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**Enantioselective remote C–H activation directed by a chiral cation**

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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 charge-inverted strategy in which cationic metal complexes are paired with chiral anions. We report metal catalyzed C–H borylation. In principle, numerous common classes of ligand could likewise be amenable to this approach.

on-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) (Fig. 1A, left). Over the past 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 diphosphotabisperoxotungstate (15) and peroxomolybdate (16) complexes as catalysts (Fig. 1A, center) (17–21). Owing to this scarcity of anionic metal complexes in the most commonly used 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) (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 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. Although 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 (Fig. 1C) (33), taking advantage of an ingenious relay strategy via the ortho position, although relatively high loadings of the chiral boron mediator (CTM, 20 to 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. By 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 noncovalent interactions offer numerous opportunities (36–38).

We recently developed anionic bipyridine ligands that bear a remote sulfonate group to impart control of regioselectivity in iridium-catalyzed C–H borylation via noncovalent interactions with the substrate (39–44). 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 CTM to 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-phosphorus 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 benzhydrylamine 2a (Fig. 2A). Numerous ion-paired ligands L–1, possessing a variety of chiral cations 1a to 1i, could be readily obtained through counterion exchange. The chiral cations were all derived from dihydroquinine (DHQ) with varying N-benzyl substituent. At room temperature in tetrahydrofuran (THF) as solvent, low but encouraging levels of enantioselectivity were obtained with 3,5-dimethoxy benzyl and 3,5-di-tert-butyl groups [L–1a and L–1b, 31 and 30% enantiomeric excess (ee)]. We next investigated placing substituted aromatic rings at the 3- and 5-positions...
of the quaternizing N-benzyl group. Encouragingly, L·1c (4-CF₃C₆H₄) gave increased enantioselectivity (39% ee) and L·1d (3,4,5-F₃C₆H₂) resulted in a further improvement (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 to 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) as being optimal, in that the reaction temperature could be reduced to −10°C while high reactivity was maintained, resulting in isolation of 3a in 72% yield and with 96% ee, following oxidation to the corresponding phenol with H₂O₂ (see inset in Fig. 2A). This derivatization aided separation from any remaining starting material or difunctionalized material. The undesired borylation of monoborylated 3a′ to give a symmetrical diborylated by-product 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...
Fig. 2. Enantioselective desymmetrizing C–H borylation of benzhydrylamides. (A) Reaction optimization. COD, 1,5-cyclooctadiene; rt, room temperature; tBu, tert-butyl. (B) Scope of enantioselective borylation using L-1g in substrates bearing no regioselectivity challenge. Et, ethyl. (C) Examples in which the catalyst is controlling regioselectivity and enantioselectivity. Yield values refer to isolated yields. Regioisomeric ratios were determined from the crude 1H–nuclear magnetic resonance (NMR) spectrum before isolation. Enantiomeric excesses determined by chiral high-performance liquid chromatography (HPLC) or supercritical fluid chromatography (SFC) analysis.
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 L1g 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 L1g in which the quinine hydroxyl group is methylated, which gave a reduced ee of 72%, and a variant of L1g in which the stereochemistry of the quinine hydroxyl group is inverted, which gave only 11% ee (see supplementary materials and table S1 for full optimization details). A survey of N-protecting groups demonstrated that trifluoroacetyl is optimal, although acetyl also performed well (fig. S3).

We proceeded to examine the scope of the reaction in terms of versatile substituents on the substrate aryl rings (Fig. 2B). Postreaction derivatization of the introduced boronic acid pinacol ester (BPin) group 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-substituted (3b), bromo-substituted (3d), and iodo-substituted (3e) arenes all delivered excellent levels of enantioselectivity, the latter being of particular note because 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 3c was determined by x-ray crystallographic analysis, and all other compounds were assigned by analogy with this. Further variation of substituents revealed that trifluoroethoxy (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 owing 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, owing 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 nonselective, we were keen to evaluate whether L1g 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 substantially change the preferred substrate conformation, potentially affecting 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 the cation. However, we were delighted to find that an ortho-chloro substrate gave the meta-borylated product 3k with excellent regioselectivity [10:1 regioisomeric ratio (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-CF3 (3m) and ortho-OCF3 (3o). We also examined a meta-fluoro substrate, which presents regioselectivity challenges using standard ligands owing to the small size of the fluorine atom (42), but with L1g, high regioselectivity was observed (3n). In addition, we carried out preliminary experiments with nonsymmetrical substrates to assess the viability of using the reaction in kinetic resolution mode. These showed that it is indeed viable, although

Fig. 3. Substrate scope of the enantioselective C–H borylation of diaryl phosphinamides. Yield values refer to isolated yields.
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 phosphorus 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). Although 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 in increasing drug development, 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 hydrogendonor. 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 owing 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).

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 used, 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 nonphenolic 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 cyana-

dition 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 owing 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 \(\mathbf{L\text{-}1j}\), 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°C, and the temperature had to be raised to 10°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 \(\mathbf{L\text{-}1g}\) was replaced with neutral 5,5′-dimethylbipyridine (8) together with the optimal chiral cation as its bromide salt (\(\mathbf{Br\text{-}1g}\)). The product was racemic, demon-
nstrating the requirement for ligand and chiral cation to be associated to achieve enantio-
induction. We also ran a reaction in which ligand \(\mathbf{L\text{-}NBu4}\), bearing achiral tetraethylammonium as the cation, was used in conjunction with \(\mathbf{Br\text{-}1g}\). 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 incorporation of an anionic sulfonate group into 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 sulfurated 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.
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Asymmetry on the plus side
Numerous positively charged metal catalysts have been paired with chiral negative ions to select for just one of two mirror-image products. Genov et al. now report a potentially general strategy to invert the charges in this paradigm. Because intrinsically negative metal catalysts are comparatively rare, the authors appended a sulfonate group to the common bipyridyl ligand. Iridium complexes of this ligand paired with chiral positive ions could borylate just one of two aryl rings appended to carbon or phosphorus centers with high enantioselectivity. Science, this issue p. 1246