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Development and Mechanistic Investigations of Enantioselective Pd-Catalyzed Intermolecular Hydroaminations of Internal Dienes

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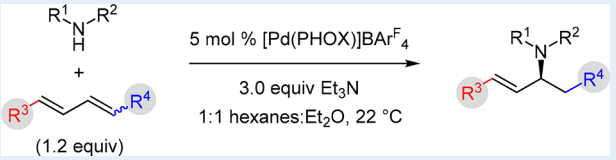
Supporting Information

ABSTRACT: We report the development of highly enantio- and regioselective Pd-catalyzed intermolecular hydroaminations of challenging 1,4-disubstituted acyclic dienes. Several aryl/alkyl-disubstituted dienes and a sterically differentiated alkyl/alkyl-disubstituted diene undergo coupling with a variety of secondary aliphatic amines, indoline, and primary anilines to generate allylic amines with myriad α-alkyl groups in up to 78% yield, >98:2 rr, and 98.5:1.5 er. A number of experiments, including deuterium labeling and transamination studies, shed light on mechanistic details of the reaction, such as the reversibility of individual steps of the proposed catalytic cycle and of the reaction as a whole.



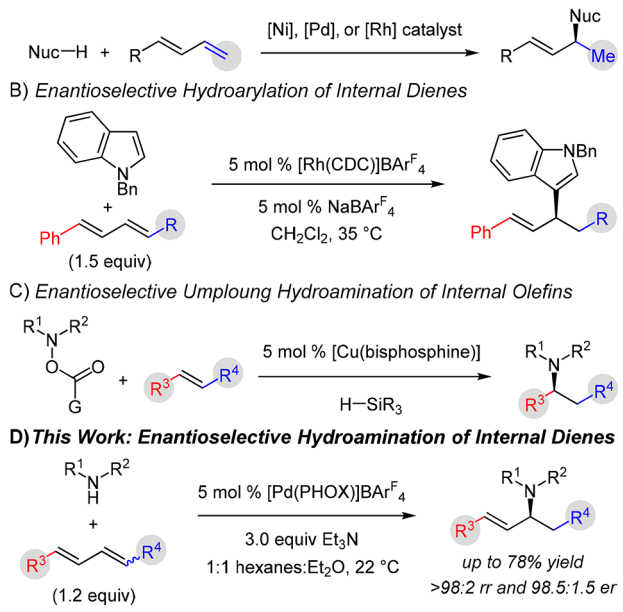
KEYWORDS: *palladium, hydroamination, allylic amines, enantioselectivity, mechanism*

INTRODUCTION

The enantioselective synthesis of molecules bearing allylic stereogenic centers is an important undertaking due to the prevalence of this motif in a large number of natural products and bioactive compounds and the influence of the stereogenic center in subsequent diastereoselective transformations of the olefin.[1] The union of two reactants through allylic substitution is a hallmark method for generating this scaffold but does not often afford compounds with 1,2-disubstituted alkenes.[2−4] Enantioselective reactions of acyclic 1,3-dienes[5] provide one route to chiral allyl fragments that bear 1,2-disubstituted olefins, and hydrofunctionalizations are a significant subset of these.

A handful of research groups, including our own, have studied enantioselective intermolecular hydrofunctionalizations of dienes. Apart from reactions of cyclohexadiene reported by the Hartwig lab,[6] existing methods have utilized terminal acyclic dienes[7−9] for C−N and C−C bond-forming transformations, exclusively affording compounds with methyl-substituted stereogenic centers (Scheme 1A). For example, we have demonstrated that Pd−PHOX catalysts are highly efficient for promoting regio- and enantioselective additions of both aliphatic amines and carbon pronucleophiles to terminal 1,3-dienes;[10] however, under the optimal conditions for these transformations, internal dienes fail to react. In general, enantioselective functionalizations of 1,4-disubstituted acyclic dienes are rare,[11−13] especially via nucleophilic addition. Meek and co-workers recently reported the first such examples, showing indole additions to this class of dienes (hydroarylation) catalyzed by a Rh−carbodicarbene (CDC) complex (Scheme 1B).[14] High levels of enantio- and regioselectivity were observed. Generally, there is a dearth of methods available for the hydroamination of disubstituted olefins via nucleophilic addition with unfunctionalized amines,[15] although recently a number of laboratories have disclosed umpolung strategies with electrophilic, prefunctionalized amination agents to achieve this aim (Scheme 1C).[16] In this work, we demonstrate that Pd−PHOX complexes with a noncoordinating BAr$^F_4$ counteranion catalyze the hydroamination[17,18] of internal 1,3-dienes (Scheme 1D). The

Scheme 1. Representative Enantioselective Intermolecular Hydrofunctionalizations of Olefins



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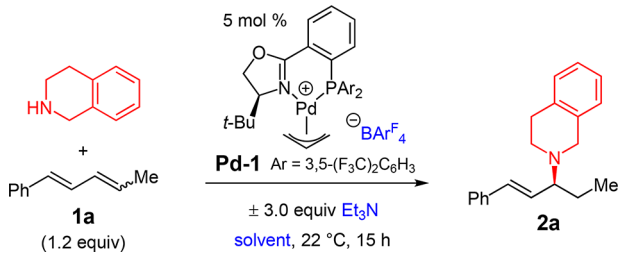
addition of Et_3N and the choice of solvent proved crucial for reaction efficiency and enantioselectivity, delivering products with allylic stereogenic centers comprised of a number of alkyl substituents in up to 78% yield, 98.5:1.5 er, and with >98:2 regiomeric ratio (rr).

RESULTS AND DISCUSSION

We initiated our investigations by examining the hydroamination of diene **1a** (Table 1) with tetrahydroisoquinoline

Table 1. Examination of Reaction Conditions for Enantioselective Hydroamination of Internal Dienes[a]



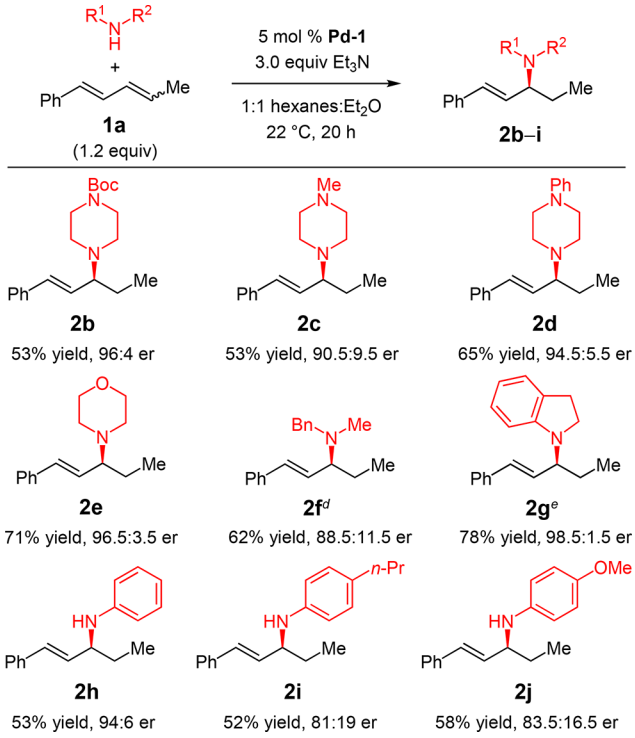
entry	solvent	Et_3N	yield (%)[b]	er[c]
1	CH_2Cl_2	N	27	57.5:42.5
2	CH_2Cl_2	Y	43	54:46
3	THF	Y	5	94:6
4	1,4-dioxane	Y	27	89:11
5	Et_2O	Y	42	94:6
6	hexanes	Y	62	80:20
7	1:1 hexanes:Et_2O	Y	65	93:7
8	1:1 hexanes:Et_2O	N	13	93:7
9[d]	1:1 hexanes:Et_2O	Y	63	96.5:3.5

[a]Reactions run under N_2 with 0.2 mmol tetrahydroisoquinoline in 0.2 mL solvent. **1a** is a 1:1.8 *E,E:E,Z* mixture of olefin isomers. >98:2 rr for **2a** in all cases. [b]Isolated yield of purified **2a**. [c]Enantiomeric ratio determined by HPLC analysis of purified **2a**. [d]7 h reaction.

(THIQ). Although the analogous catalyst bearing a BF_4 counterion does not effect hydroamination, **Pd-1** with its BAr^F_4 counteranion generates 1,2-addition product **2a** as the sole regioisomer in 27% yield but with low enantioselectivity (entry 1). Addition of Et_3N to the mixture further improved the yield of **2a** but without increasing enantioselectivity (entry 2).[19] Contrastingly, ethereal solvents lead to dramatically higher stereoselectivity (entries 3−5) with Et_2O delivering **2a** in 42% yield. Somewhat surprisingly, we discovered that hexanes as solvent further improved the yield (62%, 80:20 er, entry 6) and that a 1:1 hexanes:Et_2O mixture gives the best observed balance of yield and enantioselectivity (65% yield, 93:7 er, entry 7). As shown in entry 8, the nonpolar reaction medium is not sufficient for the observed efficiency: Et_3N is still required. We also found that reducing the reaction time from 15 to 7 h still leads to 63% yield of **2a** but with significantly higher enantioselectivity (96.5:3.5 er, entry 9), suggesting that reaction reversibility over time is responsible for product enantiomerization (*vide infra*).

Under the optimized reaction conditions, several secondary aliphatic amines undergo addition to pentadiene **1a** in 15−20 h (Table 2). N-Substituted piperazines afford allylic amines **2b−d** in moderate yield and with excellent regio- and enantioselectivity (90.5:9.5 to 96:4 er). Morpholine reacts to give **2e** in 71% yield and 96.5:3.5 er. Other secondary amines, such as piperidine and pyrrolidine, are unreactive despite their

Table 2. Amine Scope in Pd-Catalyzed Hydroamination of Internal Dienes[a,b,c]



[a]Reactions run under N_2 with 0.2 mmol amine in 0.2 mL solvent. **1a** is a 1:1.8 *E,E:E,Z* mixture of olefin isomers. > 98:2 rr for **2** in all cases unless otherwise noted. [b]Isolated yield of purified **2**. [c]Enantiomeric ratio determined by HPLC analysis of purified **2**. [d]15 h reaction. [e]1 h reaction.

greater nucleophilicity,[20] possibly due to the higher pK_a's of their conjugate acids compared to the more electron deficient morpholine, piperazines, and THIQ. Acyclic *N*-methylbenzylamine also efficiently generates allylic amine **2f** in 62% yield and 88.5:11.5 er; however, with the sterically more demanding diethyl- and dibenzylamine, no hydroamination product could be observed. Primary alkyl amines are unreactive, presumably attributable to their lower nucleophilicity in comparison to secondary amines.[20b]

Indoline proved to be an exceptionally good nucleophile for internal diene hydroamination, but the reaction is prone to reversibility. In just 1 h, tertiary amine **2g** is obtained in 78% yield and 98.5:1.5 er but the enantiomer ratio declines to 88:12 after 20 h without improving the yield. Despite the lack of reactivity of primary alkyl amines, some primary anilines participate in the hydroamination of internal dienes. At room temperature, secondary amines **2h−j** are generated in 52−58% yield as a single regioisomer. Aniline itself leads to high enantioselectivity 94:6 er for **2h**), but small perturbations in nucleophile structure greatly affect the reaction outcome as can be seen in the significantly diminished enantioselectivity in forming **2i** and **2j**. For these latter two, enantioselectivity is constant throughout the course of the reaction. More electron poor anilines show lower reactivity, epitomized by *p*-trifluoromethylaniline, which fails to deliver any product.[19] Thus, while the acidity of the aniline is important, its nucleophilicity is also a crucial factor for reaction efficiency (cf., aliphatic amines). No matter which amine was employed

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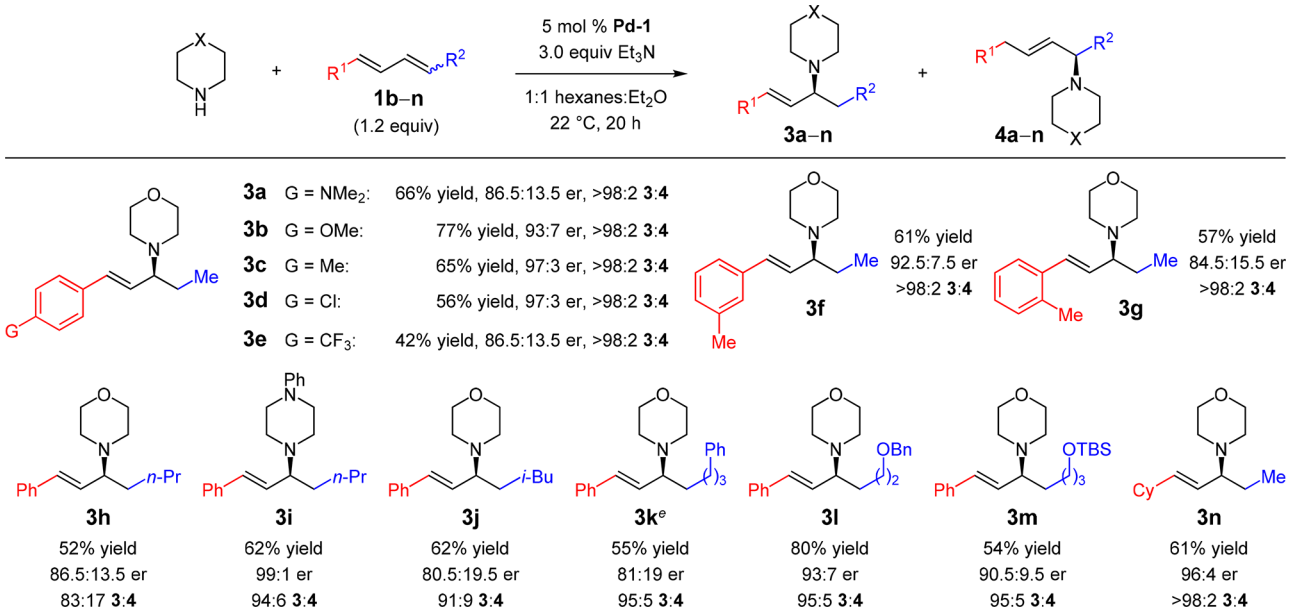
Table 3. Internal Diene Variation in Enantioselective Hydroamination[a,b,c,d]



[a]1:1 to 1:5 *E,E:E,Z* mixture of diene **1** unless otherwise noted; see the Supporting Information for details. [b]Isolated yield of purified **3**. [c]Enantiomeric ratio determined by HPLC analysis of purified **3**. [d]Regiomeric ratio of **3**:**4** determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [e]>20:1 *E,E:E,Z* diene **1k**.

in the hydroamination (Table 2), Et_3N was found to be essential for reaction efficiency.[19]

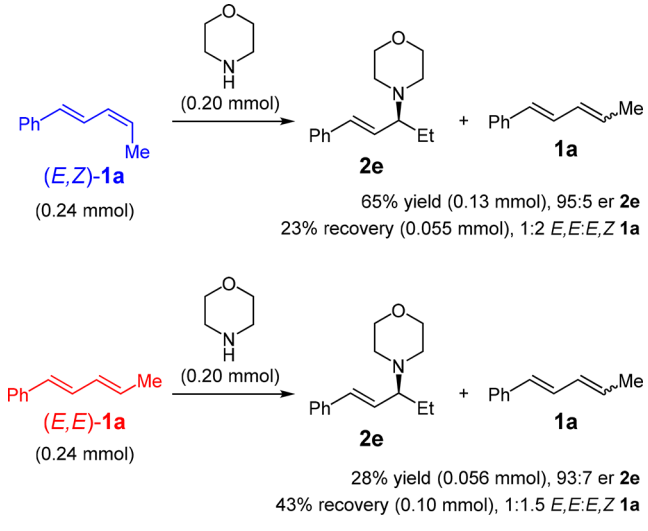
A range of unsymmetrical internal dienes take part in Pd-catalyzed hydroamination (Table 3). Substrates with electron rich aromatic rings (**1b–d**) lead to the highest yields in reactions with morpholine, delivering products **3a–c** with good to excellent levels of enantioselectivity. More electron deficient arenes are tolerated (generation of **3d–e**); yields are somewhat reduced, but enantioselectivity remains high. Notably and in contrast to electronic variation of the aryl group of terminal dienes,[10b] only 1,2-hydroamination product **3** is observed in all cases. Other positional substitution of the aromatic ring has minimal effect on the reaction yield and regioselectivity, again a significant difference to the analogous terminal dienes (formation of **3f–g**); however, enantioselectivity decreases as the substituent is moved closer to the diene's point of attachment (compare **3c**, **3f**, and **3g**).

A number of alkyl groups (R^2) were explored for the intermolecular hydroamination. As this substituent becomes larger than methyl, regioselectivity remains high but is imperfect (83:17 to 95:5 rr). Reactions proceed in moderate to good yield (52–80%) and enantioselectivity (80.5:19.5 to 99:1 er). Ethereal functionality is tolerated; however, carbonyl and amino groups inhibit catalysis. It is notable that in some cases, different amines may lead to drastically different selectivities in additions to a diene. For example, an *n*-propyl-substituted diene undergoes reaction with morpholine to generate allyl amine **3h** with only 83:17 rr and 86.5:13.5 er. In contrast, the same diene reacts with *N*-phenylpiperazine to deliver **3i** in 94:6 rr and 99:1 er. In both cases, enantioselectivity remains roughly unchanged throughout the course of the reaction. However, such disparate selectivity with these amines is not a general phenomenon, and few trends in reaction efficiency or selectivity could be gleaned from our variations in R^2 identity.

Alkyl/alkyl-substituted dienes also participate in **Pd-1**-catalyzed hydroamination. As long as the two groups are sterically differentiated, high regioselectivity is observed.[19] Morpholine addition to diene **1n** furnishes allylic amine **3n** as a single isomer in 96:4 er.

In most transformations presented in Tables 1–3, a mixture of diene stereoisomers was employed. To evaluate the impact of stereochemistry upon hydroamination, we separately prepared the two stereoisomers of diene **1a** and utilized each in the hydroamination with morpholine (Scheme 2). Each diene stereoisomer is capable of furnishing allylic amine (*S*)-**2e**, and in each case, the product is formed with excellent enantioselectivity; however, (*E,Z*)-**1a** generates substantially more product than the (*E,E*)-isomer (65 vs 28% yield). The

Scheme 2. Reaction Outcome Dependence on Diene Stereochemistry[a]



[a]Reaction conditions: **Pd-1** (0.05 equiv), Et_3N (3.0 equiv), 1:1 hexanes:Et_2O, 22 °C, 20 h.

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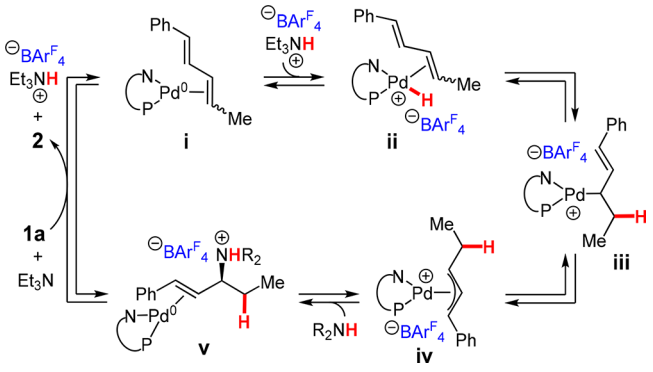
result with the (*E,Z*)-diene is similar to that obtained with the 1:1.8 *E,E*:*E,Z* stereochemical mixture. Notably, in the independent reaction of either stereoisomer, diene **1a** is recovered as a stereochemical mixture that slightly favors the (*E,Z*)-isomer. Although the stereochemical preference for recovering the (*E,Z*)-diene cannot be explained at this time, the results also highlight that isomerization of the diene stereochemistry is occurring with at least a similar if not faster rate as product formation. Additionally, the data are highly suggestive that diene coordination is faster than the isomerization process that interconverts (*E,E*)- and (*E,Z*)-**1a**.

Building upon this observation, in an effort to probe aspects of overall reaction reversibility and the reversibility of individual steps of the catalytic cycle, we carried out a series of experiments. As a framework for discussion, a proposed catalytic cycle[21] for the internal diene hydroamination is shown in Scheme 3. After initiation of **Pd-1**,[22] coordination of diene

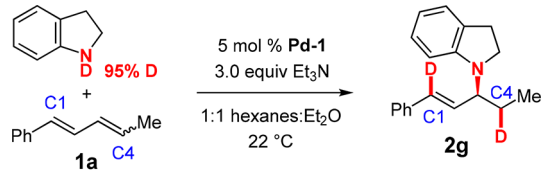
Scheme 3. Proposed Catalytic Cycle for Internal Diene Hydroamination



1a to Pd^0–PHOX affords intermediate **i**. Oxidative protonation by [Et_3NH]BAr^F_4 then forms Pd hydride **ii**. Diene migratory insertion to Pd–H leads initially to Pd–σ-allyl **iii**, which may collapse to π-allyl **iv**. Subsequent attack by the amine generates the Pd^0–allylic ammonium complex **v**, whose deprotonation with Et_3N followed by olefin exchange with diene **1a** then forms product **2** and regenerates **i**.

We first wished to separate the reversibility of the overall reaction from the reversibility of Pd–PHOX association with the diene and Pd–H migratory insertion.[10b,21,23] To accomplish this, we employed 95% N-deuterated indoline[24] (Table 4). This would enable us (1) to track the position of the label with respect to the amine within addition product **2g**, (2) to assess the degree to which the label was incorporated in this product, and (3) to evaluate whether recovered diene **1a** bore any of the label. With the labeled indoline, amine **2g** was isolated in 13% yield after 2 h (entry 1) and 28% yield after 20 h (entry 2), a significantly slower rate than the reaction of unlabeled indoline. ^{1}H NMR analysis of **2g** showed ca. 23% D incorporation at C4 in both cases (3.5% of available D in entry 1 and 6.5% in entry 2). The D content at C1 could not be accurately determined by ^{1}H NMR due to overlap of the C1 ^{1}H signal with indoline aromatic resonances. However, high resolution mass spectrometry revealed the total D content in the product is greater, illustrating that deuterium is divided between the C1 and C4 carbons.[19] Notably, although the indicated insertion at either olefin would lead to different product regioisomers, only one isomer of product is formed in the reaction.

Table 4. Deuterium Labeling Studies in Indoline Addition to Diene 1a[a]



entry	time (h)	yield **2g** (%)[b]	C4% D in **2g**[c,d]	recovered **1a** (%)[b]	*E,E*:*E,Z* of **1a**[c]	C1; C4% D *E,E*- and *E,Z*-**1a**[c]
1	2	13[e]	24	79	1.4:1	*E,E*: 15; 15
						E,Z: 38; 48
2	20	28[f]	22	56	1.8:1	*E,E*: 15; 19
						E,Z: 45; 61

[a]1:1.8 *E,E*:*E,Z* mixture of diene **1a**. >98:2 rr for **2g** in both cases. [b]Isolated purified compound. [c]Determined by 400 MHz ^{1}H NMR spectroscopy of purified compound. [d]Deuterium content at C1 in **2g** could not be accurately determined by ^{1}H NMR due to overlap of the C1 proton with indoline aryl protons. [e]95:5 er. [f]91:9 er.

Furthermore, in both cases, significantly more of the deuterium label appears in recovered diene **1a** (44% of available D in entry 1 and 35% in entry 2) than in product **2g**, and at both time points, deuterium is approximately evenly distributed between C1 and C4 (likely deuterium is roughly evenly distributed between these two sites in **2g** as well). These data suggest that Pd–H/D insertion to the diene, followed by β-hydride elimination and diene dissociation are significantly faster than formation of Pd–π-allyl **iv** and/or the amine attack upon it to deliver product. Notably, there is higher deuterium content in recovered (*E,Z*)-**1a** than in the (*E,E*)-isomer.

Importantly, the overall deuterium content in **2g** plus recovered **1a** is considerably greater than the yield of the allylic amine. For entry 1, after 2 h there is 13% yield of **2g** yet 48% of the label appears in the isolated compounds. In entry 2 (20 h reaction), 51% of the label was transferred from the amine. We infer that the balance of the label remains at indoline. These results indicate that a mechanism connected to but beyond the simple hydroamination catalytic cycle depicted in Scheme 3 exists for exchanging hydrogen from diene **1a** for deuterium from indoline and that this process is faster than hydroamination. For example, Pd–H, formed via a β-hydride elimination that generates deuterated diene **1a**, may exchange H for D by acid/base reaction with indoline, perhaps mediated by Et_3N. This equilibrium isotope effect is likely one factor contributing to the slower rate with deuterated indoline, and the 50% distribution of the label between indoline and **1a**/**2g** appears to be established early in the reaction course.

We next investigated the reversibility[25] of C–N bond formation and the stereochemical consequences in a series of experiments. THIQ addition product **2a** (95:5 er) was subjected to 5 mol % **Pd-1** and 5 mol % additional THIQ[22] in the absence of diene under otherwise standard conditions (Scheme 4). After 20 h, 80% of **2a** was recovered, but in lower enantiopurity (81:19 er), accompanied by 20% yield of diene **1a**. The isolation of **1a** from the reaction mixture confirms that the reaction is fully reversible to the free diene, thereby providing a pathway for product enantiomerization. An identical experiment involving morpholine and its addition product **2e** delivers a similar result.[19]

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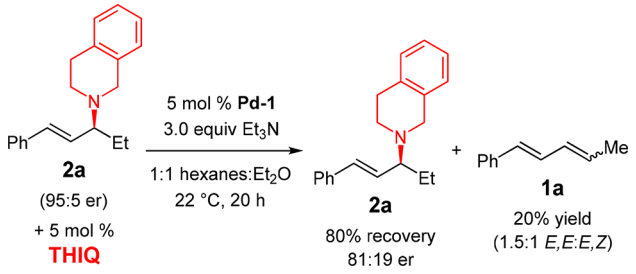
Scheme 4. Demonstration of Reaction Reversibility in Hydroaminations

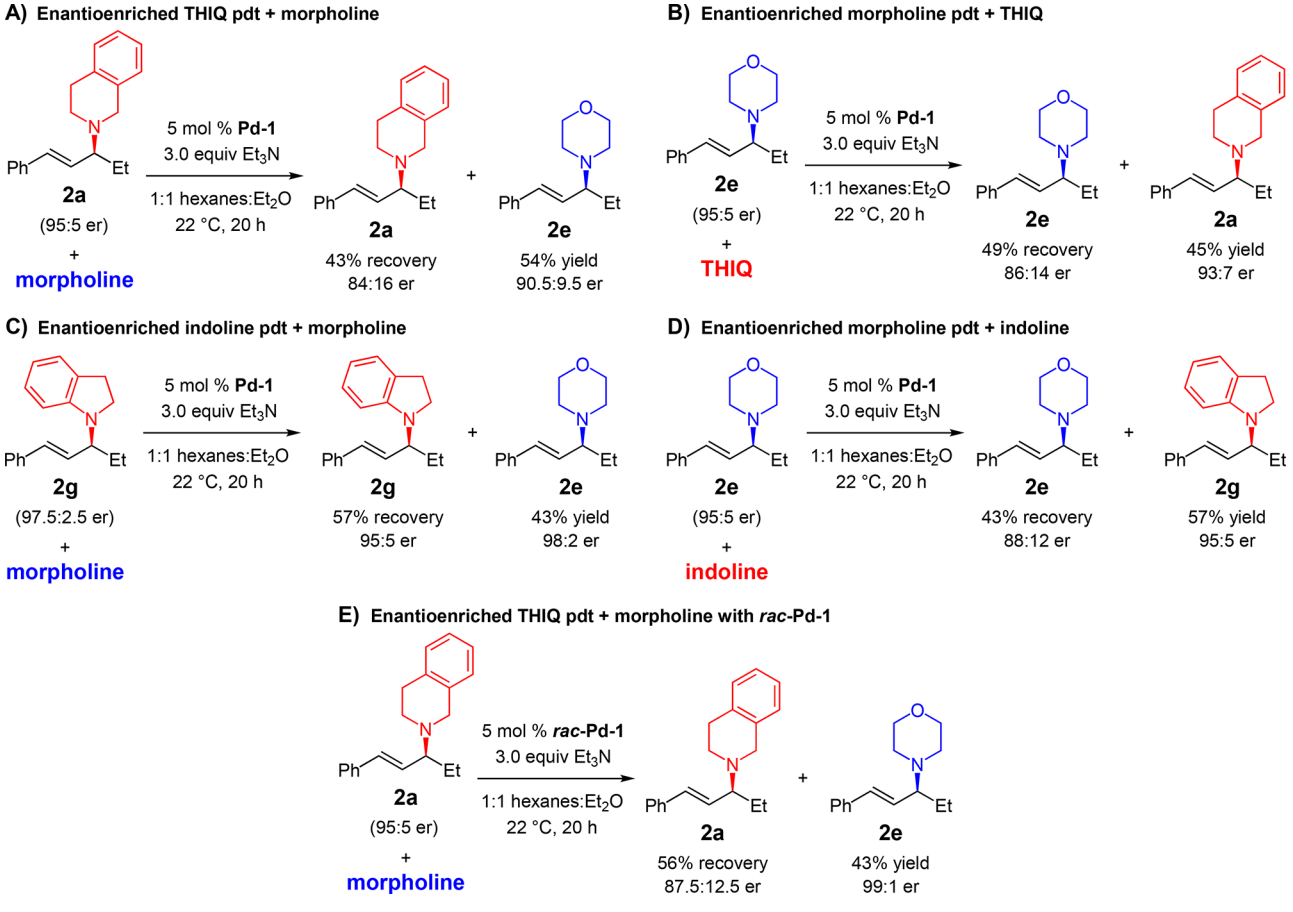


The similarity in mechanism between allylic amination and diene hydroamination bears further discussion. Considering the proposed hydroamination catalytic cycle in Scheme 3 and our observations of reaction reversibility to the diene, one might ask if product enantiomerization in Pd-catalyzed allylic amination can also occur via β-hydride elimination to a diene from a Pd−allyl species. Indeed, Bunt and co-workers[26,27] have illustrated that large quantities of diene may be formed during allylic aminations, including those catalyzed by Pd−PHOX complexes, although the amount of diene was heavily dependent on the ligand, the solvent, and the identity or presence of added base; amine bases tended to lead to more diene. Two additional points are noteworthy in comparing these two related transformations. (1) There are relatively few Pd-catalyzed allylic aminations where there is an opportunity for acyclic diene formation,[2,3] especially where Pd−PHOX catalysts have been utilized.[28] (2) Whereas allylic substitution conditions are inherently neutral to basic, hydroaminations conditions are overall acidic, even when buffered with Et_3N such as in the internal diene hydroaminations developed here. Added acid may accelerate reaction rate but can lead to product racemization, likely via diene formation.[6b,23c]

The conditions imposed in the reaction in Scheme 4—no excess of amine in the presence of Pd−π-allyl **iv**—more resemble the hypothetical situation near the end of a hydroamination reaction, allowing π-allyl **iv** to readily collapse to σ-allyl **iii**, which is in rapid equilibrium with the free diene **1a** (inferred from deuterated amine studies in Table 4). Preferential ionization of the major enantiomer of **2a** with **Pd-1** and its equilibration with **1a** account for the considerable reduction in **2a** enantiopurity.[29] In this process that begins with **2a** (1.0 M), the overall decline in enantiopurity is significantly greater over 20 h than what is observed in the hydroamination reaction that converts diene **1a** to allylic amine **2a** (Table 1).

To establish if π-allyl **iv** could be rapidly intercepted by excess amine before forming σ-allyl **iii**, thereby preserving enantiopurity, we additionally studied a handful of transamination reactions (Scheme 5).[2f,23] THIQ addition product **2a** reacts with morpholine under optimized hydroamination conditions to deliver a nearly equal mixture of THIQ and morpholine adducts **2a** and **2e**, respectively (Scheme 5A). The THIQ allyl amine **2a** is recovered with significantly lower enantiopurity but morpholine-containing **2e** is formed in only a somewhat lower 90.5:9.5 er. The reverse transamination

Scheme 5. Studies Demonstrating Enantiospecificity in Transaminations with Pd-1



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process, **2e** reaction with THIQ, affords a similar result with THIQ adduct **2a** generated in only somewhat diminished er but with morpholine adduct **2e** recovered in more significantly diminished enantiopurity (Scheme 5B).[19] Diene **1a** cannot be detected with the excess of secondary amine present in either transamination reaction, although the decreased er of the transamination products compared to the starting allylic amines suggests the diene is generated to some degree in each case. If reactions were occurring exclusively through π-allyl **iv**, the enantiomer ratio of the transamination product should be the same as the starting allylic amine (100% enantiospecificity). Therefore, the transaminations in parts A and B of Scheme 5 could be proceeding solely via conversion of the allylic amine starting material to diene **1a** followed by enantioselective hydroamination of the diene (coupled with equilibration that lowers enantiopurity over time) or largely through an enantiospecific transformation with some stereochemical erosion by reaction reversal to diene **1a**. Thus, we examined additional transaminations.

When indoline adduct **2g** is subjected to morpholine (Scheme 5C), a mixture of **2e** and **2g** is generated: incredibly, **2g** is recovered with only somewhat decreased er over the 20 h reaction (97.5:2.5 to 95:5 er), despite the fact that in the indoline hydroamination of diene **1a** that affords **2g**, the er is lowered from 98.5:1.5 to 88:12 er over the same time period (Table 2). Furthermore, morpholine addition product **2e** is furnished in 98:2 er, essentially the same enantiopurity as the starting allylic amine **2g** that was subjected to the transamination and measurably higher than in the morpholine hydroamination of diene **1a** (96.5:3.5 er, Table 2). It should be noted, however, that in the hydroamination of **1a** with morpholine the enantioselectivity in forming allylic amine **2e** is initially 98:2 er (5 h, 38% yield) but declines over the 20 h course of the reaction.[19] The reverse transamination, reaction of morpholine adduct **2e** (95:5 er) with indoline, delivers allyl indoline **2g** in the same enantiopurity as the starting material **2e** (Scheme 5D). Morpholine-containing **2e** is recovered in a diminished 88:12 er. Although this decline appears greater than the loss of enantiopurity of **2g** in Scheme 5C, it should be remembered that the conversion of morpholine adduct **2e** in Scheme 5D is greater and its starting enantiomer ratio was not as large. Therefore, in both cases, the lower enantiopurity of the recovered allylic amine is reflective of the preferential ionization of the major enantiomer with **Pd-1** and the overall level of conversion. Once more, diene **1a** cannot be detected in the transaminations in parts C and D of Scheme 5. The data support, but perhaps do not conclusively prove, that indoline-morpholine transaminations are completely enantiospecific with **Pd-1**.

The question therefore still remained to what extent the transaminations in parts A and B of Schemes 5 were enantioselective (generation of **2e** by an enantioconvergent reaction via diene **1a**, Curtin-Hammett kinetics) versus enantiospecific (generation of **2e** from Pd–π-allyl **iv**). We therefore employed racemic **Pd-1** catalyst with enantioenriched allylic amine **2a** and morpholine to distinguish between these two possibilities (Scheme 5E). We found that subjection of **2a** (95:5 er) to morpholine with racemic catalyst leads to product **2e** in 43% yield and 99:1 er,[30] indicating that the transaminations involving THIQ and morpholine are largely enantiospecific with **Pd-1**. By analogy, we presume that the transaminations in parts C and D of Scheme 5 are completely enantiospecific. Thus, the degree of enantiospecificity in transaminations with **Pd-1** appears somewhat dependent on the nature of the amine in contrast to related transaminations with Pd–BINAP.[2f,23a]

Taken together, our data suggest that the catalyst derived from **Pd-1** is capable of reversing several, if not all, hydroamination reactions of internal dienes. The equilibrium position has not been formally established, but the reaction in Scheme 4, where 80% of THIQ adduct **2a** was recovered after 20 h (81:19 er), suggests it favors the products in at least some instances. Therefore, it is notable that in THIQ hydroamination of diene **1a** with **Pd-1**, allylic amine **2a** is maximally obtained in ca. 65% yield even though the enantiomer ratio continues to decline thereafter (Table 1, entry 9:63% yield, 96.5:3.5 er after 7 h; Table 1, entry 7, 65% yield, 93:7 er after 15 h). This might be attributable to a catalyst decomposition product, which is capable of ionizing the ammonium salt of **2a** (intermediate **v**, Scheme 3) but is nonselective and/or poorly effective in promoting hydroamination, a task which is left to the remaining intact Pd catalyst. We have not yet identified any catalyst decomposition species.

Furthermore, results with isotopically labeled indoline (Table 4) indicate a rapid equilibrium of diene and σ-allyl **iii** prior to product formation (Scheme 3), yet transaminations, which necessarily proceed via π-allyl **iv**, occur with high enantiospecificity (Scheme 5). Therefore, under transamination conditions where a large concentration of nucleophilic amine is present, π-allyl **iv** is trapped by a secondary amine to give allyl ammonium salt **v** more quickly than it collapses to σ-allyl **iii**, preventing greater erosion of enantiopurity. Conversely, in hydroamination reactions, the concentration of amine available compared to the concentration of Pd–π-allyl **iv** decreases over time, another factor that may contribute to product enantiomerization as the reaction progresses.

The Et_3N additive likely helps drive the reaction forward by deprotonation of ammonium **v** to deliver product, rather than leading to catalyst exhaustion through extensive unproductive equilibration, thereby contributing to higher product yields. It remains unclear why the amine nucleophile cannot fill this role.

CONCLUSION

We have developed highly regio- and enantioselective Pd-catalyzed hydroaminations of internal dienes. The success of the transformation hinges upon a catalyst with a BAr^F_4 counterion, addition of Et_3N, and a nonpolar reaction medium. Experiments have shed light on both the reversibility of individual steps of the catalytic cycle and of the entire reaction, including the ensuing stereochemical consequences. Future efforts will be directed toward developing enantioselective hydrofunctionalizations with other classes of nucleophiles and unsaturated hydrocarbons and on further understanding the mechanisms of these transformations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.8b01914.

Experimental details, compound characterization, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(30) Enantioenrichment of product **2e** compared to starting material **2a** reflects the relative rates of ionization of the two starting material enantiomers, one present in higher concentration, plus the <50% conversion to product.

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