution. Despite this, it is clear that the distinct Cu-catalyzed
Communication

arylation process provides an effective way to produce enantioenriched TPOs in excellent yield with very high enantiomeric excess.

We demonstrated the utility of these enantioenriched TPOs through further transformations of the P-chiral scaffold (Scheme 3). We carried out Suzuki cross-coupling of 3ak to form a chiral

Scheme 3. Transformations of TPOs

A phosphine oxide analogue of the S/X-Phos-type ligands that are ubiquitous in Pd-catalyzed transformations. The corresponding phosphines are more widely used in chemical synthesis. Therefore, we were pleased to find that the arylation process provides rapid access to a range of P-chiral phosphine−BH₄ adducts, providing potential opportunities for asymmetric metal-catalyzed transformations.

In summary, we have described a general and highly enantioselective route to access P-chiral tertiary phosphines via a Cu-catalyzed arylation process using readily available diaryliodonium salts. Although its mechanism remains unclear, this arylation process provides rapid access to a range of P-chiral phosphines that have great potential as ligands in catalytic enantioselective processes. Current studies are focused on elucidating the mechanism of this reaction and exploring the applications of the new ligand scaffolds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09334.

AUTHOR INFORMATION

Corresponding Author

*mg32@cam.ac.uk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the European Commission for a Marie Curie International Outgoing Fellowship (R.J.P.), the ERC (R.B.), the EPSRC, and the Royal Society (M.J.G.) for fellowships. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

REFERENCES

(1) (a) Tang, W.; Zhang, X. Chem. Rev. 2003, 103, 3029. (b) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. Chem. Rev. 2011, 111, 2119. (c) Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis; Kamer, P. C. J., van Leeuwen, P. W. N. M., Eds.; Wiley: Chichester, U.K., 2012. (d) Borner, A. Phosphorus Ligands in Asymmetric Catalysis; Wiley-VCH: Weinheim, 2008.

(2) (a) Horner, L.; Sieged, H.; Büthe, H. Angew. Chem., Int. Ed. Engl. 1968, 7, 942. (b) Knowles, W. S.; Sabacky, M. J. Chem. Commun. 1968, 22, 1445. (c) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauf, D. J. Am. Chem. Soc. 1977, 99, 5946.

(3) For recent examples, see: (a) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Manganur, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. J. Am. Chem. Soc. 2013, 135, 2474. (b) Rast, S.; Mohar, B.; Stephan, M. Org. Lett. 2014, 16, 2688. (c) Sieber, J. D.; Chenmannadavuni, D.; Fandrick, K. R.; Qu, B.; Han, Z. S.; Savoie, J; Ma, S.; Samankumar, L. P.; Grinberg, N.; Lee, H.; Song, J. J.; Senanayake, C. H. Org. Lett. 2014, 16, 5494. (d) For a general overview, see ref 1c.

(4) (a) Kovacík, I.; Wicht, D. K.; Grewal, N. S.; Glueck, D. S.; Incarvito, C. D.; Guzei, I. A.; Rheingold, A. L. Organometallics 2000, 19, 950. (b) Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. J. Am. Chem. Soc. 2016, 138, 7524. (c) Chan, V. S.; Chiu, M.; Bergman, R. G.; Toste, F. D. J. Am. Chem. Soc. 2009, 131, 6021.

(5) (a) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. J. Am. Chem. Soc. 2015, 137, 632. (g) Liu, L.; Zhang, A.-A.; Wang, Y.; Zhang, F.; Zuo, Z.; Zhao, W.-X.; Feng, C.-L.; Ma, W. Org. Lett. 2015, 17, 2046. (h) Sun, Y.; Cramer, N. Angew. Chem. Int. Ed. 2016, DOI: 10.1002/anie.201606637.

(6) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. Am. Chem. Soc. 2008, 130, 18172. (b) Phipps, R. J.; Gaunt, M. J. Science 2009, 323, 1593. (c) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. Am. Chem. Soc. 2012, 134, 10773. (d) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. Am. Chem. Soc. 2013, 135, 5332.

(7) (a) Bigot, A.; Williamson, A. E.; Gaunt, M. J. Am. Chem. Soc. 2011, 133, 13778. (b) Harvey, J. S.; Simonovitch, S. P.; Jamison, C. R.; MacMillan, D. W. C. J. Am. Chem. Soc. 2011, 133, 13782. (c) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. Am. Chem. Soc. 2015, 137, 7986.

(8) Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y. J. Org. Chem. 2013, 78, 8176. (9) The X-ray structure of 3r confirmed the absolute stereochemistry.

(10) (a) Vedejs, E.; Donde, Y. J. Am. Chem. Soc. 1997, 119, 9293. (b) Moncarz, J. R.; Brunker, T. J.; Jevett, J. C.; Orchowski, M.; Glueck, D. S.; Sommer, R. D.; Lam, K.-C.; Incarvito, C. D.; Concolino, T. E.; Ceccharelli, C.; Zakharov, L. N.; Rheingold, A. L. Organometallics 2003, 22, 3205. Also see ref 2c.

(11) A similar acid-promoted racemization has been reported. See: Xu, Q.; Zhao, C.-Q.; Han, L.-B. J. Am. Chem. Soc. 2008, 130, 12648.

(12) (a) Surry, D. S.; Buchwald, S. L. Angew. Chem., Int. Ed. 2008, 47, 6338. (b) Martin, R.; Buchwald, S. L. Acc. Chem. Res. 2008, 41, 1461.

(13) Benaglia, M.; Rossi, S. Org. Biomol. Chem. 2010, 8, 5824.