Chiral phosphorus compounds by catalytic asymmetric C–P coupling

Phosphorus compounds with unique chirality due to the presence of a P-stereocentre are obtained through stereoselective catalytic cross-coupling of phosphoramidites and aryl halides. Axial-to-central transfer of chirality is shown to provide ready access to various classes of P-chirogenic compounds that are key to catalysis and drug development.

This is a summary of:
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The problem

Chiral phosphorus compounds, such as phosphonates and phosphines, are widely used in materials science[1], agrochemistry[2], drug development[3], oligonucleotide synthesis[4] and as ligands for metal-based catalysis[5]. A prominent example of such compounds is Remdesivir, a broad-spectrum antiviral drug that features a phosphorus stereocentre and has gained considerable interest during the COVID–19 pandemic. However, despite the importance of chiral phosphorus compounds, a major disadvantage to their use is that expensive and complicated synthetic routes are needed to access them and stereoselectivity is often poor. The main reason for this disadvantage is a lack of methodology for the synthesis of phosphorus compounds in which the chirality at the phosphorus atom can be readily controlled during carbon–phosphorus (C–P) bond formation. Indeed, in many metal-catalysed C–P coupling reactions, the level of stereocontrol is typically insufficient for practical use.

The solution

We developed a general strategy for preparing chiral phosphorus compounds that have a stereocentre at the phosphorus atom, so called P-chirogenic phosphorus compounds (Fig. 1). Specifically, we used readily accessible, axially chiral 1,1′-bi-2-naphthol (BINOL)-based phosphoramidites and aryl halides or triflates as starting materials, and Pd-catalysed cross-coupling for asymmetric C–P bond formation.

Key to the success of our approach is the axial-to-central transfer of chirality from the BINOL structure to the phosphorus atom during the catalytic cross-coupling event. We discovered that the C–P bond formation shows high chemoselectivity with a variety of aryl halides and excellent stereocontrol in the formation of the new phosphorus stereocentre, which is attributed to the fixed stereochemistry of the BINOL unit. We also discovered the involvement of a unique chiral aminophosphonium salt in this transformation. The ready access to both mirror image forms (enantiomers) of the starting material and the easy recycling of the BINOL auxiliary group adds to the practicality of our method for generating P-chirogenic phosphorus compounds.

Importantly, we found that a range of P-chirogenic phosphorus compounds and their derivatives can be synthesized as virtually single enantiomers. Pure enantiomers are essential, for instance, as chiral ligands and for drug discovery. Our catalytic asymmetric C–P coupling methodology allows the formation of a variety of structures with a high tolerance of different functional groups in the products. The flexibility of the method is demonstrated by the fact that distinct stereoisomers of chiral phosphorus compounds can be formed by simply changing the order of steps in the synthetic sequence.

The implications

We have developed a general, divergent and highly stereoselective route for synthesizing phosphorus compounds with a P-stereocentre. In particular, the easy access to this route provides a variety of homochiral phosphines and opens up many avenues for metal-catalysed asymmetric transformations. The majority of chiral phosphines currently used as ligands in asymmetric metal-catalysed transformations are axial-chiral, planar-chiral or C-stereogenic phosphines. Now, by applying the methodology we have developed, the unique stereochemistry of P-chirogenic ligands can be readily explored. The limitation of our work is that so far only aryl halides or triflates have been used for asymmetric C–P coupling, and alternative coupling partners now need to be explored. The chiral aminophosphonium salts we discovered have potential as new classes of phase-transfer catalysts or organocatalysts for asymmetric transformations, although this still needs to be explored experimentally. The versatility and flexibility of the intermediate products that are produced after the initial asymmetric C–P coupling, provide an opportunity as starting material for the generation of other important classes of chiral phosphorus compounds, in particular phosphonamidates and phosphonates that are key for agrochemical and pharmaceutical applications.

Ben L. Feringa and Anirban Mondal
Stratingh Institute for Chemistry, University of Groningen, Groningen, The Netherlands.

EXPERT OPINION

"The ability to prepare chiral-at-phosphine ligands, as presented in this manuscript, offers access to ligands that the field previously could not easily consider for the development of enantioselective reactions. The synthetic strategy is elegant, offering a straightforward and robust approach to accessing highly enantioenriched monophosphines." **Mary Watson, University of Delaware, Newark, DE, USA**.

FIGURE

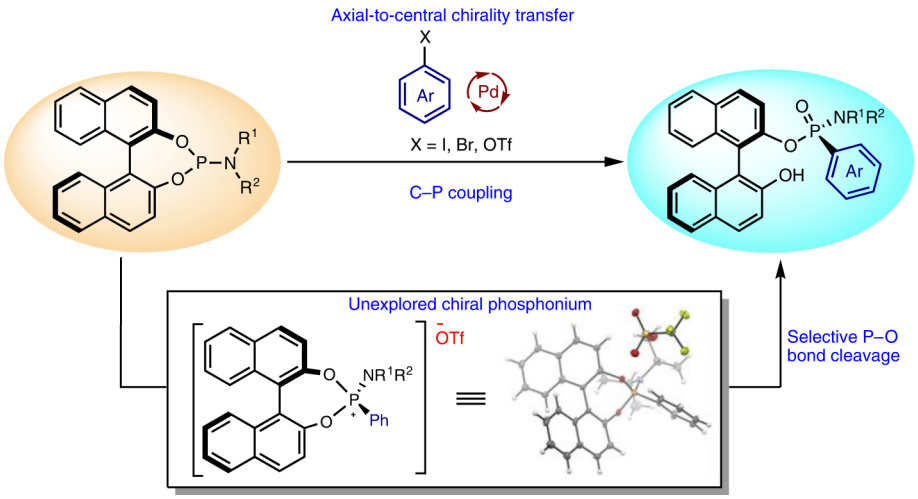

Fig. 1 | Stereoselective C–P coupling of a phosphoramidite and an aryl halide or triflate to produce useful P-chiral compounds. Palladium-catalysed C–P cross-coupling of a phosphoramidite with an aryl halide or triflate (OTf) is shown. Axial-to-central chirality was transferred from BINOL to the P centre of the newly formed P-chirogenic compound. The chiral aminophosphonium salt was found to be an unexplored phosphonium intermediate in this C–P coupling process. The product of C–P cross-coupling can then undergo various transformations to yield useful P-chirogenic compounds. Credit: © 2021, Mondal, A. et al.

BEHIND THE PAPER

When we first developed phosphoramidites as ligands in 1996, we were intrigued by their excellent stereocontrol in copper-catalysed C–C bond formation[5], which led to a breakthrough in catalytic asymmetric conjugate addition. As phosphoramidites found use in industry, we imagined utilizing them, given their unique chiral properties, as starting reagents for asymmetric transformations. Traditionally, an external chiral ligand is used for chiral induction in a C–P coupling reaction, but the competitive coordination of initial and final phosphorus compounds with the metal catalysts, together with an external chiral ligand, reduces the enantioselectivity. As BINOL-containing phosphoramidites have the properties of an intrinsic chiral ligand and simultaneously can serve as a substrate, we hypothesized that they would increase stereoselectivity in C–P coupling processes with aryl compounds, and were delighted when our data confirmed that they did. **B.L.F.**

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FROM THE EDITOR

"There are several intriguing elements in this work: broad applicability and high flexibility of the phosphorous derivatives and synthetic steps, in addition to a smart approach for chirality transfer from the cheap and readily available BINOL. These features add to the practicality of the protocol for accessing important chiral phosphorus compounds, and both academia and industry may benefit from this synthetic approach." **Editorial Team, *Nature Catalysis***