LETTER

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Asymmetric additions to dienes catalysed by a dithiophosphoric acid

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Chiral Brønsted acids (proton donors) have been shown to facilitate a broad range of asymmetric chemical transformations under catalytic conditions without requiring additional toxic or expensive metals[1–8]. Although the catalysts developed thus far are remarkably effective at activating polarized functional groups, it is not clear whether organic Brønsted acids can be used to catalyse highly enantioselective transformations of unactivated carbon–carbon multiple bonds. This deficiency persists despite the fact that racemic acid-catalysed 'Markovnikov' additions to alkenes are well known chemical transformations. Here we show that chiral dithiophosphoric acids can catalyse the intramolecular hydroamination and hydroarylation of dienes and allenes to generate heterocyclic products in exceptional yield and enantiomeric excess. We present a mechanistic hypothesis that involves the addition of the acid catalyst to the diene, followed by nucleophilic displacement of the resulting dithiophosphate intermediate; we also report mass spectroscopic and deuterium labelling studies in support of the proposed mechanism. The catalysts and concepts revealed in this study should prove applicable to other asymmetric functionalizations of unsaturated systems.

It has been known for over a century that strong Brønsted acids can catalyse the addition of alcohols and other protic nucleophiles to simple alkenes. The ability to predict the regioselectivity of these reactions is taught in every introductory organic chemistry course as Markovnikov's rule. However, successful approaches to asymmetric variants have relied on metal catalysts rather than organic Brønsted acids, particularly in the area of amine addition reactions[9–12]. Although metal-free Brønsted acids can catalyse additions to unactivated alkenes with yields comparable to those produced by the use of metals[13–15], the lone example of an attempted enantioselective variant of this reaction using a chiral acid resulted in poor selectivity (17% enantiomeric excess, e.e.)[16]. Although a number of structurally diverse strong Brønsted acid catalysts have been developed, the highly enantioselective reactions reported to date are restricted to the activation of an electrophilic carbon–heteroatom or heteroatom–heteroatom multiple bond, usually an imine or a carbonyl[1–8].

This unfortunate limitation can perhaps be explained by considering the different intermediates generated by protonation of an imine or carbonyl versus an alkene (Fig. 1a). Protonation of an imine or carbonyl generates a species that can hydrogen-bond with the conjugate base of the chiral Brønsted acid. This hydrogen bond serves as an anchor to keep the chiral information close to the reactive electrophile and also contributes to the molecular organization that favours one particular diastereomeric transition state. On the other hand, protonation of an alkene leads to a carbocation. Although the conjugate base of the chiral acid can still be held in proximity to the carbocation through electrostatic interactions, the lack of rigidity in this association presumably results in poor discrimination between the enantiotopic faces of the carbocation. In fact, a recent review on chiral Brønsted acid catalysis goes as far as to say that "The key to realizing enantioselective catalysis using a chiral Brønsted acid is the hydrogen-bonding interaction between a protonated substrate and the chiral conjugate base"[3]. Clearly, a conceptually different approach is needed to achieve the desired enantioselective additions to alkenes.

We considered that this problem could be overcome for nucleophilic additions to dienes by using a chiral Brønsted acid with a nucleophilic conjugate base that could form a covalent bond with the carbocation (Fig. 1b). In a second step, the nucleophile could displace the chiral leaving group in an S_N2' reaction (displacement of an allylic leaving group by nucleophilic attack at the alkene). Because the chiral catalyst is directly bound to the substrate in the nucleophilic addition step, we hypothesized that this mechanistic scheme might facilitate a highly enantioselective transformation. Notably, two of the most important modes of organocatalysis, namely enamine and iminium catalysis, also take advantage of 'covalent catalysis' mechanisms[17].

A challenge in implementing such a strategy is finding an acid that is strong enough to protonate an alkene, but which also possesses a nucleophilic conjugate base. We considered that dithiophosphoric acids might be ideal candidates to fulfil both criteria[18]. The increased polarizability of sulphur (2.90) versus oxygen (0.802) makes dithiophosphoric acids more acidic and nucleophilic than their oxygenated analogues[19–21]. For the purpose of our desired reaction, it was encouraging to note that the addition of achiral dithiophosphoric acids to dienes is known to proceed efficiently with Markovnikov regioselectivity under radical-free conditions[22]. We suspected that the challenge in reaction development would therefore arise in achieving a highly selective reaction, especially given that the single previously reported reaction using a chiral dithiophosphoric acid catalyst proceeded with low diastereoselectivity and enantioselectivity (7:3 diastereomeric ratio (d.r.), 63% e.e.)[23].

Putting our idea into practice, we found that chiral dithiophosphoric acid **3a** catalysed the intramolecular hydroamination of diene **1** to form the desired pyrrolidine product **2** with excellent yield and moderate

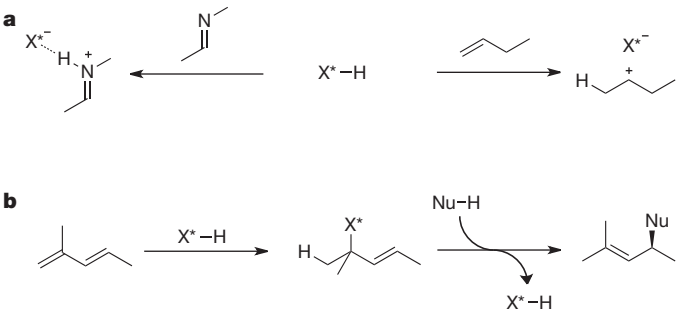

Figure 1 | A possible solution to the mechanistic challenge of asymmetric acid-catalysed additions to alkenes. **a**, Protonation of an imine with a chiral Brønsted acid (X*–H) leads to a hydrogen-bonded intermediate (left), while protonation of an alkene results in a carbocation (right) that cannot form a hydrogen bond. **b**, Proposed mechanism wherein a nucleophilic chiral acid adds to a diene then undergoes enantioselective S_N2' displacement.

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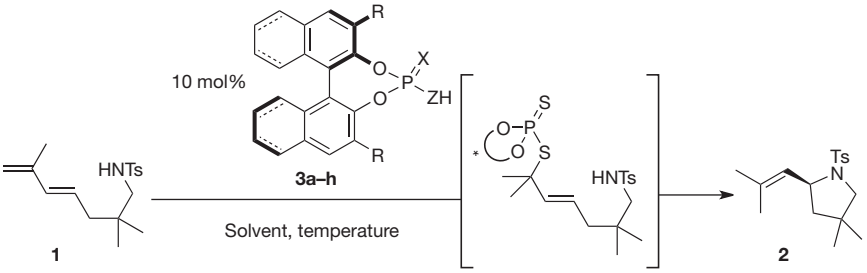
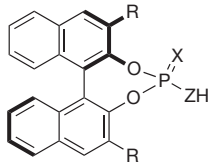
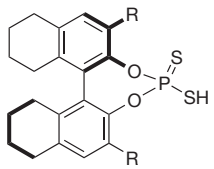
Table 1 | Optimization of the reaction conditions of the asymmetric hydroamination



Entry	Catalyst structure	Catalyst number	Solvent	Temperature (°C)	Yield (%)	e.e. (%)
1		**3a** X = Z = S, R = 1-naphthyl	$CDCl_3$	30	91	41
2		**3b** X = Z = O, R = 1-naphthyl	$CDCl_3$	30	0	NA
3		**3c** X = S, Z = NTf, R = 1-naphthyl	$CDCl_3$	30	89	46
4		**3d** X = O, Z = NTf, R = 1-naphthyl	$CDCl_3$	30	0	NA
5		**3e** R = 9-anthracenyl	$CDCl_3$	30	98	62
6		**3e** R = 9-anthracenyl	FC_6H_5	15	91	78
7		**3f** R = 10-phenylanthracenyl	FC_6H_5	15	92	94
8		**3g** R = 10-(3,5-bis-*t*-Bu-C_6H_3)-9-anthracenyl	FC_6H_5	15	96	96
9		**3h** R = 10-(2,4,6-$(CH_3)_3$-C_6H_2)-9-anthracenyl	FC_6H_5	23	98	96

Ts, *p*-toluenesulphonyl; Tf, trifluoromethanesulphonyl. Reactions were all run for 48 h. Yields were determined by NMR analysis versus an internal standard; e.e.s were determined by chiral HPLC. NA, not available.

enantioselectivity (Table 1, entry 1). As expected, the oxygenated phosphoric acid analogue **3b** did not promote the reaction at all (entry 2). We also found that an *N*-trifluoromethanesulphonyl (*N*-triflyl) thiophosphoramide catalyst of the type reported in ref. 6 catalysed the reaction with comparable e.e. (Table 1, entry 3), whereas the corresponding oxygen analogue **3d** did not give any desired product (entry 4). Attempts to optimize the catalyst structure by synthesizing more sterically encumbered *N*-triflyl thiophosphoramides resulted in unacceptably low yields, so we continued our investigation with dithiophosphoric acids.

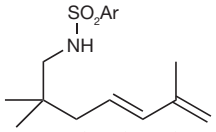
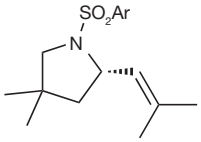
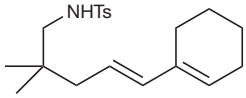
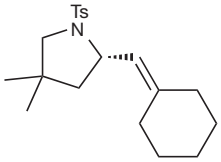
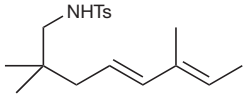
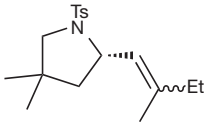
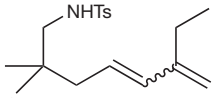
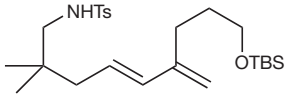
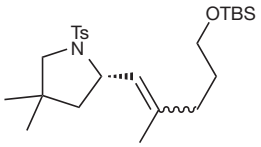
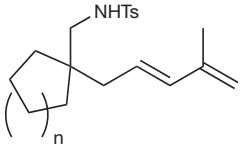
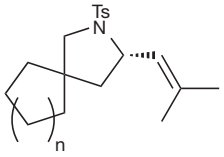
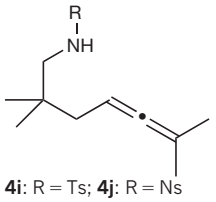
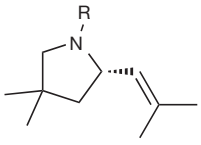
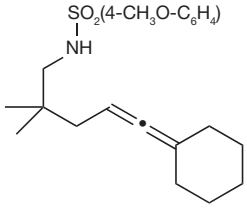
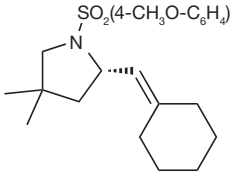
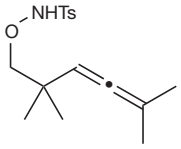
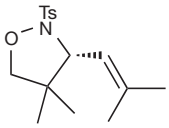
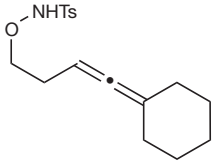
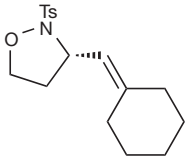
Changing the 3,3′ substituents to bulkier anthracenyl groups led to a substantial boost in enantioselectivity, as did using a catalyst with a partially hydrogenated backbone (Table 1, entry 5). We also noted that performing the reaction in fluorobenzene as solvent in the presence of 4 Å molecular sieves at a slightly reduced temperature (15 °C) further improved the selectivity (Table 1, entry 6). Finally, based on the proposed S_N2'-type mechanism in which the incoming nucleophile is some distance away from the chiral dithiophosphate, we hypothesized that extending the catalyst structure could lead to even better results by more effectively 'projecting' the chiral information. Consistent with this proposal, addition of an aromatic substituent at the 10-position of the anthracene moiety allowed us to achieve excellent enantioselectivity (Table 1, entries 7–9). Notably, the mesityl catalyst **3h** provided exceptional enantioinduction even at room temperature. Because in some cases one catalyst offered slightly better selectivity than the other, we used both **3g** and **3h** for exploring the scope of the reaction.

A number of structural modifications could be made to the substrates while preserving the excellent yield and enantioselectivity of the catalytic hydroamination (Table 2). The sulphonyl group on the amine can be varied while maintaining the excellent yield and enantioselectivity of the reaction (Table 2, entries 1 and 2). The terminal alkene can also be freely substituted with cyclic or acyclic groups (Table 2, entries 3 and 4). Diene **4d** showed selectivity for the *E*-isomer of the product, although both geometric isomers were formed with high enantioselectivity and had the same absolute configuration at the newly formed stereogenic centre. Interestingly, complementary selectivity for the *Z*-alkene could be achieved by using the isomeric diene **4e** (Table 2, entry 5). In both cases, the major product was obtained in higher enantiomeric excess than the other alkene isomer. With regard to functional group tolerance, it is remarkable to note that a primary *t*-butyldimethylsilyl (TBS) ether was stable in the presence of the strongly acidic catalyst in spite of the general acid lability of this protecting group (Table 2, entry 6). The tendency of the dithiophosphate to add covalently to the diene rather than remain free in solution may explain this surprising chemoselectivity. Additionally, the tether between the nucleophile and the diene can be varied to generate spirocyclic products (Table 2, entries 7 and 8).

In considering our mechanistic hypothesis, we realized that we should be able to access the same type of allylic dithiophosphate ester intermediate from addition of the Brønsted acid catalyst to allenes (1,2-dienes). We found that allene substrate **4i** was indeed converted to the pyrrolidine product **2** with essentially the same yield and enantioselectivity as was observed starting from the corresponding 1,3-diene (Table 2 entry 9, compare Table 1 entry 8). This observation also held true for other substrates. Although sulphonyl-pyrrolidines are themselves useful compounds from a medicinal chemistry standpoint[24,25], we also wanted to prepare products where the nitrogen substituent could be cleaved under mild conditions. Towards this end, we found that a 2-nitrosulphonyl (nosyl)-protected amine could be synthesized with only a modest decrease in enantioselectivity (Table 2, entry 10, 90% e.e.). Perhaps unsurprisingly, a more drastic change to a phosphinyl protecting group resulted in a slightly greater drop in selectivity (Table 2, entry 11). Hydroxylamines also proved to be useful substrates for the reaction, providing isoxazolidine products with very good enantioselectivities (Table 2, entries 13 and 14). Although in general we obtained the best results with substrates that possess geminal disubstitution in the alkyl tether, an observation probably attributable to the Thorpe-Ingold effect, the high enantioselectivity obtained using allene **4n** demonstrates that this is not strictly necessary for the success of our reaction.

A number of additional experiments were performed in order to further elucidate the mechanism of this transformation (Fig. 2). We began by analysing aliquots taken during the course of the catalytic reaction of **1** using time-of-flight mass spectrometry (TOF-MS). We observed a new peak that was fully consistent (mass-to-charge ratio *m/z* and isotopic distribution) with proposed intermediate **6** (Fig. 2a, Supplementary Figs 4 and 5). The proposed formation of this intermediate is also supported by the fact that the addition of dithiophosphoric acids across alkenes and dienes is a well-established process[20,22,26,27].

Table 2 | Performance of various 1,2- and 1,3-dienes in the enantioselective hydroamination reaction

Entry	Diene (**4a–4n**)	No.	Temperature (°C)	Product (**5a–5n**)	No.	Yield (%*E*:%*Z*)	e.e. (%)
1		**4a**	23		**5a**	99	92
2	**4a:** Ar = 3,5-$(CH_3)_2C_6H_3$ **4b:** Ar = 4-Cl-C_6H_4	**4b**	23		**5b**	99	95
3		**4c**	30		**5c**	70	94
4		**4d**	30		**5d**	90 (4.7:1)	95 (*E*) 90 (*Z*)
5	 6:1 E/Z	**4e**	23		**5d**	75 (1:2)	91 (*E*) 99 (*Z*)
6		**4f**	23		**5f**	91 (1:3.6)	80 (*E*) 99 (*Z*)
7		**4g**	23		**5g**	99	96
8	**4g**: *n* = 1; **4h**: *n* = 2	**4h**	23		**5h**	91	97
9	 **4i**: R = Ts; **4j**: R = Ns **4k**: R = $POPh_2$	**4i**	23		**2**	99	95
10		**4j**	23		**5j**	81	90
11		**4k**	23		**5k**	99	83
12		**4l**	40		**5l**	67	97
13		**4m**	23		**5m**	70	90
14		**4n**	60		**5n**	67	92

Reactions were run in fluorobenzene for 48 h using 10 mol% **3g** (entries 3 and 4) or 10 mol% **3h** (all others, 20 mol% for entry 14) in the presence of 4 Å molecular sieves. Yields refer to isolated material. TBS, *t*-butyldimethylsilyl; Ns, 2-nitrophenylsulphonyl.

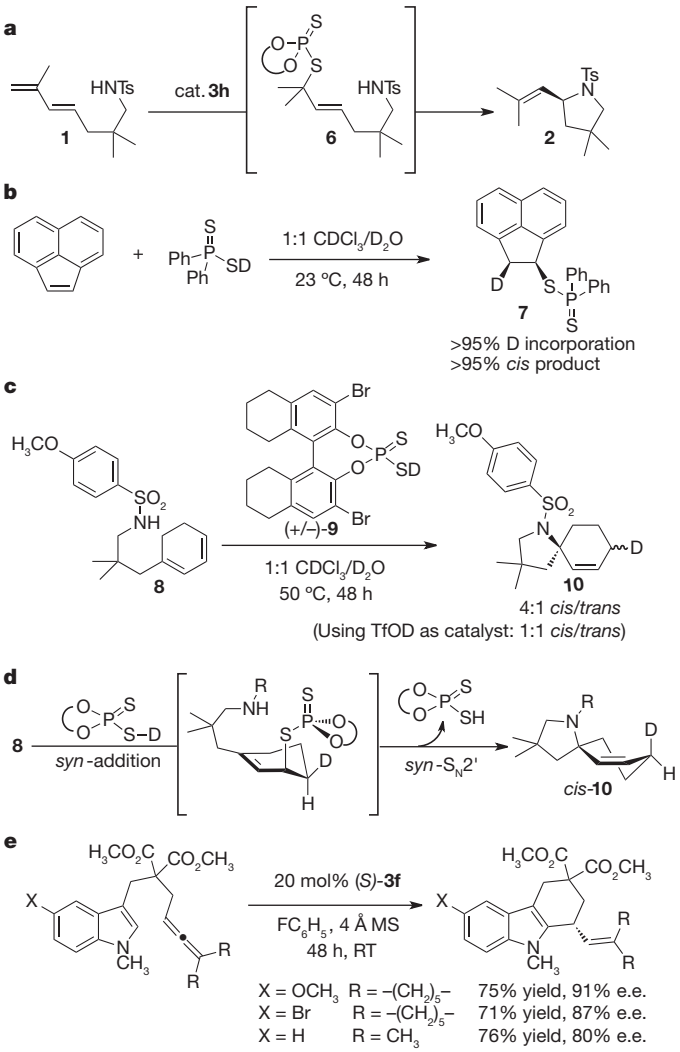


Figure 2 | Experiments to elucidate the reaction mechanism and application to indole nucleophiles. a, Proposed reaction mechanism involving a covalently bound catalyst–substrate intermediate that undergoes S_N2' displacement. Ts (tosyl), *p*-toluenesulphonyl. **b**, Addition of an achiral dithiophosphinic acid across an alkene proceeds with *syn* stereoselectivity. **c**, Reaction of a cyclic substrate using deuterated catalyst reveals 1,4-*syn*-stereoselectivity. Tf (triflyl), trifluoromethanesulphonyl. **d**, The overall mechanistic picture suggested by these experiments involves initial *syn*-addition of the S–H(D) bond across the alkene, followed by *syn*-S_N2' displacement. R, $SO_2(4\text{-}CH_3O\text{-}C_6H_4)$. **e**, Dithiophosphoric acid-catalysed hydroarylation of indole derivatives. MS, molecular sieve; RT, room temperature.

An investigation of the diastereoselectivity of the protonation and nucleophilic addition steps revealed some more insights regarding the mechanism. A deuterated achiral dithiophosphinic acid added across acenaphthylene, a cyclic alkene often used as a stereochemical probe, with a very high level of *syn*-stereoselectivity (Fig. 2b). No epimerization of the product was observed, even after a prolonged reaction time with heating (50 °C, 72 h). Thus, at least in this case, the dithiophosphinate ester intermediate does not ionize under conditions harsher than those used in the catalytic reaction. We next examined the reaction of a cyclic diene-tethered sulphonamide substrate using a deuterated catalyst (Fig. 2c). The obtained spirocyclic product was substantially enriched (4:1 d.r.) in the isomer where the sulphonamide nucleophile and the deuterium have a *cis* orientation. Taken together, these two experiments suggest that this observed *syn* diastereoselectivity is a result of initial *syn*-addition of the dithiophosphoric acid across the distal alkene, followed by a *syn*-S_N2' displacement (Fig. 2d). Excluding metal-mediated processes, S_N2' reactions are known to proceed preferentially though *syn* pathways[28,29].

At this point we cannot describe with certainty the degree of bonding that exists between the nucleophile, allylic system, and dithiophosphate in the S_N2' displacement step. This step may be concerted, or it may involve the formation of an allylic carbocation-dithiophosphate tight ion pair that is rapidly trapped by the tethered sulphonamide. In either mechanism, the remarkable feature is that the catalyst is able to mediate the attack of the nucleophile on the carbon electrophile with sufficient organization to greatly favour one diastereomeric transition state. In addition, it should be noted that cyclization of stereochemical probe **8** using catalytic deuterated triflic acid proceeds with no diastereoselectivity (Fig. 2c). This result strongly supports the notion that the dithiophosphoric acid catalysed reaction is mechanistically distinct from simple Brønsted acid catalysis.

To demonstrate the generality of this approach, we examined indoles as useful carbon nucleophiles that would be structurally and mechanistically distinct from the sulphonamides used in the rest of the study. Although a large number of efficient additions of indoles to imine and unsaturated carbonyl derivatives have been discovered, the proposed organocatalytic enantioselective hydroarylation of an unactivated carbon unsaturated system has not been demonstrated[30]. When indole substrates were subjected to our reaction conditions, the hydroarylations proceeded readily to afford the tetrahydrocarbazole products in good to excellent enantiomeric excess (80–91% e.e.; Fig. 2e). An X-ray structure of a crystalline sample of the brominated derivative confirmed the structure and revealed the absolute configuration of the products (Supplementary Fig. 11 and Supplementary Table 1).

The high enantioselectivity of this carbon–carbon bond forming reaction is particularly striking because the *N*-alkylated indole substrates do not possess any apparent hydrogen-bond donors to assist in the catalyst–substrate organization. As previously mentioned, the presence of hydrogen-bonding functionality has been a signature of nearly all of the previously demonstrated chiral Brønsted acid catalysed reactions[3]. It is possible that in our system, the covalent attachment of the catalyst eliminates the need for the hydrogen-bonding that is typically required for reactions that proceed by an ion pair mechanism. We believe that the applicability of these catalysts and concepts to this different type of bond formation augurs well for the scope of future developments.

In spite of the remarkable developments in the field of asymmetric catalysis, there are still a great number of important transformations that are beyond the reach of current synthetic approaches. We have reported here a method using dithiophosphoric acids that enables metal-free catalytic asymmetric nucleophilic additions to all-carbon π-systems. In addition to serving as a useful means of obtaining valuable chiral hetero- and carbo-cyclic products, the reported hydroamination and hydroarylation reactions are fundamentally distinct from those reactions that have been previously achieved using chiral organocatalysts. Finally, we have presented experimental evidence that is most consistent with a unique covalent catalysis mechanism.

METHODS SUMMARY

General procedure: to a 1-dram screw-cap vial was added the diene or the allene substrate (0.1 mmol, 1.0 equiv) followed by the dithiophosphoric acid catalyst **3f**, **3g** or **3h** (0.01 mmol, 0.1 equiv) and activated 4 Å molecular sieves (20 mg). To the mixture was added fluorobenzene (0.5 ml) at room temperature. The vial was sealed and allowed to stand for 48 h at the indicated temperature. After the reaction was complete, the entire mixture was loaded onto silica gel and the product was eluted with EtOAc/hexanes. For complete experimental details, including procedures and full characterization (^1H and ^{13}C NMR, high-resolution mass spectrometry) of all new compounds, see Supplementary Information.

Full Methods and any associated references are available in the online version of the paper at www.nature.com/nature.

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Author Contributions N.D.S. initiated the hydroamination study. V.R. optimized the catalysts and initiated the hydroarylation study. N.D.S., V.R., G.L.H. and J.W. performed the experiments. N.D.S., G.L.H. and F.D.T. developed the mechanistic concepts. G.L.H. and N.D.S. wrote the manuscript with input from all authors.

Author Information X-ray crystallographic data have been deposited in the Cambridge Crystallographic Data Centre database (http://www.ccdc.cam.ac.uk/) under code CCDC 800545. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Readers are welcome to comment on the online version of this article at www.nature.com/nature. Correspondence and requests for materials should be addressed to F.D.T. (fdtoste@berkeley.edu).

METHODS

General reaction procedure: to a 1-dram screw-cap vial was added the diene or the allene substrate (0.1 mmol, 1.0 equiv) followed by the dithiophosphoric acid catalyst **3f**, **3g** or **3h** (0.01 mmol, 0.1 equiv) and activated 4 Å molecular sieves (20 mg). To the mixture was added fluorobenzene (0.5 ml) at room temperature. The vial was sealed and allowed to stand for 48 h at the indicated temperature. After the reaction was complete, the entire mixture was loaded onto silica gel, and the product was eluted with ethyl acetate/hexanes. Unless otherwise noted, all commercial materials were used without further purification. Small-scale reactions were conducted in one-dram vials fitted with a threaded cap. All other reactions were conducted in flame-dried glassware under an N_2 atmosphere with magnetic stirring and dried solvent. Solvents were dried by passage through an activated alumina column under argon. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Merck silica gel 60 F254 TLC plates and visualized by a combination of ultraviolet and potassium permanganate staining. Flash column chromatography was carried out on Merck 60 silica gel (32–63 μm). Nuclear magnetic resonance (NMR) spectra were recorded with Bruker AV-600, AVB-400, AVQ-400 and AV-300 spectrometers. ^{1}H and ^{13}C chemical shifts are reported in p.p.m. relative to tetramethylsilane, ^{31}P chemical shifts are reported relative to 85% aqueous phosphoric acid, and ^{19}F chemical shifts are reported relative to $CFCl_3$. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; br, broad resonance. Enantiomeric excesses (e.e.s) were determined on a Shimadzu VP Series Chiral HPLC. Mass spectral data were obtained by the QB3/Chemistry Mass Spectrometry Facility at UC Berkeley.