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Rh(I)−Bisphosphine-Catalyzed Asymmetric, Intermolecular Hydroheteroarylation of α-Substituted Acrylate Derivatives

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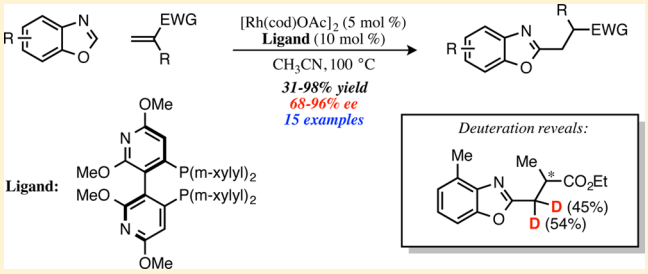
Supporting Information

ABSTRACT: Asymmetric hydroheteroarylation of alkenes represents a convenient entry to elaborated heterocyclic motifs. While chiral acids are known to mediate asymmetric addition of electron-rich heteroarenes to Michael acceptors, very few methods exploit transition metals to catalyze alkylation of heterocycles with olefins via a C−H activation, migratory insertion sequence. Herein, we describe the development of an asymmetric, intermolecular hydroheteroarylation reaction of α-substituted acrylates with benzoxazoles. The reaction provides 2-substitued benzoxazoles in moderate to excellent yields and good to excellent enantioselectivities. Notably, a series of mechanistic studies appears to contradict a pathway involving enantioselective protonation of a Rh(I)−enolate, despite the fact that such a mechanism is invoked almost unanimously in the related addition of aryl boronic acids to methacrylate derivatives. Evidence suggests instead that migratory insertion or beta-hydride elimination is enantiodetermining and that isomerization of a Rh(I)−enolate to a Rh(I)−heterobenzyl species insulates the resultant α-stereocenter from epimerization. A bulky ligand, CTH-(*R*)-Xylyl-P-Phos, is crucial for reactivity and enantioselectivity, as it likely discourages undesired ligation of benzoxazole substrates or intermediates to on- or off-cycle rhodium complexes and attenuates coordination-promoted product epimerization.



INTRODUCTION

Catalytic, enantioselective addition of a C−H bond of a heterocycle across an alkene represents a conceptually simple and atom economical method for the preparation of elaborated heterocyclic scaffolds. This concept has been implemented in a formal sense in the asymmetric Friedel−Crafts alkylation of electron-rich heteroarenes, such as indoles, with Michael acceptors.[1] Yet methods exploiting transition metals to mediate asymmetric hydroheteroarylation (HH) of alkenes via a C−H activation, insertion sequence remain quite elusive.[2,3] This deficiency is somewhat surprising given the diverse methods for asymmetric hydroarylation of olefins with activated arenes[4] or with arenes containing directing groups for C−H functionalization.[5] In the early 2000s, Bergman and Ellman pioneered the achiral, intramolecular HH of unactivated alkenes with a Rh(I)−phosphine catalyst.[3a] This discovery was expanded in a great body of work to the intermolecular HH reaction of alkenes[6] and to several discrete asymmetric, intramolecular HH reactions.[7] In 2012, Shibata provided an early example of an asymmetric intermolecular HH reaction mediated by a transition metal (TM):[8] an Ir(I)−SDP-catalyst promotes the branched-selective alkylation of *N*-benzoylindole and styrene in 42% ee (Figure 1, eq 1). Notably, alkylation occurs at the indole 2-position, whereas functionalization typically proceeds at the 3-position under Friedel-Craft conditions.[1] Though only modestly selective, Shibata's example foreshadows that TM-catalyzed HH may eventually serve as a selective and general complement to established methods using chiral acids. Indeed,

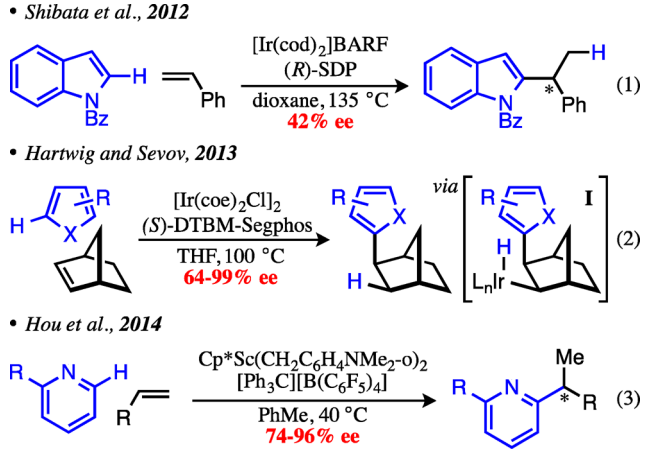


Figure 1. TM-catalyzed, asymmetric, intermolecular hydroheteroarylation reactions previously reported in the literature.

Hartwig and Sevov described in short succession the asymmetric HH of norbornene with diverse heterocycles using a chiral Ir(I) catalyst (Figure 1, eq 2).[9] Most recently, Hou and co-workers reported the enantioselective alkylation of 2- substituted pyridines with unactivated, terminal alkenes using a chiral, half-sandwich scandium complex. (Figure 1, eq 3).[10]

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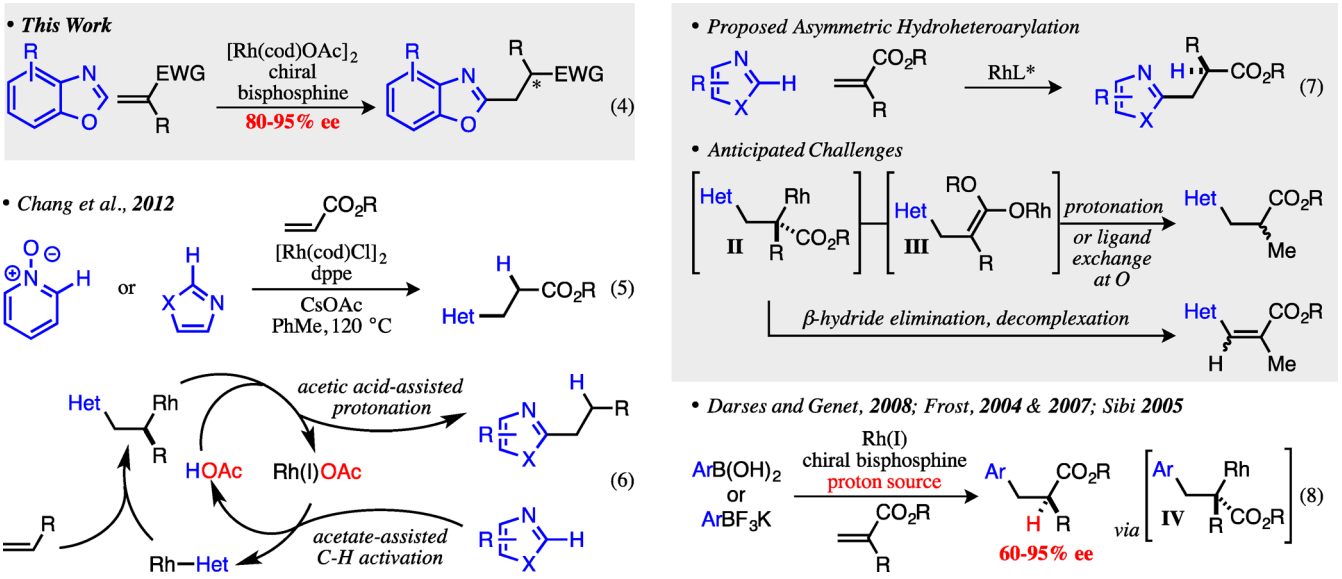

Figure 2. Our HH reaction of benzoxazoles and α-substituted acrylates and precedent inspiring its development.

While the work of Hartwig and Hou provides a powerful proof of concept, room for complementary asymmetric HH methods remains. Specifically, we sought to expand the scope of the olefin coupling partner. Hartwig's HH reaction is demonstrated only with the strained cyclic alkene, norbornene,[9] and Hou's pyridine alkylation appears limited to relatively unfunctionalized, electron neutral alkenes.[10] Herein, we describe a Rh(I)-catalyzed asymmetric alkylation of benzoxazoles with acrylate derivatives (Figure 2, eq 4). To our knowledge, this work represents the first example of an enantioselective, transition-metal-mediated, intermolecular HH of acyclic, electron-deficient alkenes. Moreover, the described reaction makes products of potential medicinal value; isosteres for purine bases and certain amino acids, 2-substituted benzoxazoles are known to exhibit tremendous biological activity.[11]

We found inspiration for the described HH reaction in chemistry developed by Chang et al.[3j] This group reported the HH of acrylates and acrylate derivatives with benzheterocycles or pyridine oxides (Figure 2, eq 5). Chang et al. invoke catalysis by a Rh(I)–acetate species—acetate counterion mediates C–H activation, while liberated acetic acid protonates an eventual C–Rh bond (Figure 2, eq 6). We envisioned that use of a substituted acrylate in a system related to Chang's would enable the asymmetric preparation of branched products (Figure 2, eq 7). Notably, the Rh(I)–dppe system used by Chang et al. lends itself to enantioselective modification: in contrast to relatively scarce chiral cyclopentadienyl ligands ubiquitous in Rh(III) catalysis,[5d,e,h] chiral bisphosphine ligands abound.[12]

Despite the overt similarity between the known and proposed reactions, several complications could accompany the envisioned asymmetric method. The mechanism proposed by Chang invokes protonation of Rh–enolate **II** (Figure 2).[3j] While protonation of C-bound **II** could provide enantioenriched products, protonation or ligand exchange of O-bound **III** at oxygen would give racemic product. Additionally, β-H elimination and dissociation of resultant conjugated alkene would furnish undesired Heck product.[3j] Indeed, success of Hartwig's and Hou's chemistry may be understood in light of these anticipated difficulties; the privileged nature of norbornene in eq 2 (Figure 1) likely derives in part from the fact that presumed intermediate **I** cannot undergo β-H elimination. Hou's pyridine alkylation (Figure 1, eq 3) is also presumably more insulated from β-H elimination than a Rh(I)-system, since the enhanced thermodynamic stabilization of metal–hydrogen bonds over metal–carbon bonds is smaller for early TMs than for late ones.[13]

While we were aware that the described pitfalls could plague our desired reaction with low stereo- or product-selectivity, work by Reetz, Genet, and others offered hope that these obstacles would not be insurmountable.[14] These groups report that a Rh(I)–chiral bisphosphine system mediates the asymmetric hydroarylation of α-substituted acrylates with boronic acid derivatives (Figure 2, eq 8). Importantly, this reaction is presumed to intercept analogous Rh–enolate intermediate **IV**.[14b–d] Similar opportunities for stereochemical scrambling or Heck reactivity exist for **IV** as for our presumed Rh–enolate **II**. Yet these pathways must not be competitive in the described systems, since saturated products are obtained in good to excellent enantioselectivities.[14] These groups invoke asymmetric protonation of Rh–enolate **IV** or O-bound Rh-isomer to explain high product enantioselectivities,[14,15] but aside from Genet et al.,[14e] none provide rigorous mechanistic evidence in favor of this claim (vide infra).

RESULTS AND DISCUSSION

Encouraged that our asymmetric HH could succeed, we decided to begin by investigating mechanistic aspects of the parent, achiral reaction (Figure 2, eq 5). The first question we sought to address was the role of the CsOAc. If, as Chang and co-workers postulated, CsOAc serves to generate a Rh(I)–acetate catalyst in situ, then perhaps the same reactivity could be accomplished with a premade Rh(I)–acetate catalyst. Chatani and co-workers have indeed observed that $[Rh(cod)OAc]_2$ can be used in place of a KOAc–$[Rh(cod)Cl]_2$ system in the directed hydroarylation of acrylates with 8-aminoquinoline-derived benzamides.[16,17] We prepared $[Rh(cod)OAc]_2$ by treating $[Rh(cod)Cl]_2$ with KOAc in refluxing acetone according to a known procedure.[18] Recrystallization from EtOAc provided X-ray quality crystals of the air-stable, orange solid. These were characterized by X-ray crystallography to

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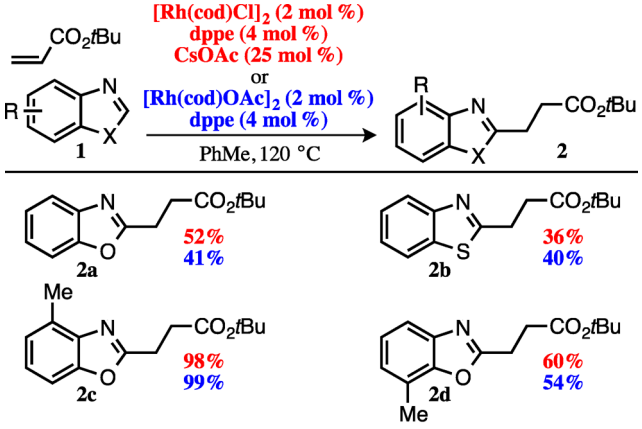
provide what we believe is the first reported crystal structure of the complex (see Supporting Information).[19] As predicted, $[Rh(cod)OAc]_2$ performs with equal efficiency as Chang's in situ generated catalyst in the HH of several benzheterocycles **1** with *tert*-butyl acrylate (Chart 1). CsOAc thus appears to serve primarily as an acetate source in Chang's chemistry.

Chart 1. HH Using Chang's Established Conditions (Red)[3j] or $[Rh(cod)OAc]_2$ (Blue)[a,b]



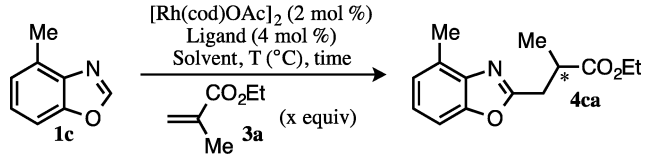
[a]To ensure uniformity for comparison, all reactions were performed by the first author. [b]Yields were determined with respect to 4,4′-di-*tert*-butylbiphenyl (DTBB) by ^1H NMR of the reaction mixture.

With $[Rh(cod)OAc]_2$ in hand, we screened the asymmetric HH of ethyl methacrylate (**3a**) and 4-methylbenzoxazole (**1c**) (Table 1), since this heterocycle proved most reactive in the achiral reaction with *tert*-butyl acrylate (Chart 1, vide supra). Ligands resembling dppe were chosen at the outset. In PhMe at 120 °C, **1c** and **3a** react in the presence of a Rh(I)−prophos (**L1**) catalyst to deliver α-substituted product **4ca** in quantitative yields and 29% ee (Table 1, entry 1). Ees remain modest with Chiraphos (**L2**) and Me−Duphos (**L3**) (entries 2 and 3). Significant improvement in ee is achieved with Binap (**L4**), but yields of **4ca** suffer. Since bite angle is known to have a pronounced effect on reaction selectivity and efficiency,[20] we examined Binap derivatives, Synphos (**L5**) and Segphos (**L6**), whose bite angles we hoped would compare more favorably to dppe.[21,22] Gratifyingly, a Rh(I)−Segphos system delivers product **4ca** in acceptable 56% yield, and good selectivity (85% ee, entry 6). A twofold increase in acrylate concentration further increases reactivity, providing comparable yields in 24 h to what is obtained in 60 h with lower acrylate concentrations (entries 6−9). Concurrently, a solvent and temperature screen (entries 9−17) revealed acetonitrile (CH_3CN) to be optimal for selectivity (95% ee, entry 11). Combining results, execution of the HH reaction in CH_3CN with 8 equiv of acrylate **3a** and 5 mol % rhodium dimer provides satisfactory yields of **4ca** in excellent enantioselectivity (entry 18).

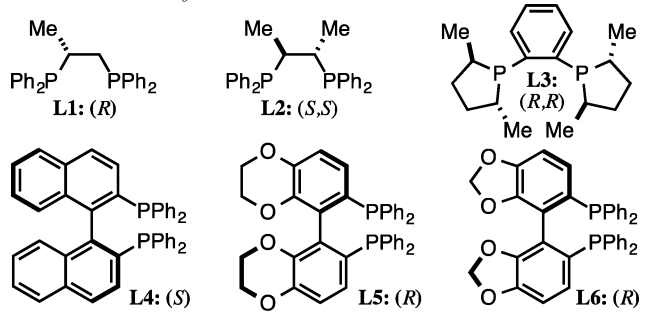
Although we were pleased with this result, we anticipated that reaction efficiency would need to be further improved in order to extend the substrate scope to less reactive heterocycles. For instance, when benzoxazole **1a** is reacted under the conditions shown in entry 2 of Table 1 (which provide nearly quantitative yields of **4ca**), no discernible product **4aa** is obtained (eq 9). Before refining our conditions, we sought to understand what made 4-methylbenzoxazole (**1c**) so much more reactive than its unsubstituted or 6-substituted counterparts (Chart 1, **1a**−**1b**, and **1d**). Yields displayed in Chart 1 fail to adequately capture this striking reactivity difference—while reaction of **1c** is complete in 3 h, reaction of **1a**, **1b**, and **1d** stall at about 50% after 60 h. To gain insight into this disparate reactivity, we performed two competition experiments—one between **1b**-D and **1c**-H (Figure 3 and eq 10),[23] and one between **1b**-H and **1c**-H (eq 11).

From the former, the following significant observations are made: (a) crossover substrates **1b**-H and **1c**-D are observed by ^1H and ^2H NMR (Figure 3); (b) ^2H is incorporated into the alkyl backbone of both products **2b** and **2c** (eq 10); and (c) ^2H is incorporated predominantly at the β-position of both products (eq 10). From this data, we propose a mechanistic

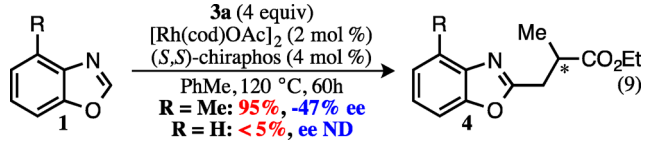
Table 1. Initial Reaction Optimization



entry	ligand	solvent	equiv **3a**	T (°C)	time (h)	**4ca**[a] (%)	ee[b] (%)
1	**L1**	PhMe	4	120	60	100	29
2	**L2**	PhMe	4	120	60	95	−47
3	**L3**	PhMe	4	120	60	39	57
4	**L4**	PhMe	4	120	60	9	−78
5	**L5**	PhMe	4	120	60	20	84
6	**L6**	PhMe	4	120	**60**	56	85
7	**L6**	PhMe	**4**	120	**24**	19	89
8	**L6**	PhMe	**6**	120	24	29	85
9	**L6**	PhMe	**8**	**120**	24	58	77
10	**L6**	PhMe	4	**100**	24	17	88
11	**L6**	CH_3CN	4	100	24	15	**95**
12	**L6**	TFE	4	100	24	<5	16
13	**L6**	DCE	4	100	24	<5	95
14	**L6**	DME	4	100	24	6	91
15	**L6**	DMF	4	100	24	22	88
16	**L6**	$PhCF_3$	4	100	24	10	95
17	**L6**	*o*-DCB	4	**160**	24	7	17
18[c]	**L6**	CH_3CN	**8**	**100**	**24**	**58**	**95**



[a]Determined with respect to DTBB by LC analysis of the reaction mixture on a chiral stationary phase. [b]Determined at the same time as % yield by LC analysis of the crude reaction mixture on a chiral stationary phase. [c]Reaction conducted with 5 mol % $[Rh(cod)OAc]_2$ and 10 mol % **L6**.



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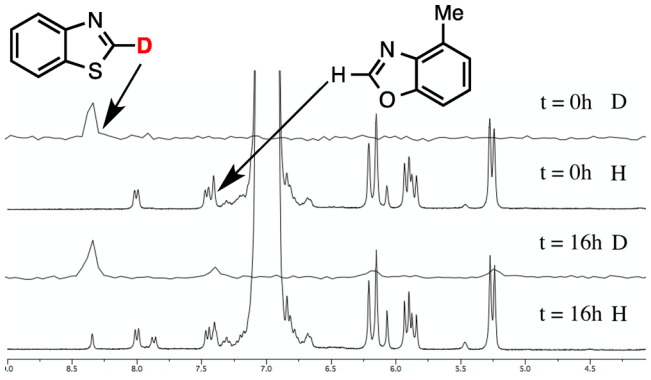
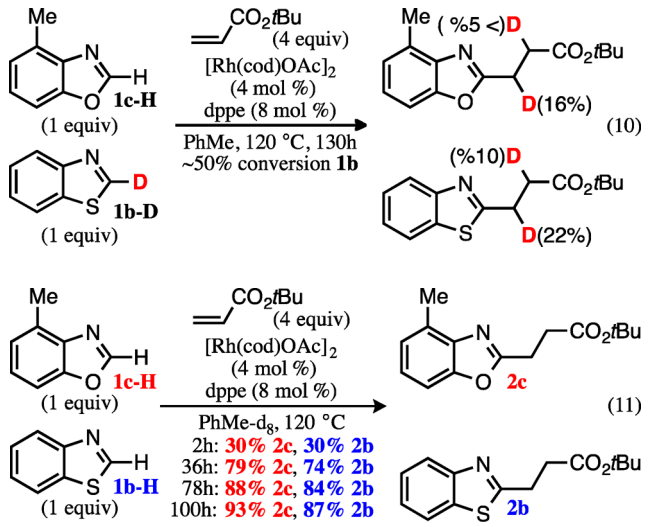


Figure 3. ^{1}H and ^{2}H NMR of competition experiment between **1c**-H and **1b**-D in PhMe implicates reversible C−H activation.



cycle similar to that offered by Chang et al. (Figure 4).[3j,24] A Rh−acetate catalyst mediates reversible C−H activation of heteroarene **1** (observation a) to provide Rh−heteroaryl complex **V**. Migratory insertion (MI) across the terminal acrylate (R = H) furnishes Rh−enolate **VI**, which isomerizes via a β-H elimination, hydrorhodation sequence to heterobenzyl-Rh **VIII** (observation c). Protonation appears to occur predominantly from **VIII** (or the N-bound isomer, vide infra). Protonation likely proceeds via an outer-sphere mechanism (observation b), but an inner-sphere mechanism after D−H exchange cannot be ruled out.

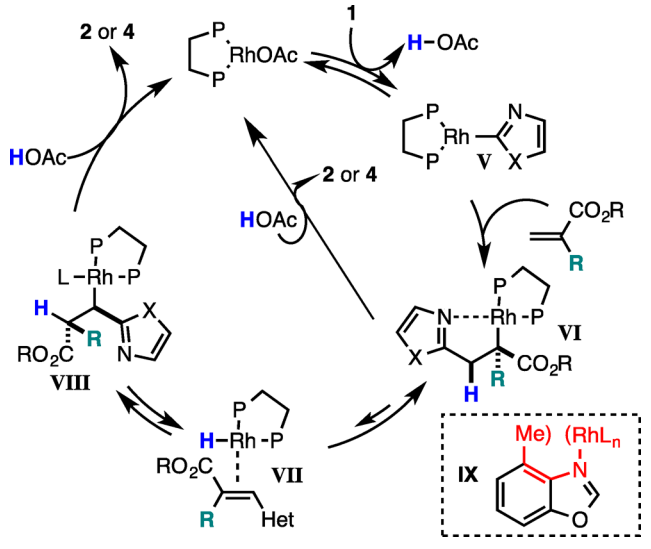


Figure 4. Proposed mechanistic cycle for the HH of terminal (**R** = H) or α-substituted (**R** ≠ H) acrylates.

Competition between **1b**-H and **1c**-H provides further mechanistic insights (eq 11). When reactive **1c** and sluggish **1b** (Chart 1) are subjected to the standard conditions, products **2b** and **2c** form in roughly equal rates (eq 11). We rationalize the identical rates of formation of **2b** and **2c** in one of two ways, both of which invoke the different ligating abilities of **1b** and **1c**. Given that C−H activation is reversible, one explanation assumes that there exists one or more irreversible steps before the turnover-limiting step (TLS) of sluggish substrate **1b**.[25] In the context of the mechanism shown in Figure 4, we assume that MI is irreversible and therefore product determining and that protonation of **1b**-derived intermediates **VI** or **VIII** is turnover limiting. Sluggish protonation of **1b**-derived **VI** or **VIII** is understood by invoking coordination of the heterocycle to rhodium in **1b**-derived intermediate **VI**. Ligation blocks a free coordination site necessary for either protonation of **VI** or isomerization to **VIII** via β-H elimination. While unhindered azoles such as **1b**, **1a**, and **1d** can presumably bind in the fashion described, A[1,3]-strain would disfavor analogous coordination of **1c**-derived **IX**, accelerating the reactivity of **1c** relative to its unsubstituted counterparts. Indeed, ^{15}N NMR studies suggest that bulky substitution adjacent to the coordinating nitrogen of various oxazoles impedes their coordination to Rh(II)-complexes.[26] To sum up, then, so long as the C−H activation, MI sequence proceeds at roughly equal rates for both substrates, products **2b** and **2c** will form in a one-to-one ratio, since all catalyst will eventually funnel to **1b**-derived **VI**.

In perhaps a more simple explanation, strongly coordinating **1b** (and **1a** and **1d**) but not weakly coordinating **1c** acts as a competitive ligand toward important intermediates on or off the catalytic cycle, slowing catalysis of both **1b** and **1c**.

Although it would be difficult to discriminate between these two explanations—one invoking an intramolecular coordination event and one invoking an intermolecular coordination event—both suggest similar avenues for reaction optimization. Specifically, if deleterious coordination of the heteroarene were responsible for low reactivity of **1a**−**1b** and **1d**, then perhaps it could be discouraged by increasing the bulk of the bisphosphine ligand. We were optimistic that increasing ligand bulk might offer additional advantages. A congested coordination environment could also encourage a difficult MI event for steric reasons, since MI necessarily reduces the metal coordination number by one.[27]

To this end, we sought to further optimize the reaction of ethyl methacrylate (**3a**) and **1c** by screening bulky Segphos derivatives (Table 2). While DTBM-Segphos (**L8**) is fairly unreactive (entry 3), DM-Segphos (**L7**) improves yields by about 20% relative to Segphos (Table 2, entries 1 vs 2). With the arene held constant, exploration of the phosphine backbone revealed CTH-(*R*)-Xylyl-P-Phos (**L11**) to be a superior ligand.[28] It provides quantitative yield of product **4ca** in excellent enantioselectivity after 24 h (entry 6). A control reaction confirms that the acetate counterion is crucial for reactivity—no product is obtained under optimal conditions when $[Rh(cod)Cl]_2$ is used.[29]

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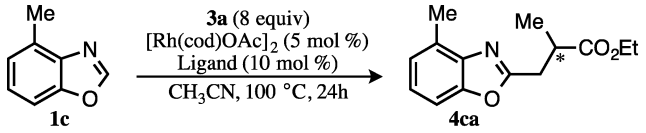
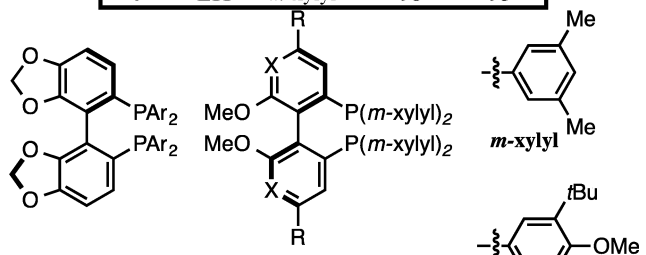
Table 2. Reaction Optimization with Second Generation, Bulky Bisphosphine Ligands



entry	ligand	Ar	4ca (%)[a]	ee (%)[b]
1	L6	Ph	58	95
2	L7	*m*-xylyl	79	93
3[c]	L8	DTBM	23	57
4	L9	*m*-xylyl	33	93
5	L10	*m*-xylyl	29	92
6	L11	*m*-xylyl	> 98	95



L6: Ar = Ph
L7: Ar = *m*-xylyl
L8: Ar = DTBM
L9: R = H X = CH
L10: R = OMe X = CH
L11: R = OMe X = N

[a,b]See footnotes for Table 1. [c]With 2 mol % $[Rh(cod)OAc]_2$, 4 mol % **L8**, 4 equiv **3a** in PhMe at 120 °C for 60 h: these conditions give **4ca** in 56% yield and 85% ee when **L6** is used as a ligand.

With these second-generation conditions in hand, we sought to examine the substrate scope of our HH reaction (Chart 2).[30] Variation of the ester group provides products **4ca**–**4cc** in excellent yields and selectivities. Methacrylonitrile (**3d**) participates in moderate yield and good enantioselectivity. The HH reaction is also tolerant of diverse acrylate backbones, although α-substitution appears crucial—racemic product **4ce** is obtained in low yield from the reaction of **1c** and ethyl crotonate (**3e**). Acrylates with benzyl, *n*-butyl, and sterically bulky isobutyl substituents at the α-position react in good yield to give products **4cf**–**4ch** in very high enantioselectivities despite the opportunity for β-H elimination into the alkyl backbone. Dimethyl itaconate (**3i**) provides good yields of functionalized product **4ci** albeit in modest enantioselectivity. Acrylate **3j** containing a protected alcohol reacts without difficulty to give silyl ether **4cj** in excellent enantioselectivity.

Notably, it was found that addition of 25 mol % CsOAc is necessary to promote reactivity for these more hindered acrylates—indeed, no product is obtained from the reaction of benzyl-substituted **3f** in its absence (Chart 2).[31] While the beneficial effect of CsOAc is not fully understood, acetate rather than cesium ion appears to be responsible for the yield improvement, since no product is obtained from the reaction of **3f** and **1c** when CsI is used in the place of CsOAc.

Finally, and much to our gratification, variation of the benzoxazole backbone is possible with bulky P-Phos ligand **L11**. Unsubstituted benzoxazole **1a** reacts smoothly; chloro- and fluoro-products **4ea**–**4fa** are assembled in high ees albeit in diminished yields. Isomeric methoxy products **4ga**–**4ha** are obtained in moderate yield and moderate to high enantioselectivities. While addition of 25 mol % CsOAc also appears to accelerate reactions with these benzoxazole substrates, its effect is less pronounced (**4aa**, 50% vs 67%). The HH reaction is not without limitations. Acrylates substituted with aryl or secondary alkyl groups do not participate effectively, nor do α,β-disubstituted acrylates or acrylates containing β-leaving groups (Figure 5).

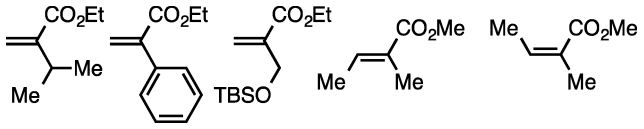
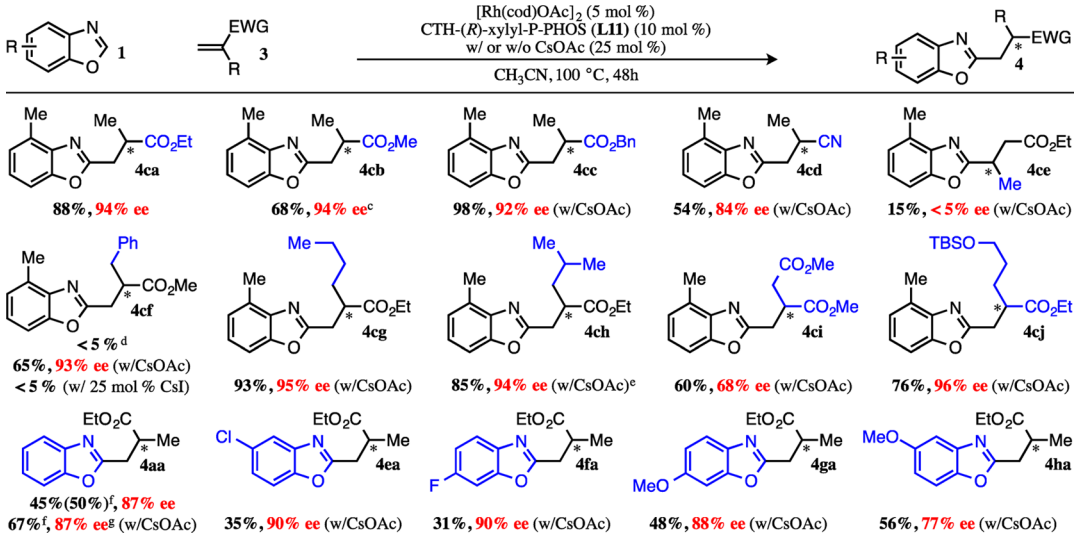


Figure 5. Acrylates that do not provide product in the HH reaction with benzoxazoles.

Chart 2. Scope of the Rh(I)–P-Phos-Catalyzed HH of Benzoxazoles and Methacrylate Derivatives[a,b]



[a]Isolated yields after column chromatography on silica gel. [b]Ees of isolated products determined by LC analysis on chiral stationary phase. [c]Reaction run for 24 h. [d]Yield determined with respect to 4,4′-di-*tert*-butylbiphenyl by LC analysis of the crude reaction mixture on a chiral stationary phase. [e]Reaction run for 80 h. [f]Yield determined with respect to 4,4′-di-*tert*-butylbiphenyl by ^{1}H NMR of the crude reaction mixture. [g]Ee determined by LC analysis of the crude reaction mixture on a chiral stationary phase.

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At this point in our studies, we wanted to better understand the origin of enantioselectivity of our HH reaction. Asymmetric protonation of a Rh−enolate (e.g., **IV** or O-bound isomer, Figure 2, eq 8) is classically invoked as the enantio-determining step of the Rh(I)−bisphosphine-mediated addition of boronic acids to α-substituted acrylates, although mechanistic evidence is sparse.[14] We chose to test plausibility of this enantio-determining step with a labeling study using deuterated **1c** (**1c**-D) (Figure 6, eq 12). Were our HH mechanism to proceed via

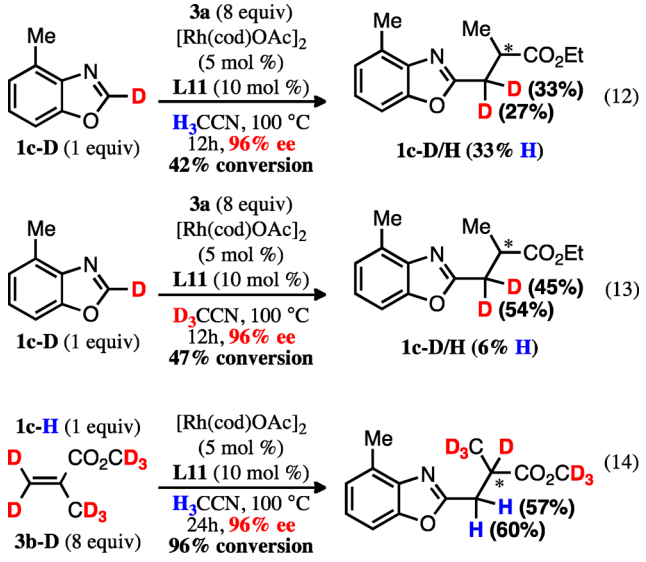

Figure 6. Labeling experiments rule out a mechanism involving enantioselective protonation of a rhodium enolate.

protonation of a Rh-enolate (e.g., **II** or **III**, Figure 2; or **VI**, Figure 4), then we should see D-incorporation at the α-position of product **4ca**, since **1c** is the terminal proton source. Contrary to this expectation, reaction of **1c**-D with **3a** to 42% conversion under standard conditions provides product **4ca**, in which D is incorporated exclusively at the β-position (eq 12). **1c** is recovered with 33% H incorporation, consistent with a reversible C−H activation event. The proton source responsible for formation of **1c**-H in eq 12 is presumably solvent: indeed, when the experiment is repeated in CD_3CN, virtually no H−D exchange in **1c**-D is observed (eq 13). All ^2H from **1c**-D is accounted for in product **4ca**, since CH_3CN cannot serve as a competitive proton source (eq 13). β-deuterium incorporation in **4ca** does not likely arise from in situ generation and subsequent preferential reaction of β-deutero **3a**, since the reciprocal reaction of **1c**-H and **3b**-d_8 gives **4ba** with ^1H-incorporation at the β-position exclusively (eq 14).

These labeling studies provide considerable insight into the reaction mechanism. First, they give grounds for dismissal of several possible elementary steps. For instance, protonation of a Rh−enolate cannot be enantiodetermining, as protonation takes place predominantly at the β- rather than the α-position.

The labeling study also seems to contradict a mechanism involving migratory insertion of a Rh(III)−heteroarene (in a 3,2 sense) or a Rh(III)−hydride (in a 2,3 sense) across acrylate **3** followed by reductive elimination to form a C−H or C−C bond respectively—this mechanism, too, would deliver products deuterated at the α- not the β-position.[32] To account for the results of our labeling experiment, then, we propose a mechanism analogous to that proffered by Chang and co-workers for the hydroheteroarylation of terminal acrylates (Figure 4, R ≠ H).[3j] Reversible C−H activation liberates a molecule of acetic acid and gives a Rh−heteroaryl complex **V**, which undergoes MI across the acrylate. At this point, a β-H elimination, hydrorhodation sequence isomerizes resultant Rh−enolate **VI** to alkyl−Rh **VIII**, which is protonated by acetic acid, regenerating RhOAc complex.

We believe that the proposed isomerization event is crucial for the high enantioselectivities obtained in our reaction. In our preferred mechanism, enantiodetermining MI delivers C-bound Rh−enolate **X** in a stereodefined fashion (Figure 7). One might

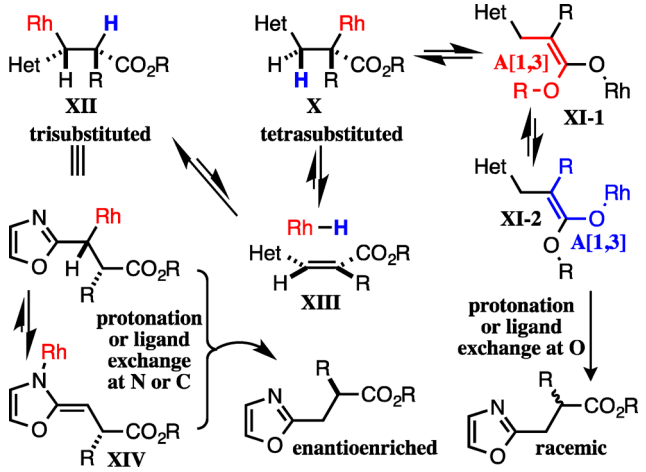

Figure 7. Rationale for isomerization of a rhodium enolate intermediate.

imagine that C-bound **X** could equilibrate with O-bound isomer **XI**(**1**−**2**). Protonation or ligand exchange of **XI** on O would deliver racemic product, and ees would suffer to the extent that this path is operative. Isomerization of Rh−enolate **X** to isomer **XII**, then, insulates the α-stereocenter from epimerization, as long as isomerization is stereospecific. Stereospecificity is guaranteed if the β-H elimination, hydrorhodation steps take place from the same face of alkene **XIII**, or said another way, if Rh−H intermediate **XIII** stays bound to the alkene in a sigma fashion. Indeed, β-H-elimination, hydrometalation sequences mediated by late transition metals have been shown to preserve with high fidelity the stereochemistry set by MI events.[4m]

This mechanism may also help explain why α-substituted acrylates are privileged substrates for our HH reaction and perhaps even for the Rh(I)−bisphosphine-mediated asymmetric hydroarylation reported by Darses and others.[14] When an α-substituted acrylate is used, C-bound Rh−enolate **X** is tetrasubstituted (Figure 7), and O-bound isomer **XI** experiences significant allylic strain, either between the ester OR group and the heterobenzylic carbon (red, **XI-1**) or between rhodium and the α-R substituent (blue, **XI-2**). Sterics may thus discourage formation of **XI** and promote isomerization to less hindered trisubstituted alkyl rhodium **XII**. Trisubstituted **XII** is further stabilized as the heterobenzyl complex. Protonation or ligand exchange may be facilitated by isomerization to Rh−enamido complex **XIV**.[33]

Final evidence for our proposed mechanism is provided by epimerization studies (Figure 8). We wanted to know why the reaction of **1c** appeared significantly more selective than the reaction of other benzoxazole substrates, particularly **1h**. We

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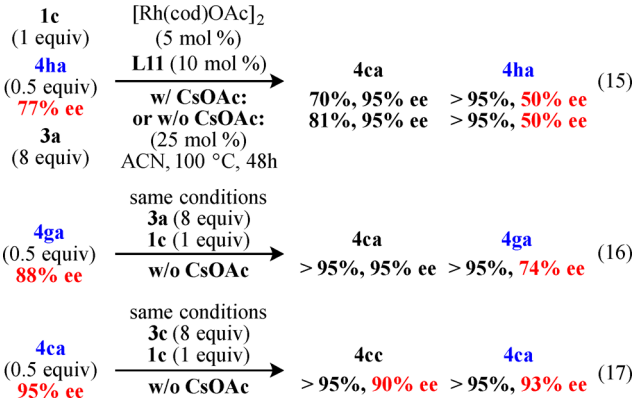

Figure 8. Epimerization experiments of **4ha**, **4ga**, and **4ca**.

speculated that epimerization over the long reaction time might be partially responsible, but we struggled to rationalize why **4ha** would epimerize more quickly than other products: the most simple racemization pathway that can be imagined is deprotonation–reprotonation of the α-stereocenter by an acetate–acetic acid couple. Yet electronics of the benzoxazole backbone should not affect acidity of the remote stereocenter. Nevertheless, we resubjected low (**4ha**), intermediate (**4ga**), and high (**4ca**) ee products to the reaction of **1c** and an appropriate acrylate (Figure 8, eqs 15–17). When low ee product **4ha** is resubjected to the reaction of **1c** and **3a** under standard conditions, it is indeed found to epimerize to 50% ee (eq 15). In contrast, the ee of product **4ca** drops to only 93% ee when it is resubjected to the reaction of **1c** and benzyl methacrylate **3c** under identical conditions (eq 17).[34] Yet epimerization does not appear to be solely responsible for the low ees of **4ha**, since intermediate ee product **4ga** also shows significant stereochemical scrambling under the reaction conditions (eq 16).

That rates of epimerization of product **4** depend crucially on the benzoxazole backbone challenges an epimerization mechanism via traditional base-assisted deprotonation of the α-stereocenter. Tenuousness of this racemization pathway is reinforced by the fact that product **4ha** epimerizes at the same rate in the presence or absence of added base (eq 15)[35] and that CsOAc alone fails to epimerize product **4ha** even after prolonged heating (data not shown).

In light of insights gained from labeling studies in eqs 12–14, we wondered whether epimerization takes place by the microscopic reverse of the mechanism proposed in Figure 7: coordination of the benzoxazole nitrogen to rhodium acidifies the heterobenzylic H of product **4**, which is abstracted by acetate (Figure 9, step **1**).[36] Resultant Rh–enamido complex **XVI**, which is in equilibrium with C-bound **XVII** (step **2**), isomerizes back into the acrylate backbone via a series of β-H-elimination, hydrorhodation events (steps **3**–**5**) to eventually give O-bound Rh–enolate **XX**. Enolate **XX** is shown as, but need not exist as, the rhodacycle. Protonation or ligand exchange of **XX** at oxygen epimerizes the α-stereocenter of product **4** (step **6**).[37] While intermediate **XVII** is shown with a specific stereochemistry at the carbon bearing rhodium, this is only intended to illustrate that no stereochemical scrambling of the α-stereocenter occurs prior to formation of O-bound **XX** if alkene **XVIII** remains coordinated to rhodium (i.e., the stereochemistry of the starting material is relayed to the stereochemistry of C-bound **XIX**).

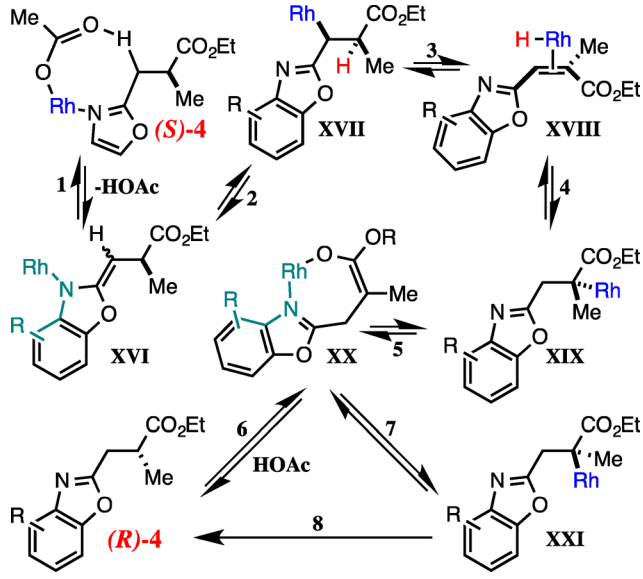

Figure 9. Proposed epimerization mechanism.

We tested credence of this mechanism by treating product **4ha** (75% ee) with $[Rh(cod)OAc]_2$ and CTH-(*R*)-xylyl-P-Phos in CD_3CN (Figure 10, eq 18), since we knew CD_3CN to be a

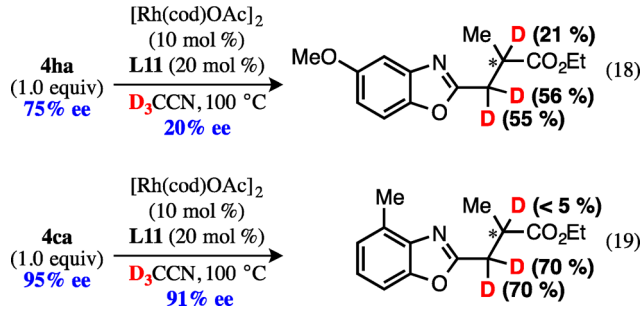

Figure 10. Epimerization–labeling experiment.

competent proton source (Figure 6, eqs 12–13). If epimerization were occurring via a typical deprotonation–reprotonation sequence at the α-carbon, then we should see ^2H incorporation at the α-position of product **4ha**. On the other hand, if the epimerization mechanism depicted in Figure 9 were operative, we would see ^2H incorporation at both β- and α-positions of product. In accord with our hypothesis, **4ha** is isolated from the reaction in eq 18 in 20% ee with significant deuterium incorporation at the α-position and predominant deuterium incorporation at the β-position.

While this data cannot unequivocally debunk a mechanism by which deuteration at the α- and β-positions occurs by independent deprotonation–reprotonation events at vicinal carbons, the level of D incorporation at the α-position of product **4ca** strongly suggests that the two incorporation events are coupled by a common intermediate. Specifically, 21% ^2H at the α-position of **4ca** does not nearly account for a 55% loss in ee of **4ca** (eq 18).[38] Thus, **4ca** must epimerize by at least one other mechanism besides protonation. We propose that Rh–enolate intermediate **XX** has two opportunities to scramble α-stereochemistry. It can, as already discussed, protonate or undergo ligand exchange on oxygen to give enantiomeric product (Figure 9, step 6). Yet protonation is not necessary for epimerization to occur. To the extent that the α-stereo-

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chemistry of C-bound **XIX** is lost in O-bound **XX**, then isomerization back to the C-bound isomer should be able to deliver diastereomeric complex **XXI** in which α-stereochemistry is inverted (step 7). A reverse sequence of elimination, addition events relays **XXI** to enantiomeric product (step 8).

We wondered how the epimerization mechanism depicted in Figure 9 could account for the very different fates of low ee product **4ha** and high ee product **4ca** when they are resubjected to our Rh−bisphosphine system. Interestingly, when highly enantioenriched product **4ca** (95% ee) is treated with rhodium and ligand under identical conditions to those described for **4ha**, it also deuterates considerably at the β-position (Figure 10, eq 19). In contrast to **4ha**, however, product **4ca** epimerizes quite slowly (to 91%) even at high dimer loading, and it shows no discernible ^{2}H incorporation at the α-position. We provide two possible explanations to account for the data in eqs 18−19, but alternatives are possible. As illustrated in Figure 9, deprotonation of **4** gives Rh−enamido complex **XVI** (step **1**). It is possible that A[1,3]-strain between the axial methyl of **4ca** and rhodium shortens the lifetime of **XVI** such that a rapid backward reaction—protonation of **XVI**—outcompetes isomerization into the acrylate backbone (step **2**).

An alternative explanation invokes differential stability of **4ha** and **4ca** Rh−enolate complexes **XX** (Figure 9). Whereas coordination of the heterocyclic nitrogen to rhodium could stabilize a **4ha**-derived Rh−enolate **XX**, A[1,3]-strain would prevent analogous stabilization of **4ca**-derived **XX**. In either case, relative coordinating abilities of **4ca** and other benzoxazoles appear to crucially influence product epimerization rates. If this is true, then our bulky P-Phos ligand may serve an additional service: it may discourage ligation-promoted racemization.

SUMMARY

In summary, mechanistic insights gained from a known reaction of heterocycles and *tert*-butyl acrylate[3j] have enabled development of an asymmetric, hydroheteroarylation reaction of benzoxazoles and α-substituted methacrylate derivatives. The reaction is mediated by a Rh(I)−acetate precatalyst and bulky bisphosphine ligand, CTH-(*R*)-xylyl-P-Phos, and it delivers diverse elaborated benzoxazole products in moderate to excellent yields and good to excellent enantioselectivities. Mechanistically, the reaction is thought to proceed via a C−H activation, MI, and protonation sequence in which acetate serves as a proton shuttle. Labeling studies implicate MI as a possible enantiodetermining step, after which stereospecific isomerization to a Rh−heterobenzyl complex insulates the newly formed stereocenter from epimerization. Products that are good ligands for rhodium can epimerize by a reverse sequence: coordination and subsequent C−H activation at the heterobenzylic position provide a Rh−enamido complex. A series of β-H elimination, hydrorhodation events relays the enamido complex to O-bound Rh−enolate, in which α-stereochemistry is lost. Our proposed mechanism differs importantly from those implicated in studies describing the related Rh(I)−bisphosphine-mediated hydroarylation of α-substituted acrylates with boronic acids.[14] These studies invoke protonation of a rhodium enolate as the enantio-determining step of the reaction. Since little mechanistic evidence is provided in these studies, it is conceivable that an isomerization pathway such as ours is operative in these systems. Finally, a bulky bisphosphine ligand is found to be crucial for reactivity and selectivity in our HH reaction, as it likely discourages deleterious coordination of benzoxazole substrates to on- or off-cycle intermediates, accelerates a difficult MI step, and discourages coordination-initiated epimerization. In short, careful mechanistic analysis has enabled the development of an efficient and highly selective catalytic, asymmetric HH of readily accessible reagents to produce chiral compounds of high biological importance.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; characterization data, ^{1}H NMR, ^{13}C NMR, and HPLC spectra for new compounds; crystallographic data for [Rh(cod)OAc]$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(23) Substrate **1b** (vs **1a**) was chosen for the experiment, since the C−H resonance of the azole is easily resolved from that of **1c**.

(24) Chang et al. also see deuterium scrambling in the products of a reaction between ethyl acrylate and a mixture of proteo- and deutero-pyridine oxides (ref 3j.).

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(29) In the absence of CsOAc, $[Rh(cod)Cl]_2$ is also an ineffective precatalyst in the chemistry of Chang et al. (ref 3j).
(30) Absolute configuration was not determined. Thus, product stereocenters are indicated with an asterisk.
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(34) 93% ee may overestimate the degree of epimerization of **4ca** under the described conditions, since a minor impurity coelutes with the minor enantiomer. Some epimerization may very well occur, however, since **4ca** does indeed epimerize in presence of higher catalyst concentrations (vide infra, Figure 10, eq 19).
(35) The higher yield of **4ca** obtained in the reaction with CsOAc is consistent with the accelerating effect of CsOAc reported earlier (see Chart 2, **4aa** and **4cf** and discussion).
(36) For reversible formation of a Rh(I)−enamido complex from an imine precursor, see: Zhao, P.; Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 12066−12073.
(37) For simplicity, this figure shows only formation of (*R*)-product from O-bound XX (step 6), yet (*S*)-product is presumably also formed.
(38) Since the amount of deuterium in CD_3CN presumably overwhelms the amount of H^+ liberated from product **4**, we approximate that 1% ^2H will incorporate into the α-position for each protonation event. Each (*R*) → (*S*) conversion contributes 2% ee, which means we would need (75% starting ee − 20% final ee)/2 ∼ 28 protonation events *if all were selective for the minor enantiomer*. In reality, protonation should give both enantiomers of product. A significant excess of protonation events is needed, then, to account for the observed 55% ee difference. The deuterium incorporation in **4ca** should reflect this excess.

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