Title: Enantioselective remote C-H activation directed by a chiral cation

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Abstract: Chiral cations have been used extensively as organocatalysts but their application to rendering transition metal catalyzed processes enantioselective remains rare. This is despite the success of the analogous charge-inverted strategy in which cationic metal complexes are paired with chiral anions. We report here a strategy to render a common bipyridine ligand anionic and pair its iridium complexes with a chiral cation derived from quinine. We have applied these ion-paired complexes to long-range asymmetric induction in the desymmetrization of the geminal diaryl motif, located on a carbon or phosphorus center, by enantioselective C-H borylation. In principle, numerous common classes of ligand could likewise be amenable to this approach.

One Sentence Summary: Chiral cations are used to induce asymmetry in a challenging, long-range, transition metal-catalyzed C-H activation reaction.

Main Text:

Ion-pairing has been put to extensive use as a key design feature in the field of asymmetric catalysis (*1*). In the 1980s, pioneering studies on enantioselective phase-transfer catalysis paired a chiral cation with a reactive anionic intermediate in the enantiodetermining transition state (*2*), with cinchona alkaloid-derived cations dominating as effective and readily-accessible scaffolds (*3*). The numerous subsequent developments in this area have had enormous impact in the field of asymmetric organocatalysis, encapsulating such important transformations as Michael and aldol additions, as well as Mannich, fluorination, alkylation, and oxidative cyclization reactions, to name but a few (*4-7*) (Figure 1A, left panel). Over the last decade, the inverse strategy of using a chiral anion to associate with a cationic reaction intermediate has also proven extremely successful (*1*, *8*, *9*). This latter strategy has been effective not only in an organocatalytic context (*10*, *11*) but also in powerful combination with transition metal catalysts (*12-14*), cleverly capitalizing on the relatively common occurrence of cationic transition metal complexes in catalytic cycles. In contrast, it is far rarer to encounter anionic transition metal complexes as key intermediates. As such, the charge-inverted approach of pairing a chiral cation with an anionic transition metal catalyst has only been demonstrated in a handful of pioneering cases, notably asymmetric oxidation reactions involving anionic diphosphatobisperoxotungstate (*15*) and peroxomolybdate (*16*) complexes as catalysts (Figure 1A, center panel) (*17-21*). Due to this scarcity of anionic metal complexes in the most commonly employed processes, the broader potential of uniting chiral cations with the versatile reactivity of transition metals has remained underexplored, despite the obvious potential presented by several privileged classes of chiral cation. Given the success of these motifs as chiral controllers in asymmetric organocatalysis (*vide supra*), a general strategy to integrate them with transition metal catalysis would likely have broad impact in the field of asymmetric catalysis.

In an important advance, which compellingly demonstrates this potential, Ooi and co-workers incorporated a chiral cation covalently into the structure of a phosphine ligand, resulting in highly stereocontrolled formation of contiguous all-carbon quaternary stereocenters under palladium catalysis (Fig. 1A, right panel) (*22, 23*). At the outset of this project, we envisioned a potentially more generally applicable approach whereby an anionic handle is incorporated into a common ligand scaffold, providing the key point-of-interaction with the chiral cation (Fig. 1B). Judicious placement of this anionic group would be crucial to success – not close enough to the metal center to disrupt reactivity, but not so far that the chiral environment imparted by the cation would be ineffective. Various chiral cations could be introduced in the final step by simple ion exchange, allowing for rapid catalyst optimization. In pioneering work, Ooi and co-workers have previously demonstrated the productive combination of cationic ligands with chiral anions, as demonstrated effectively in enantioselective allylic alkylation (*24*, *25*). We envisaged that, in principle, a wide variety of privileged ligand scaffolds for transition metal catalysis could be rendered anionic, creating exciting opportunities to explore the use of chiral cations as chiral controllers in a wealth of powerful transition metal catalyzed reactions.

In seeking a rigorous and relevant test of the above-described approach, we targeted a transformation that lies at the cutting edge of what is currently possible in enantioselective catalysis. Whilst enantioselective, desymmetrizing C-H activation of arenes has been extensively explored with palladium (*26, 27*), rhodium (*28, 29*) and iridium (*30, 31*) catalysis, all but a single case functionalize at the arene *ortho* position (*32*). Only very recently did Yu and co-workers achieve enantioselective desymmetrization through direct arylation at the arene *meta* position (Figure 1, C) (*33*), taking advantage of an ingenious relay strategy via the *ortho* position, although relatively high loadings of the chiral norbornene mediator (**CTM**, 20-50 mol%) were required. C-H borylation reactions have the useful attribute that the new C-B bond can undergo numerous diverse transformations (*34, 35*), but so far enantiocontrol in arene borylation has been realized only in two recent reports, from Shi, Hartwig and co-workers (*30*) and Xu, Ke and co-workers (*31*). In both cases the chiral information is covalently incorporated into the ligand scaffold in the conventional manner and a directing group guides borylation to the *ortho* position. In contrast, the creation of chirality over long ranges, where the enantiotopic site is far from the new stereocenter, is an outstanding challenge in which catalyst designs that incorporate non-covalent interactions offer unique opportunities (*36-38*).

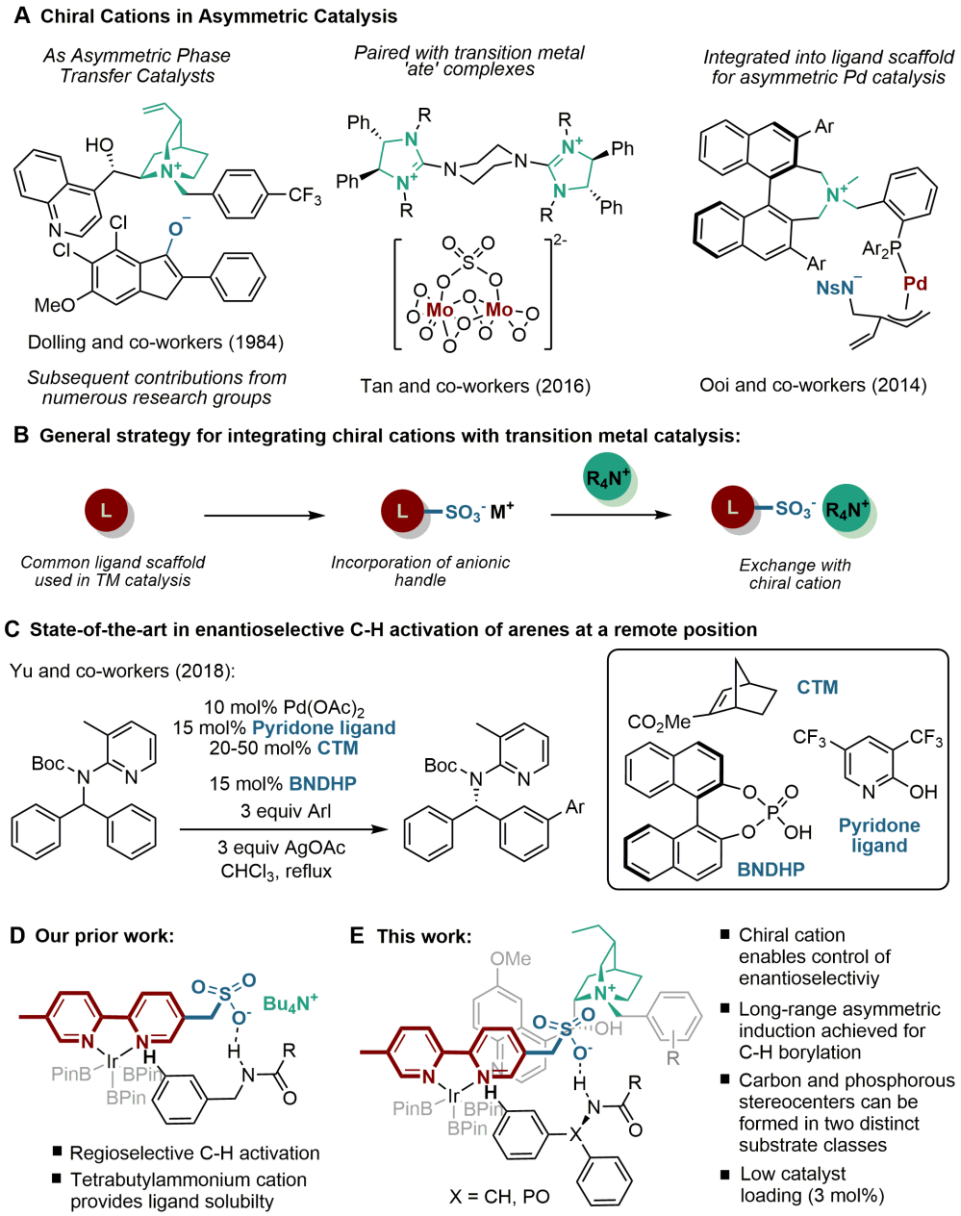

Fig. 1. Strategy for incorporating chiral cations with transition metals. (**A**) Applications of chiral cations in asymmetric catalysis. (**B**) General strategy for integration of transition metal catalysis with chiral cations. **(C)** State-of-the-art in enantioselective remote C-H activation of arenes. (**D**) Our prior work controlling regioselectivity in arene borylation. (**E**) Summary of this work.

We have recently developed anionic bipyridine ligands that bear a remote sulfonate group in order to impart control of regioselectivity in iridium-catalyzed C-H borylation via non-covalent interactions with the substrate (*39-41*). Throughout these studies, a single ligand scaffold consistently gave the optimal regiocontrol. In one particular study, we attributed the high regioselectivity for borylation at the arene *meta* position to the existence of a hydrogen bond between the substrate and the sulfonate group of the ligand in the regiodetermining transition state for C-H activation (Fig 1D) (*40*). We hypothesized that exchange of the achiral tetrabutylammonium counterion of the ligand for a chiral cation might allow enantioselective,

desymmetrizing C-H activation in a prochiral substrate (as in Fig. 1E). Herein we demonstrate that, using this approach, remote, enantioselective C-H borylation can be achieved for formation of chiral-at-carbon and chiral-at-phosphorous compounds, showcasing the thus far unexplored approach of combining a chiral cation with an anionic ligand for a reactive transition metal.

We commenced our studies with symmetrical benzhydrylamide **2a** (Fig. 2A). Numerous ion-paired ligands **L·1,** possessing a variety of chiral cations **1a**–**1i,** could be readily obtained through counterion exchange. The chiral cations were all derived from dihydroquinine (DHQ) with varying *N*-benzyl substitution. At room temperature in tetrahydrofuran (THF) as solvent, low but encouraging levels of enantioselectivity were obtained with 3,5-di-*tert*butyl and 3,5-dimethoxy benzyl groups (**L·1a** and **L·1b**, 31 and 30% ee). We next investigated placing substituted aromatic rings at the 3- and 5- positions of the quaternizing *N*-benzyl group. Encouragingly, **L·1c** (4-$CF_3C_6H_4$) gave increased enantioselectivity (39% *ee*) and **L·1d** (3,4,5-$F_3C_6H_2$) resulted in a further improvements (52% *ee*). Focusing attention on the *meta* positions of the outer arenes of the teraryl system, we then evaluated a series of substituents (**L·1e** - **L·1i**). Trifluoromethyl (**L·1e**) and methoxy (**L·1f**) substitution again gave increases (both 60% *ee*), but the biggest gain came from the *tert*-butyl substituted **L·1g** (73% *ee*). At this point we investigated aryl groups in these positions to extend the reach even further, but both of these proved detrimental (**L·1h** and **L·1i**). Thus, we shifted our attention to other reaction parameters with **L·1g**. A solvent evaluation identified cyclopentyl methyl ether (CPME) and as being optimal in that the reaction temperature could be reduced to -10 ^oC whilst high reactivity was maintained, resulting in isolation of **3a** in 72% yield and with 96% ee, following oxidation to the corresponding phenol with H_2O_2 (see inset box). This derivatization aided separation from any remaining starting material or difunctionalized material. The undesired borylation of monoborylated **3a'** to give a symmetrical diborylated byproduct did occur to varying degrees in the reactions, being unavoidable at higher conversions. We thus carried out careful experiments to establish whether kinetic resolution may be occurring in such instances, resulting in possible enhancement of the observed ee of **3a'** at the end of the reaction. Evaluating ee of **3a'** at various levels of conversion as well as submitting racemic **3a'** to the enantioselective borylation conditions with **L·1g** showed that there is no appreciable kinetic resolution occurring (Figs. S1 and S2). Finally, we evaluated a ligand paired with a Maruoka-type chiral cation which gave racemic product, a variant of **L·1g** in which the quinine hydroxyl group is methylated, which gave a reduced *ee* of 72%, and a variant of **L·1g** in which the stereochemistry of the quinine hydroxyl group is inverted, which gave only 11% *ee* (see Supplementary Materials, Table S1 for full optimization details). A survey of *N*-protecting groups under the optimized conditions demonstrated that trifluoroacetyl is optimal, although acetyl also performed well (Fig. S3).

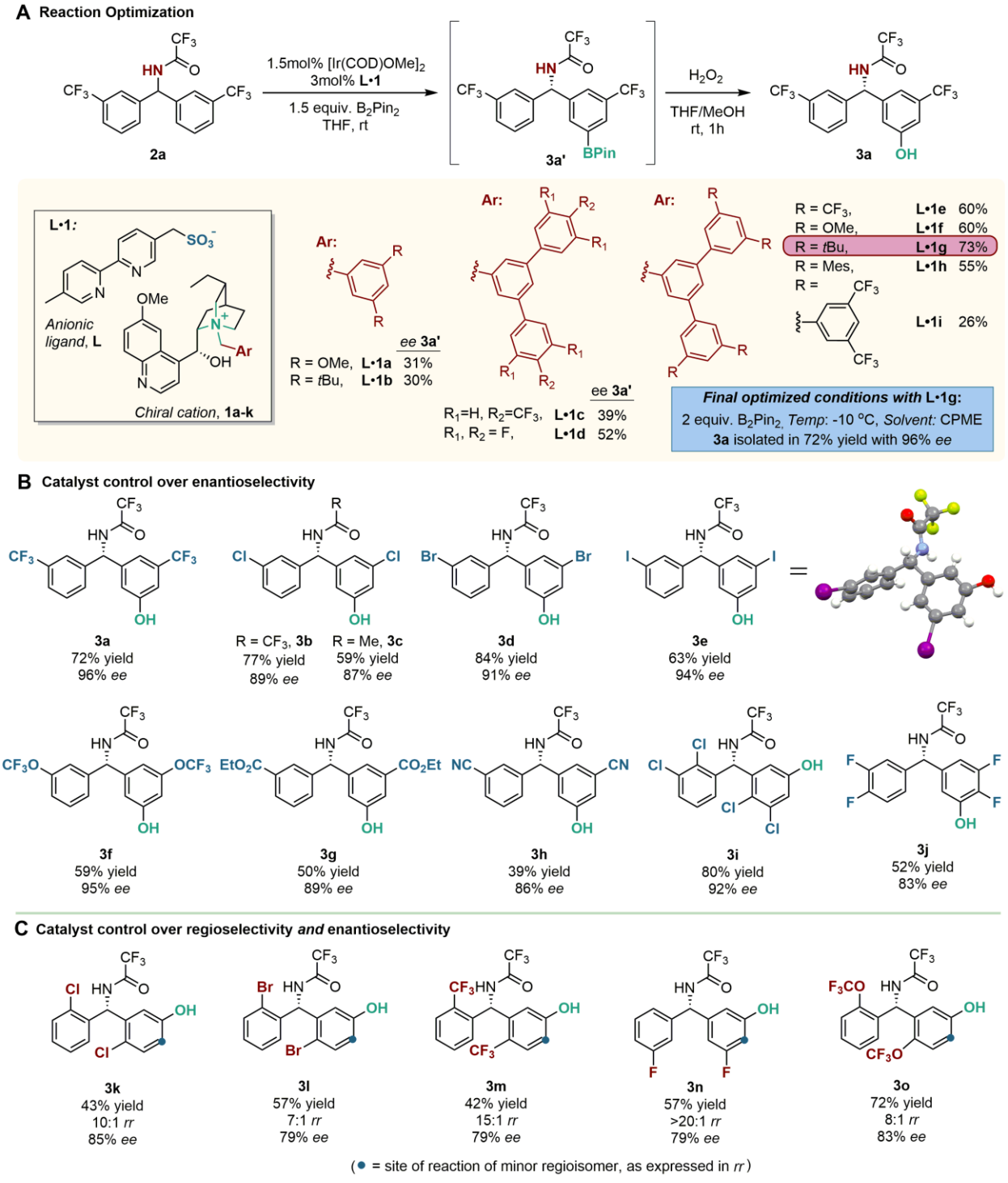

Fig. 2. Enantioselective desymmetrizing C-H borylation of benzhydrylamides. (**A**) Reaction optimization. (**B**) Scope of enantioselective borylation using **L·1g** in substrates bearing no regioselectivity challenge. (**C**) Examples in which catalyst is controlling regioselectivity and enantioselectivity. Yield values refer to isolated yields. Regioisomeric ratios (*rr*) were

determined from the crude ^{1}H-NMR spectrum prior to isolation. Enantiomeric excesses (*ee*) determined by chiral HPLC or SFC analysis.

We proceeded to examine the scope of the reaction in terms of versatile substituents on the substrate aryl rings (Fig. 2B). Post-reaction derivatization of the BPin facilitated purification and we used oxidation with hydrogen peroxide to give the corresponding phenols. We were pleased to find that halide substitution was very well tolerated in the enantioselective borylation. Chloro- (**3b**), bromo- (**3d**) and iodo- (**3e**) substituted arenes all delivered excellent levels of enantioselectivity, the latter being of particular note as it would likely be incompatible with palladium catalysis and is a testament to the mild conditions and functional group tolerance of iridium-catalyzed borylation. The *N*-trifluoroacetyl group could be replaced by acetyl with little drop in *ee*, as demonstrated on substrate **3c**. The absolute stereochemistry of compound **3e** was determined by x-ray crystallographic analysis and all other compounds were assigned by analogy with this. Further variation of substituents revealed that trifluoromethoxy (**3f**), ester (**3g**) and nitrile (**3h**) were all well-accommodated at the 3-position of the substrates. We also examined vicinally dichlorinated (**3i**) and difluorinated (**3j**) substrates, which both worked effectively. Substrates bearing electron donating substituents exhibited lower reactivity under our conditions – 3-methoxy gave no conversion and 3-methyl gave <5% conversion, likely due to the reaction temperatures being lower than those typically used in C-H borylation. Performing the reactions at room temperature gave conversion, but with moderate enantioselectivity (Fig. S4). The substrates examined so far have all presented no regioselectivity challenge, due to the well-established preference for C-H borylation at the least hindered arene position (*42*). Given that the sulfonated bipyridine ligand scaffold was originally designed for the purpose of controlling regioselectivity in substrates that would typically be non-selective, we were keen to evaluate whether **L·1g** would be able to control both of these important selectivity factors for a substrate that possessed *ortho*-substituted aromatic rings (Fig. 2C) (*40*). We were concerned that the introduction of *ortho* substituents may significantly change the preferred substrate conformation, potentially impacting on crucial interactions with the chiral cation. Also, it was possible that the complex chiral cation might disrupt the regioselectivity that we had previously observed when using tetrabutylammonium as cation. However, we were delighted to find that an *ortho*-chloro substrate gave the *meta*-borylated product **3k** with excellent regioselectivity (10:1 *rr*) and only a small reduction in enantioselectivity (85% *ee*). In contrast to this, the control borylation with standard borylation ligand **dtbpy** resulted in a 1.6:1 ratio of regioisomers (Fig. S5). An *ortho*-bromo substrate performed similarly (**3l**), as did an *ortho*-CF_3 (**3m**) and *ortho*-OCF_3 (**3o**). We also examined a *meta*-fluoro substrate which presents regioselectivity challenges using standard ligands due to the small size of the fluorine atom (*42*), but with **L·1g** high regioselectivity was observed (**3n**). In addition, we carried out preliminary experiments with non-symmetrical substrates to assess the viability of using the reaction in kinetic resolution mode. These showed that it is indeed viable, although further investigations and optimization are likely required to enable this to be a general procedure (Fig. S6).

At this stage, we envisaged that a compelling demonstration of the potential of this approach would be to successfully apply it to a different class of compound entirely. For this purpose, we identified symmetrical diarylphosphinamides which contain a prochiral, configurationally stable phosphorous atom at the heart of the compound. We reasoned that such substrates would test our chiral cation directed C-H borylation strategy in tackling an additional prominent challenge to synthetic chemists – that of how to synthesize *P*-chiral compounds in a catalytic asymmetric manner (*43*). Whilst there are several recently reported methods for

enantioselective desymmetrizing C-H activation of phosphinamides using chiral Pd and Rh complexes, both result in *ortho*-functionalized products (*44*, *45*). Given the broad utility of *P*-chiral compounds in catalysis as well as increasingly in medicinal chemistry, we envisaged that remote desymmetrization would be of substantial practical utility (*46*). We were pleased to observe that a symmetrical phosphinamide, bearing a *para*-methoxy phenyl group on the phosphinamide nitrogen, was borylated to give **3p** with 90% *ee* using ligand **L·1g**, which had been optimal for the benzhydrylamide substrate class (Fig. 3). X-ray crystallographic analysis of **3p** showed that this product had analogous absolute stereochemistry to that obtained in the amide series, relative to the position of the NH hydrogen bond donor. Experiments stopped at various conversions demonstrated that secondary kinetic resolution to form diborylated product is not contributing to the observed high enantioselectivity (Fig. S7). *N*-substitution was found not to be limited to aromatic moieties, as demonstrated by *N*-*tert*-butyl substituted **3q** (95% ee). As in the amide substrate class, a variety of useful functional groups were tolerated on the aromatic ring, encompassing bromide (**3r**), ester (**3s**), iodide (**3t**), trifluoromethoxy (**3u**), trifluoromethyl (**3v**) and nitrile (**3w**). In some cases, yields are modest due to poor substrate solubility under the reaction conditions (as in **3s**). There are numerous established avenues for the manipulation of the phosphinamide functional group in a stereospecific manner, such as to tertiary phosphine oxides, which have been amply demonstrated elsewhere (*44*). To test whether the catalyst may be able to influence both regioselectivity and enantioselectivity in this substrate class we tested an *ortho*-substituted symmetrical phosphinamide but found that both outcomes were poor (Fig. S8). We speculate that this may arise due to the *ortho*-substituted aromatic ring and bulky nature of the quaternary phosphorous center, relative to the benzhydrylamide, having a conformational impact on the substrate that adversely affects crucial substrate-ligand interactions.

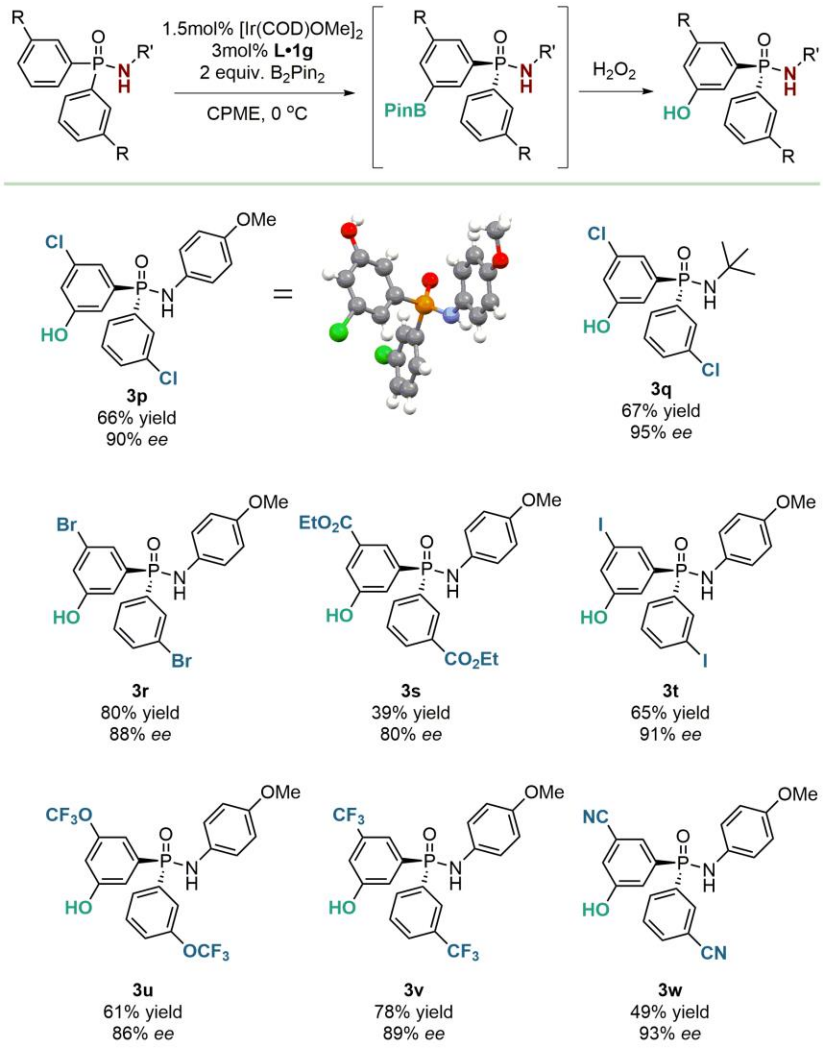

Fig. 3. Substrate scope of the enantioselective C-H borylation of diaryl phosphinamides. Yield values refer to isolated yields.

For both classes of compounds demonstrated, the C-H borylation products typically possess three versatile functional groups on the aromatic rings for further elaboration into complex scaffolds, at the heart of which lies the newly formed stereocenter. By virtue of the desymmetrization strategy employed, two of these functional groups must necessarily be identical and we sought to demonstrate that site-selectivity between these in the product should be possible in many instances by electronic differentiation arising from introduction of the new substituent. In the first example, we carried out borylation and oxidation of dichloride **2b** to give the phenol **3b** with good yield and high enantioselectivity (Fig 4A, upper scheme). By carrying out Suzuki-Miyaura coupling on **3b** in the presence of one equivalent of tetrabutylammonium hydroxide, we were able to achieve >20:1 site selectivity for cross-coupling on the non-phenolic aromatic ring. We anticipate that this is a result of the highly electron-rich nature of the *in situ* generated phenolate disfavoring oxidative addition to the C-Cl bond on the same ring. In the second case, we carried out borylation of diester **2g** followed by cyanation to obtain **6** (Fig 4A, lower scheme)(*47*). Careful treatment of **6** with NaOH selectively hydrolyzed the ester on the same ring as the nitrile

due to electronic factors that can be readily rationalized and predicted using substituent Hammett parameters (*48*), giving **7** in >20:1 *rr* after amide coupling.

To emphasize the practicality of our process, we demonstrated borylation using ligand **L·1j**, possessing a diastereomeric chiral cation derived from quinidine, the pseudoenantiomer of quinine. This proceeded smoothly giving *(R)*-**3a** with 90% *ee* (Fig. 4B). Next, we performed experiments to probe the hydrogen bonding interaction of substrate with ligand. The *N*-methylated variant (**2x**) of successful substrate **2d** underwent no borylation under the optimized conditions at -10 ^{o}C and the temperature had to be raised to +10 ^{o}C to obtain product, which was found to have only 8% *ee* (Fig. 4C). This outcome highlights the importance of the hydrogen bond donor in the substrate for both reactivity and selectivity, in line with our initial hypothesis (Fig. 1E). We also performed an experiment in which ion-paired ligand **L·1g** was replaced with neutral 5,5'dimethylbipyridine (**8**) together with the optimal chiral cation as its bromide salt (**Br·1g**). The product was racemic, demonstrating the requirement for ligand and chiral cation to be associated to achieve enantioinduction. We also ran a reaction in which ligand **L·NBu$_4$**, bearing achiral tetrabutylammonium as cation, was used in conjunction with **Br·1g**. In this case, 58% *ee* was obtained in the product, consistent with some degree of counterion exchange occurring between the two, leading to moderate enantioinduction.

We have demonstrated a strategy for pairing privileged chiral cations with an iridium-bipyridine complex, enabled by substitution of an anionic sulfonate group to the ligand scaffold. In principle, numerous widely-used transition metal catalyzed reactions could be amenable to this approach, as evidenced by the numerous common ligand classes that have been sulfonated for the purpose of engendering water solubility (*49*). We anticipate that wider incorporation of chiral cations into mainstream transition metal catalysis could have broad implications in asymmetric organic synthesis.

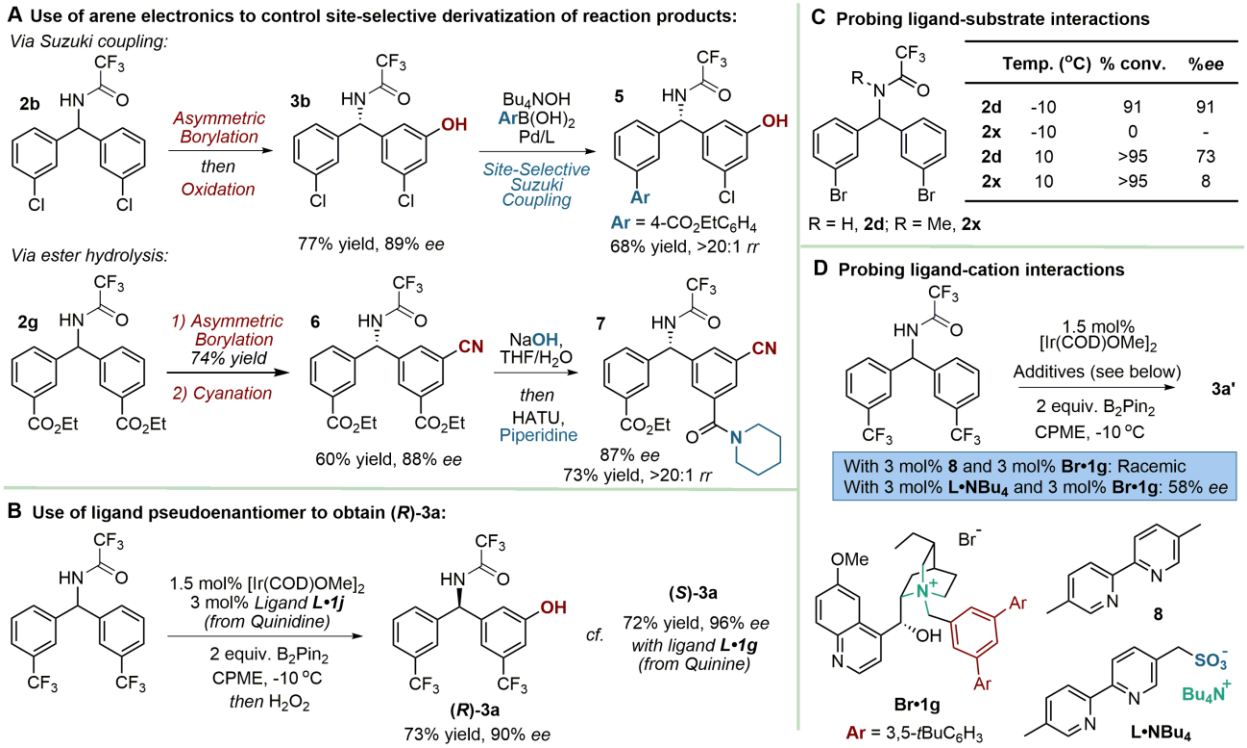

Fig. 4. Product elaboration and further experiments. (A) Use of arene electronics to control site-selective derivatization of reaction products. HATU, hexafluorophosphate azabenzotriazole tetramethyl uronium. **(B)** Use of a pseudoenantiomeric chiral cation to form *(R)*-**3a**. **(C)** Control experiments to probe ligand-substrate interactions. **(D)** Control experiments to probe ligand-cation interactions. Yield values refer to isolated yields

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Supplementary Materials:

Materials and Methods

Tables S1 to S2

Figures S1 to S8

HPLC and SFC Traces

NMR Spectra

References (*50-64*)

References

1. K. Brak, E. N. Jacobsen, Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.* **52**, 534-561 (2013).
2. U. H. Dolling, P. Davis, E. J. J. Grabowski, Efficient catalytic asymmetric alkylations. 1. Enantioselective synthesis of (+)-indacrinone via chiral phase-transfer catalysis. *J. Am. Chem. Soc.* **106**, 446-447 (1984).
3. in *Cinchona Alkaloids in Synthesis and Catalysis*, C. E. Song, Ed. (Wiley, 2009).
4. T. Ooi, K. Maruoka, Recent Advances in Asymmetric Phase-Transfer Catalysis. *Angew. Chem. Int. Ed.* **46**, 4222-4266 (2007).
5. S. Shirakawa, K. Maruoka, Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem. Int. Ed.* **52**, 4312-4348 (2013).
6. M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, Quaternary Ammonium (Hypo)iodite Catalysis for Enantioselective Oxidative Cycloetherification. *Science* **328**, 1376-1379 (2010).
7. M. T. Oliveira, J.-W. Lee, Asymmetric Cation-Binding Catalysis. *ChemCatChem* **9**, 377-384 (2017).
8. R. J. Phipps, G. L. Hamilton, F. D. Toste, The progression of chiral anions from concepts to applications in asymmetric catalysis. *Nat. Chem.* **4**, 603-614 (2012).
9. M. Mahlau, B. List, Asymmetric Counteranion-Directed Catalysis: Concept, Definition, and Applications. *Angew. Chem. Int. Ed.* **52**, 518-533 (2013).
10. S. Mayer, B. List, Asymmetric Counteranion-Directed Catalysis. *Angew. Chem. Int. Ed.* **45**, 4193-4195 (2006).
11. G. L. Hamilton, T. Kanai, F. D. Toste, Chiral Anion-Mediated Asymmetric Ring Opening of meso-Aziridinium and Episulfonium Ions. *J. Am. Chem. Soc.* **130**, 14984-14986 (2008).
12. G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, A Powerful Chiral Counterion Strategy for Asymmetric Transition Metal Catalysis. *Science* **317**, 496-499 (2007).
13. S. Mukherjee, B. List, Chiral Counteranions in Asymmetric Transition-Metal Catalysis: Highly Enantioselective Pd/Brønsted Acid-Catalyzed Direct α-Allylation of Aldehydes. *J. Am. Chem. Soc.* **129**, 11336-11337 (2007).
14. S. Liao, B. List, Asymmetric Counteranion-Directed Transition-Metal Catalysis: Enantioselective Epoxidation of Alkenes with Manganese(III) Salen Phosphate Complexes. *Angew. Chem. Int. Ed.* **49**, 628-631 (2010).
15. X. Ye *et al.*, Enantioselective Sulfoxidation Catalyzed by a Bisguanidinium Diphosphatobisperoxotungstate Ion Pair. *Angew. Chem. Int. Ed.* **55**, 7101-7105 (2016).

16. L. Zong *et al.*, Bisguanidinium dinuclear oxodiperoxomolybdosulfate ion pair-catalyzed enantioselective sulfoxidation. *Nature Commun.* **7**, 13455 (2016).
17. R. C. D. Brown, J. F. Keily, Asymmetric Permanganate-Promoted Oxidative Cyclization of 1,5-Dienes by Using Chiral Phase-Transfer Catalysis. *Angew. Chem. Int. Ed.* **40**, 4496-4498 (2001).
18. C. Wang, L. Zong, C.-H. Tan, Enantioselective Oxidation of Alkenes with Potassium Permanganate Catalyzed by Chiral Dicationic Bisguanidinium. *J. Am. Chem. Soc.* **137**, 10677-10682 (2015).
19. L. Zong, C.-H. Tan, Phase-Transfer and Ion-Pairing Catalysis of Pentanidiums and Bisguanidiniums. *Acc. Chem. Res.* **50**, 842-856 (2017).
20. S. Paria, H.-J. Lee, K. Maruoka, Enantioselective Alkynylation of Isatin Derivatives Using a Chiral Phase-Transfer/Transition-Metal Hybrid Catalyst System. *ACS Catal.* **9**, 2395-2399 (2019).
21. K. Ohmatsu, T. Ooi, Cationic Organic Catalysts or Ligands in Concert with Metal Catalysts. *Topics Curr. Chem.* **377**, 31 (2019).
22. K. Ohmatsu, N. Imagawa, T. Ooi, Ligand-enabled multiple absolute stereocontrol in metal-catalysed cycloaddition for construction of contiguous all-carbon quaternary stereocentres. *Nature Chem.* **6**, 47-51 (2014).
23. K. Ohmatsu, S. Kawai, N. Imagawa, T. Ooi, Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of 5-Vinyloxazolidinones with Imines Using Chiral Ammonium-Phosphine Hybrid Ligand. *ACS Catal.* **4**, 4304-4306 (2014).
24. K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, Ion-paired chiral ligands for asymmetric palladium catalysis. *Nature Chem.* **4**, 473-477 (2012).
25. K. Ohmatsu, M. Ito, T. Kunieda, T. Ooi, Exploiting the Modularity of Ion-Paired Chiral Ligands for Palladium-Catalyzed Enantioselective Allylation of Benzofuran-2(3H)-ones. *J. Am. Chem. Soc.* **135**, 590-593 (2013).
26. X.-F. Cheng *et al.*, Pd(II)-Catalyzed Enantioselective C–H Activation/C–O Bond Formation: Synthesis of Chiral Benzofuranones. *J. Am. Chem. Soc.* **135**, 1236-1239 (2013).
27. L. Chu, K.-J. Xiao, J.-Q. Yu, Room-temperature enantioselective C–H iodination via kinetic resolution. *Science* **346**, 451-455 (2014).
28. B. Ye, N. Cramer, Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C–H Functionalization. *Science* **338**, 504-506 (2012).
29. B. Ye, N. Cramer, Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C–H Functionalizations. *Acc. Chem. Res.* **48**, 1308-1318 (2015).
30. B. Su, T.-G. Zhou, P.-L. Xu, Z.-J. Shi, J. F. Hartwig, Enantioselective Borylation of Aromatic C−H Bonds with Chiral Dinitrogen Ligands. *Angew. Chem. Int. Ed.* **56**, 7205-7208 (2017).
31. X. Zou *et al.*, Chiral Bidentate Boryl Ligand Enabled Iridium-Catalyzed Asymmetric C(sp2)–H Borylation of Diarylmethylamines. *J. Am. Chem. Soc.* **141**, 5334-5342 (2019).
32. C. G. Newton, S.-G. Wang, C. C. Oliveira, N. Cramer, Catalytic Enantioselective Transformations Involving C–H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **117**, 8908-8976 (2017).
33. H. Shi, A. N. Herron, Y. Shao, Q. Shao, J.-Q. Yu, Enantioselective remote meta-C–H arylation and alkylation via a chiral transient mediator. *Nature* **558**, 581-585 (2018).

34. J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, M. R. Smith, Remarkably Selective Iridium Catalysts for the Elaboration of Aromatic C-H Bonds. *Science* **295**, 305-308 (2002).
35. T. Ishiyama *et al.*, Mild Iridium-Catalyzed Borylation of Arenes. High Turnover Numbers, Room Temperature Reactions, and Isolation of a Potential Intermediate. *J. Am. Chem. Soc.* **124**, 390-391 (2002).
36. B. Kim *et al.*, Distal Stereocontrol Using Guanidinylated Peptides as Multifunctional Ligands: Desymmetrization of Diarylmethanes via Ullman Cross-Coupling. *J. Am. Chem. Soc.* **138**, 7939-7945 (2016).
37. A. J. Metrano, S. J. Miller, Peptide-Based Catalysts Reach the Outer Sphere through Remote Desymmetrization and Atroposelectivity. *Acc. Chem. Res.* **52**, 199-215 (2019).
38. S. Y. Hsieh, Y. Tang, S. Crotti, E. A. Stone, S. J. Miller, Catalytic Enantioselective Pyridine N-Oxidation. *J Am Chem Soc* **141**, 18624-18629 (2019).
39. H. J. Davis, M. T. Mihai, R. J. Phipps, Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C–H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **138**, 12759-12762 (2016).
40. H. J. Davis, G. R. Genov, R. J. Phipps, meta-Selective C−H Borylation of Benzylamine-, Phenethylamine-, and Phenylpropylamine-Derived Amides Enabled by a Single Anionic Ligand. *Angew. Chem. Int. Ed.* **56**, 13351-13355 (2017).
41. M. T. Mihai, H. J. Davis, G. R. Genov, R. J. Phipps, Ion Pair-Directed C–H Activation on Flexible Ammonium Salts: meta-Selective Borylation of Quaternized Phenethylamines and Phenylpropylamines. *ACS Catal.* **8**, 3764-3769 (2018).
42. J. F. Hartwig, Regioselectivity of the borylation of alkanes and arenes. *Chem. Soc. Rev.* **40**, 1992-2002 (2011).
43. M. Dutartre, J. Bayardon, S. Jugé, Applications and stereoselective syntheses of P-chirogenic phosphorus compounds. *Chem. Soc. Rev.* **45**, 5771-5794 (2016).
44. Z.-J. Du *et al.*, Pd(II)-Catalyzed Enantioselective Synthesis of P-Stereogenic Phosphinamides via Desymmetric C–H Arylation. *J. Am. Chem. Soc.* **137**, 632-635 (2015).
45. Y. Sun, N. Cramer, Rhodium(III)-Catalyzed Enantiotopic C−H Activation Enables Access to P-Chiral Cyclic Phosphinamides. *Angew. Chem. Int. Ed.* **56**, 364-367 (2017).
46. D. A. DiRocco *et al.*, A multifunctional catalyst that stereoselectively assembles prodrugs. *Science* **356**, 426-430 (2017).
47. C. W. Liskey, X. Liao, J. F. Hartwig, Cyanation of Arenes via Iridium-Catalyzed Borylation. *J. Am. Chem. Soc.* **132**, 11389-11391 (2010).
48. C. Hansch, A. Leo, R. W. Taft, A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **91**, 165-195 (1991).
49. K. H. Shaughnessy, Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions. *Chem. Rev.* **109**, 643-710 (2009).

Remaining references:

50. A. Rérat, C. Michon, F. Agbossou-Niedercorn, C. Gosmini, Synthesis of Symmetrical Diaryl Ketones by Cobalt-Catalyzed Reaction of Arylzinc Reagents with Ethyl Chloroformate. *Eur. J. Org. Chem.* 4554–4560 (2016).
51. S. K. Goforth, R. C. Walroth, L. McElwee-White, Evaluation of Multisite Polypyridyl Ligands as Platforms for the Synthesis of Rh/Zn, Rh/Pd, and Rh/Pt Heterometallic Complexes. *Inorg. Chem.* **52**, 5692–5701 (2013).
52. S. Santra, J. Guin, Enhanced Reactivity of Aerobic Diimide Olefin Hydrogenation with Arylboronic Compounds: An Efficient One-Pot Reduction/Oxidation Protocol. *European J. Org. Chem.* 7253–7257 (2015).
53. S. K. Das, S. Roy, H. Khatua, B. Chattopadhyay, Ir-Catalyzed Intramolecular Transannulation/C(sp^2)–H Amination of 1,2,3,4-Tetrazoles by Electrocyclization. *J. Am. Chem. Soc.* **140**, 8429–8433 (2018).
54. S. Asghar, T. Shahzadi, M. Alazmi, X. Gao, A.-H. Emwas, R. Saleem, F. Batool, G. Chotana, Iridium-Catalyzed Regioselective Borylation of Substituted Biaryls. *Synthesis*. **50**, 2211–2220 (2018).
55. A. D. Finke, J. S. Moore, Iterative Synthesis of 1,3,5-Polyphenylene Dendrons *via* C−H Activation. *Org. Lett.* **10**, 4851–4854 (2008).
56. P. S. Pregosin, Applications of NMR diffusion methods with emphasis on ion pairing in inorganic chemistry: a mini-review. *Magn. Reson. Chem.* **55**, 405-413 (2017).
57. C. A. Malapit, M. D. Visco, J. T. Reeves, C. A. Busacca, A. R. Howell, C. H. Senanayake, Nickel- or Cobalt-Catalyzed Cross-Coupling of Arylsulfonic Acid Salts with Grignard Reagents. *Adv. Synth. Catal.* **357**, 2199–2204 (2015).
58. S. Shimada, O. Yamazaki, T. Tanaka, M. L. N. Rao, Y. Suzuki, M. Tanaka, 5,6,7,12-Tetrahydrodibenz[*c*,*f*][1,5]azabismocines: Highly Reactive and Recoverable Organobismuth Reagents for Cross-Coupling Reactions with Aryl Bromides. *Angew. Chem. Int. Ed.* **42**, 1845–1848 (2003).
59. R. Siles, M. Zhou, F. Ackley, K. G. Pinney, S.-E. Chen, W. Milenka, A. Angulo, M. L. Trawick, US 2009/0076076 A1 (2009), pp. 1–27.
60. M. Lindner, M. Valášek, J. Homberg, K. Edelmann, L. Gerhard, W. Wulfhekel, O. Fuhr, T. Wächter, M. Zharnikov, V. Kolivoška, L. Pospíšil, G. Mészáros, M. Hromadová, M. Mayor, Importance of the Anchor Group Position (*Para* versus *Meta*) in

Tetraphenylmethane Tripods: Synthesis and Self-Assembly Features. *Chem. Eur. J.* **22**, 13218–13235 (2016).

61. L. Lin, S. Fukagawa, D. Sekine, E. Tomita, T. Yoshino, S. Matsunaga, Chiral Carboxylic Acid Enabled Achiral Rhodium(III)-Catalyzed Enantioselective C−H Functionalization. *Angew. Chem. Int. Ed.* **57**, 12048–12052 (2018).
62. J. R. Cox, J. H. Simpson, T. M. Swager, Photoalignment Layers for Liquid Crystals from the Di-π-methane Rearrangement. *J. Am. Chem. Soc.* **135**, 640–643 (2013).
63. H. J. Davis, M. T. Mihai, R. J. Phipps, Ion Pair-Directed Regiocontrol in Transition-Metal Catalysis: A Meta-Selective C–H Borylation of Aromatic Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **138**, 12759–12762 (2016).
64. M. Zielińska-Błajet, M. Kucharska and J. Skarżewski, Simple Enantiospecific Synthesis of Sulfides of Cinchona Alkaloids. *Synthesis*, **7**, 1176–1182 (2006).