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Branch-Selective and Enantioselective Iridium-Catalyzed Alkene Hydroarylation via Anilide-Directed C−H Oxidative Addition

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Supporting Information

ABSTRACT: Tertiary benzylic stereocenters are accessed in high enantioselectivity by Ir-catalyzed branch selective addition of anilide *ortho*-C−H bonds across styrenes and α-olefins. Mechanistic studies indicate that the stereocenter generating step is reversible.

Tertiary benzylic stereocenters are of recognized value in the design of pharmaceuticals (Scheme 1A). The most powerful methodologies to access these motifs establish the stereocenter via a C−C bond forming fragment union step.[1] Commonly, this is achieved by cross-coupling of a nucleophile with an electrophile;[2] however, effective methods that harness two electrophiles[3] or two nucleophiles have also emerged.[4] Recent methods that allow the direct use of alkenes as a coupling partner are notable.[5] Arguably, the most general approaches exploit arylation of stereodefined secondary alkyl boronic acid derivatives (Scheme 1B).[2a,c,g,h,4] Within this context, Pd-catalyzed Suzuki couplings with aryl halides have been developed; however, isomerization of the alkyl-Pd(II) intermediate often leads to isomeric products.[1a,b,2a,g,h] Metal-free cross-couplings of aryl lithium reagents with alkyl boronic esters, which require external oxidants, circumvent this problem and offer good scope.[4] For all of these approaches, step and atom economy are imperfect because of the requirement for prefunctionalization and/or the need for additional reagents in the coupling step. For example, alkyl boronic esters are often accessed by enantioselective hydroboration of an alkene precursor,[6] whereas aryl halides are usually prepared by regioselective halogenation of an aryl C−H bond.

The fact that alkenes and aryl C−H bonds can be considered feedstock precursors for the approaches summarized in Scheme 1B raises the question of whether tertiary benzylic stereocenters might be accessed directly via C−H activation-triggered enantioselective addition of an aryl C−H bond across an alkene. In this context, the most challenging processes are likely to be those that harness nonpolarized acyclic alkenes (i.e., styrenes and α-olefins), because these offer minimal electronic control for achieving regioselective C−C bond formation. Indeed, synthetically useful intermolecular enantioselective alkene hydroarylations invariably exploit polarized alkenes to enforce regiocontrol.[7−9] Enantioselective alkene hydro*hetero*arylations have also been developed under a range of mechanistic regimes, but are limited to specific classes of heteroarene or alkene.[7a,10] To our knowledge, no general protocol exists for the highly enantioselective addition of aryl C−H bonds across styrenes and α-olefins.

Building on seminal studies from Togni,[7c,d] Shibata,[11a] and Krische,[11b] we previously identified Ir-catalysts that overturn the usual linear selectivity of Murai-type alkene hydroarylation reactions to provide branched products (Scheme 1C).[7a,12,13] Here, cationic systems modified with d^Fppb, a wide bite angle and electron poor achiral bisphosphine ligand, were effective for branch selective hydroarylations of styrenes and α-olefins, whereas narrow bite angle ligands (e.g., dppm) afforded linear products.[13] The efficacy of these methods provided the impetus for the development of enantioselective variants.[14] In particular, anilide-based processes (DG = NHAc) emerged as a key objective because (a) a large number of anilines are commercially available at low cost and (b) derivatizations of

Scheme 1

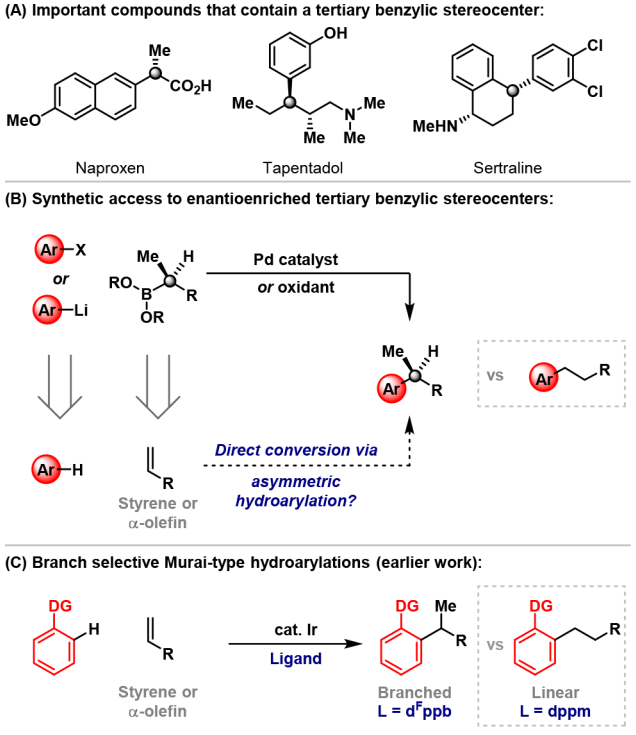

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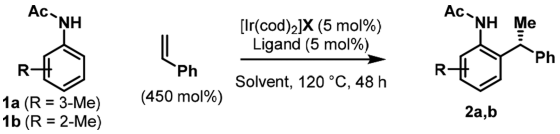
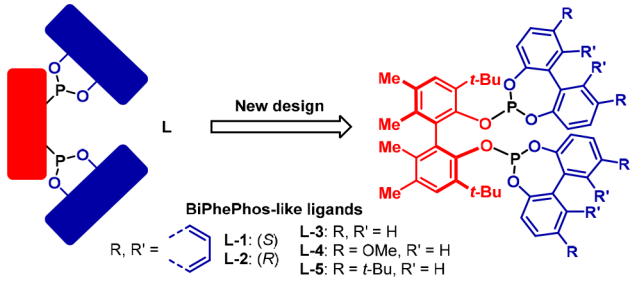
Table 1. Optimization of an Enantioselective Alkene Hydroarylation Process Using a Modular Ligand Design



entry	R	X	ligand	solvent (M)	B:L[a]	yield[b]	e.r.[c]
1	3-Me	OTf	**Josiphos SL-J418-1**	dioxane (1.5)	2:1	44%	73:27
2	3-Me	OTf	**(*S,S*)-BDPP**	dioxane (1.5)	1:1	71%[d]	37:63
3	3-Me	OTf	**(*R*)-SDP**	dioxane (1.5)	19:1	11%[d]	48:52
4	3-Me	OTf	**(*R,R*)-Kelliphite**	dioxane (1.5)	>25:1	31%	33:67
5	2-Me	OTf	**L-1**	dioxane (0.25)	>25:1	99%	90:10
6	2-Me	OTf	**L-2**	dioxane (0.25)	>25:1	<20%	n.d.
7	2-Me	OTf	**L-3**	dioxane (0.25)	>25:1	87%	92:8
8	2-Me	OTf	**L-3**	dioxane (0.025)	>25:1	39%	93:7
9	2-Me	OTf	**L-4**	dioxane (0.05)	>25:1	87%	91:9
10	2-Me	OTf	**L-5**	dioxane (0.05)	>25:1	100%	94.5:5.5
11	2-Me	OTf	**L-5**	toluene (0.05)	>25:1	83%	95:5
12	2-Me	OTf	**L-5**	hexyl acetate (0.05)	>25:1	100%	93.5:6.5
13	2-Me	OTf	**L-5**	DME (0.05)	>25:1	83%	94:6
14[e]	**2-Me**	**BF_4**	**L-5**	**toluene (0.05)**	**>25:1**	**87%**	**96:4**
15[f]	2-Me	BF_4	**L-5**	toluene (0.05)	>25:1	52%	96.5:3.5

[a]Branched to linear (B:L) ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yields. [c]Determined by chiral SFC analysis. [d]Vinylation product was observed in 11% and 4% for entries 2 and 3 (see later). [e]The reaction was performed at 110 °C for 72 h. [f]The reaction was performed at 105 °C for 72 h.



the products can be achieved via the anilide unit. However, the development of an enantioselective alkene hydroarylation process was considered challenging because of the prescriptive ligand features required for achieving high branch selectivity. As described below, we have now succeeded in identifying a modular ligand family that allows alkene hydroarylation of styrenes and α-olefins to be used for the efficient and highly enantioselective synthesis of tertiary benzylic stereocenters.

We began by undertaking an exhaustive screen of commercially available chiral ligands for the hydroarylation of styrene with acetanilide **1a**. These studies failed to reveal a system that could provide both high enantioselectivity and high branched to linear (B:L) regioselectivity, with the *most promising* results shown in Table 1, entries 1−4. Accordingly, a library of new chiral ligands was required, and we were drawn to variants of Kelliphite[15] because the modularity of this system leads to general structure **L**, where one or both of the blue and red components is a homochiral unit. An attractive feature of this design is that it allows tuning of the ligand substructure to provide an effective system for any given substrate. For the conversion of **1b** to **2b**, this approach led initially to BiPhePhos-like[16] ligand **L-1**, which afforded **2b** in 90:10 e.r., >25:1 B:L selectivity, and 99% yield. Further refinement was sought by altering the blue BINOL unit of **L-1**, and we found that **L-3**, which contains a conformationally flexible biphenol moiety,[17] generated **2b** in 92:8 e.r. Here, increased enantioselectivity was observed using higher dilution (entry 7 vs 8). Further studies revealed that *t*-Bu-substituted variant **L-5** could generate **2b** in 96:4 e.r. and high B:L selectivity using toluene as solvent (entry 14). **L-5** is a novel, bench stable bisphosphite ligand that can be prepared in two steps.

As outlined in Table 2A, the method tolerates a wide range of interesting and sensitive acetanilides, including indole-based system **2e** and halogen-substituted systems **2l** and **2m**. For anilides with two available *ortho*-positions competing bis-*ortho*-alkylation was observed in certain cases using 250 mol % styrene (e.g., **2c**), but high selectivity for mono-*ortho*-alkylation was achieved by using 110 mol % of this component. C−C bond formation is highly selective for the less hindered *ortho*-position of *meta*-substituted substrates (e.g., **2g**), which presumably reflects the steric demands of the ligand. The reaction conditions tolerate protic functionality (**2i**), and can be extended to elaborate substrates, such as steroid-derived system **2ac** (Table 2D). The protocol offers good scope with respect to the styrene component (Table 2B), with *para*- (**2q**) and *meta*-substituted systems (e.g., **2r**) participating efficiently. Hydroarylation of *ortho*-substituted styrenes is more demanding, but adduct **2p** was still formed in 53% yield. Significantly, the process extends to α-olefins (Table 2C), as demonstrated by the hydroarylation of hex-1-ene, which provided **2t** in 96% yield and 94:6 e.r. Even very sterically demanding alkenes are tolerated, such that hydroarylation of *tert*-butylethylene led to **2aa** in 81% yield and 95:5 e.r. The absolute stereochemistry of

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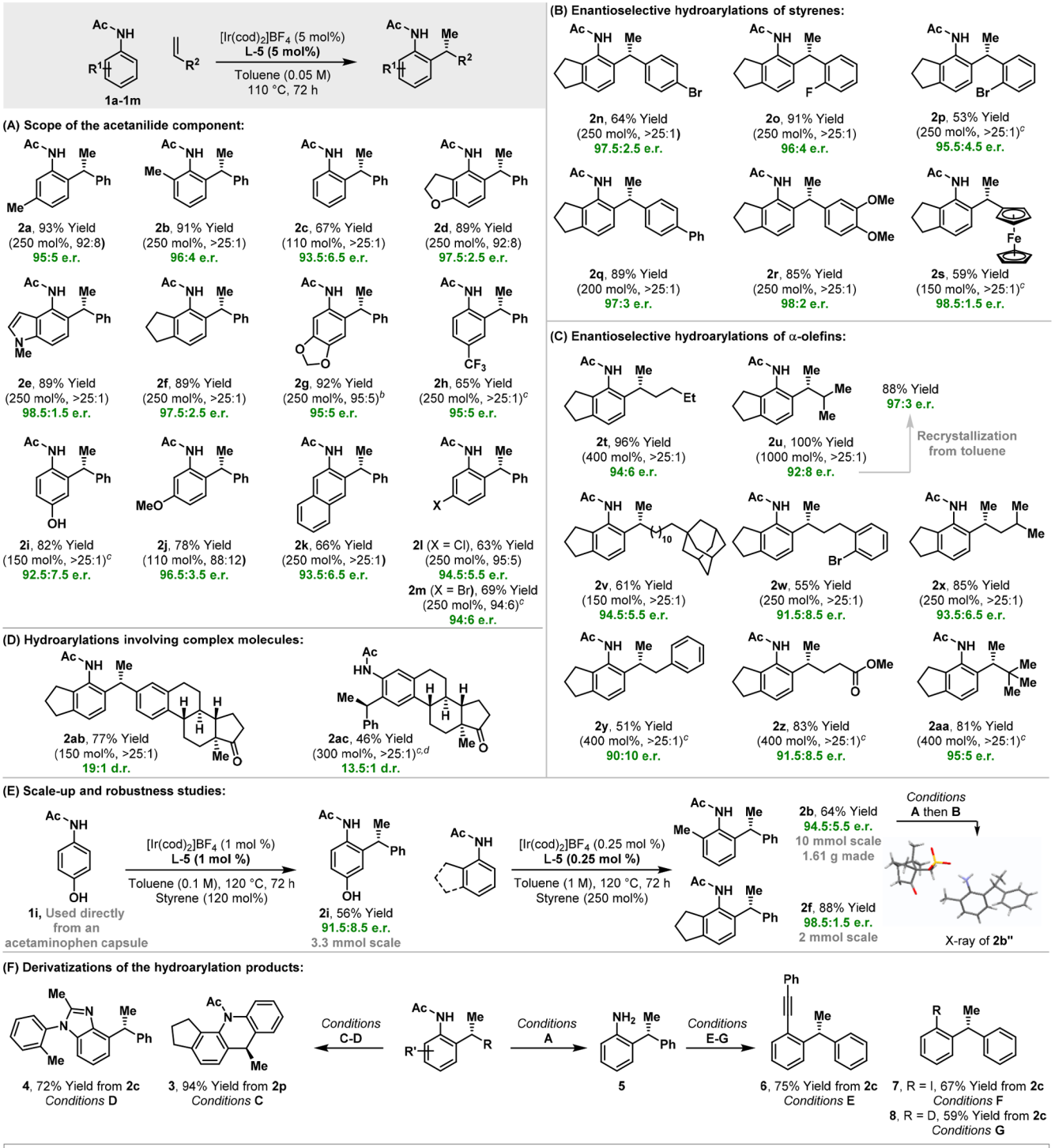
Table 2. Scope of the Enantioselective Alkene Hydroarylation Process[a]



Reaction conditions: A: 3 M HCl, Dioxane, 110 °C, 6-12 h; **B**: (+)-CSA (1 equiv.), CH_2Cl_2, r.t., 12 h; **C**: $Pd_2(dba)_3$ (3 mol%), BINAP (4 mol%), K_2CO_3 (1.5 equiv.), Dioxane, 120 °C, 18 h; **D**: NBS (1.1 equiv.), $Pd(OAc)_2$ (5 mol%), TsOH (50 mol%), Toluene, 50 °C, 24 h *then* o-toluidine (1.5 equiv.), $Pd_2(dba)_3$ (1 mol%), X-Phos (8 mol%), K_3PO_4 (1.5 equiv.), *t*-BuOH, 120 °C, 18 h; **E**: *t*-BuONO (1.1 equiv.), AcOH (1.1 equiv.), MeCN, 0 °C, 1 h *then* $Pd(OAc)_2$ (2 mol%), P(2-furyl)$_3$ (6 mol%), PhCCH (1 equiv.), 50 °C, 18 h; **F**: $NaNO_2$ (1.1 equiv.) H_2O/H_2SO_4, -10 to 0 °C, 0.5 h *then* KI (3 equiv.), 0 °C, 2 h; **G**: *t*-BuONO (1.2 equiv.), salicylic acid (10 mol%), THF-d^8, r.t., 2 h.

[a]Alkene equivalents and branched to linear selectivities are indicated in parentheses (determined by ^{1}H NMR analysis of the crude mixture). [b]*Ortho*-regioselectivity was 93:7. [c]The reaction was performed at 120 °C. [d]Concentration was 0.025 M.

2b was determined by X-ray analysis of (+)-CSA salt **2b″**, and stereochemical assignments of the other products were tentatively made on this basis.

The scalability of the process is demonstrated by the hydroarylation of styrene (250 mol %) with **1f** on 2 mmol scale, which formed **2f** in 88% yield and 98.5:1.5 e.r. using only 0.25 mol % Ir-catalyst (Table 2E). Similarly, 1.61 g of **2b** was prepared with satisfactory levels of efficiency on a 10 mmol scale. In these examples, the lower catalyst loading (vs Table 2A) allowed the processes to be run at higher concentration with respect to the substrate (1.0 M vs 0.05 M), while maintaining the same concentration with respect to the

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catalyst. The protocol also tolerates low level contaminants: hydroarylation of styrene with pharmacy grade anilide **1i**, sourced directly from acetaminophen (paracetamol) tablets, gave **2i** in 91.5:8.5 e.r. This result, although less efficient than from pure **1i**, shows that the conditions are tolerant to additives (e.g., magnesium stearate) used in the commercial formulation process. Finally, manipulation of the anilide unit of the products allows easy access to heterocycles (**3** and **4**), iodoarenes (**7**), and cross-coupled products (**6**) (Table 2F). The results in Table 2 show that the protocol offers very good levels of scope for enantioselective hydroarylations of styrenes and α-olefins. Another significant aspect is that the method provides a formal enantioselective alternative to Friedel–Crafts alkylation. Processes of this type are highly challenging, even without factoring in other issues that our method addresses, such as *ortho* vs *para* regiocontrol and high monoalkylation selectivity.[18]

A series of experiments have led to the mechanistic outline given in Scheme 2D. As supported by deuterium exchange experiments (see the Supporting Information (SI)), the process likely commences with reversible *N*-acetyl directed C–H oxidative addition to form **III**. From **IV**, reversible hydrometalation generates linear and branched intermediates **V** and **VI**; exposure of styrene *deuterio*-**9** to optimized reaction conditions resulted in scrambling of the deuterium labels in product *deuterio*-**2q** and recovered *deuterio*-**9** (Scheme 2A). C–C bond formation could occur either via C–C reductive elimination from **VI** or via carbometalation from π-complex **IV**. Support for the latter is provided by the observations that (a) bulky alkene substituents are tolerated (cf. **2aa**) and (b) trace amounts (1–5%) of C–H vinylation adducts (cf. **VII**) form in certain cases; these are most easily rationalized by invoking β-hydride elimination from carbometalation product **VIII**. Natural abundance ^{13}C KIE experiments have been used to distinguish unequivocally between C–C reductive elimination and carbometalation pathways;[19] this method shows which alkene carbon centers are involved in the first irreversible step. When the hydroarylation of styrene **9** (100 mol %) with acetanilide **1f** (150 mol %) was run to approximately 75% conversion, analysis of recovered **9** revealed a significant KIE at the terminal alkene carbon only (Scheme 2B). This effectively discounts C–C reductive elimination as the productive pathway, while indicating that (a) C–H reductive elimination is the first irreversible step and (b) carbometalation from **IV** to **VIII** is reversible. To gain further evidence, we sought to generate intermediate **VIII** via a distinct pathway. To this end, we exposed alkene **10** (cf. **VII**) to optimized conditions, but under an atmosphere of hydrogen on the presumption that hydrometalation by an in situ generated iridium-dihydride species would provide an intermediate akin to **VIII**.[20] This experiment generated **2f** (6% e.e.) and anilide **1f** in a 3:2 ratio (Scheme 2C). The formation of **1f** seemingly confirms that the stereocenter generating carbometalation step (**IV** to **VIII**) is reversible; this is rather unusual given that high enantioselectivity is observed in Table 2. Two mechanistic extremes could account for this. In one scenario, alkene carbometalation (**IV** to **VIII**) exhibits low (or inconsequential) facial selectivity but C–H reductive elimination to the major enantiomer is faster than to the minor. In the second scenario, carbometalation facial selectivity is high and subsequent C–H reductive elimination is less discriminating for both enantiomers. The low enantioselectivity obtained for product **2f** in Scheme 2C suggests the second option predominates, although this interpretation assumes that reduction of **10** proceeds solely via intermediates of type **VIII**. The mechanism in Scheme 2D is distinct from that proposed in our earlier work using d^{F}ppb,[13b] where ^{13}C KIE experiments are suggestive of a C–C reductive elimination pathway (see the SI).

A key feature of the ligand design outlined here is that its modularity allows tailoring to specific substrate classes. To demonstrate this, we optimized the hydroheteroarylation of styrene with thiophene **11a** to provide **12a**; this process performed poorly using **L-5** (44% yield, >25:1 B:L, 26:74 e.r.) (Table 3), and the low enantioselectivity necessitated a redesign of the ligand system. In the event, we found that ferrocene-based bisphosphonite systems incorporating SPINOL-derived units as the blue component are effective. Ligand **L-6** (R = H) provided **12a** in 77% yield, >25:1 B:L selectivity, and 91:9 e.r. Substituted variants **L-7** (R = Ph) and **L-8** (R = mesityl) can be accessed via earlier stage Suzuki cross-coupling. The latter offered increased selectivity, with **12a** formed in 77% yield and 97.5:2.5 e.r. using 120 mol % styrene. This new ligand was applied to thiophenes **12b–f**, with satisfactory results achieved for hydroarylations of styrenes and α-olefins, and in the diastereoselective hydroarylation that forms steroid

Scheme 2. Mechanistic Studies

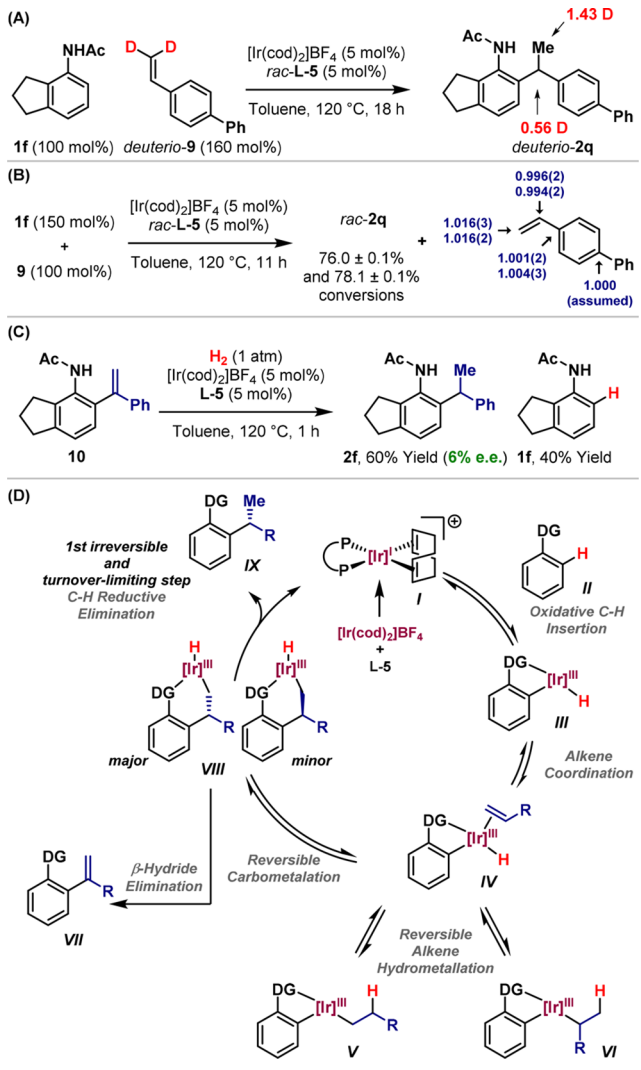

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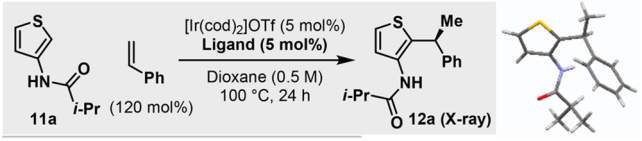
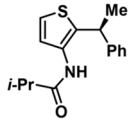
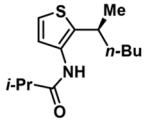
Table 3. Reoptimization for a Challenging Substrate Class



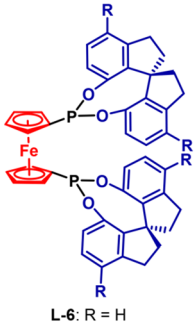
Entry	Ligand	Yield	B:L[a]	e.r.[b]
1	L-5	44%	>25:1	26:74[c]
2	L-6	77%	>25:1	91:9
3	L-7	59%	>25:1	85:15
4	L-8	77%	>25:1	97.5:2.5



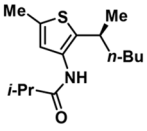
12a, 77% Yield[d]
(120 mol%, >25:1)
97.5:2.5 e.r.



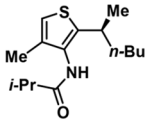
12b, 83% Yield[d]
(120 mol%, >25:1)
98:2 e.r.



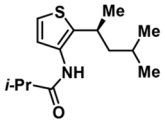
L-6: R = H
L-7: R = Ph
L-8: R = Mesityl



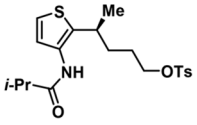
12c, 79% Yield[d]
(120 mol%, >25:1)
92:8 e.r.



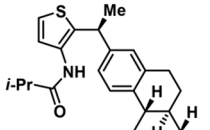
12d, 71% Yield[d]
(150 mol%, >25:1)
96.5:3.5 e.r.



12e, 71% Yield[d]
(120 mol%, >25:1)
96.5:3.5 e.r.



12f, 82% Yield[d,e]
(120 mol%, >25:1)
92:8 e.r.



12g, 78% Yield[d]
(100 mol%, >25:1)
>19:1 d.r.

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Determined by chiral SFC analysis. [c]The reaction was performed at 120 °C. [d]Alkene equivalents and branched to linear selectivities are indicated in parentheses. [e]The reaction was performed at 90 °C.

derivative **12g**. The absolute stereochemistry of **12a** was determined by X-ray diffraction, and other assignments were tentatively made on this basis. These results indicate that the broad ligand design in Table 1 will facilitate enantioselective alkene hydroarylations across a diverse range of substrates. Studies into this aspect are ongoing.

In summary, catalyst systems that promote highly branch selective and enantioselective hydroarylations of styrenes and α-olefins are described. Thus, tertiary benzylic stereocenters are generated directly and with complete atom economy. The method simplifies access to this important structural motif because prefunctionalization of the reaction partners is avoided. Further evolution of our approach will include processes that harness other classes of directing group and more highly substituted alkene partners.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04627.

Experimental details, characterization data (PDF)
Crystallographic data for **2b′′** (CIF)
Crystallographic data for **12a** (sample 1) (CIF)
Crystallographic data for **12a** (sample 2) (CIF)

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Notes

The authors declare no competing financial interest.

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