Communication

Enantioselective Intermolecular Addition of Aliphatic Amines to Acyclic Dienes with a Pd—PHOX Catalyst

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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 28 Apr 2017

Enantioselective Intermolecular Addition of Aliphatic Amines to Acyclic Dienes with a Pd—PHOX Catalyst

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Supporting Information Placeholder

ABSTRACT: We report a method for the catalytic, enantioselective intermolecular addition of aliphatic amines to acyclic 1,3-dienes. In most cases, reactions proceed efficiently at or below room temperature in the presence of 5 mol % of a Pd catalyst bearing a PHOX ligand, generating allylic amines in up to 97:3 er. The presence of an electron-deficient phosphine within the ligand not only leads to a more active catalyst but is also critical for achieving high site-selectivity in the transformation.

Hydrofunctionalization reactions of unsaturated hydrocarbons are highly atom economical means of generating complex molecules from simple and readily accessible materials. Strategies to catalyze this broad class of transformations enantioselectively have been greatly sought after. Among this cohort, hydroamination reactions[1,2] are prized as an expedient way to generate valuable chiral amines. Despite this, enantioselective intermolecular olefin hydroaminations are rare.

Until recently, successful enantioselective additions of amines have been limited to aryl amines (Scheme 1). In 2001, the Hartwig lab showed that anilines could be added to symmetrical cyclic dienes in the presence of a chiral Pd catalyst prepared from a Trost ligand.[3–5] Although a Brønsted acid additive permits a shorter reaction time, it also leads to product racemization. Dong and coworkers demonstrated a Rh-catalyzed 1,2-hydroamination of unsymmetrical acyclic dienes utilizing indoline nucleophiles; in this case, an acid additive positively impacts enantioselectivity.[6] Recently, the Hou lab disclosed the first highly enantioselective intermolecular hydroaminations with aliphatic amines, where chiral lanthanide half-sandwich catalysts allow for stereoselective amine additions to cyclopropenes.[7–10] In this work, we report the enantioselective 1,2-addition of alkyl amines to unsymmetrical acyclic dienes[11–13] catalyzed by a cationic Pd—PHOX complex.[14] Transformations afford allylic amines[15] in up to 91% yield in 3–24 hours without added Brønsted acid. An electron deficient phosphine enhances both catalyst reactivity and site-selectivity for the 1,2-addition product.

Previous work by the Hartwig group showed that Pd-catalyzed hydroamination of dienes proceeds via Pd–H migratory insertion to generate a Pd-π-allyl complex, followed by outer sphere amine attack.[5] The resulting ammonium salt may then oxidatively protonate Pd to regenerate the metal hydride (Scheme 1).[16] We therefore began by examining ligands known for promoting enantioselective nucleophilic additions to metal-π-allyl complexes for the hydroamination of 1-phenylbutadiene (**1a**, Table 1) with tetrahydroisoquinoline (THIQ). Unlike in previously reported aniline additions to cyclohexadiene,[3] Trost ligands, in combination with $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, fail to promote hydroamination of **1a** with THIQ. Other classes of bis(phosphine) ligands lead to more reactive catalysts; however, although they provide high selectivity for the desired 1,2-hydroamination product **2a**, poor enantioselectivity is observed (<70:30 er).[17]

Scheme 1. Catalytic Enantioselective Intermolecular Diene Hydroamination Reactions.

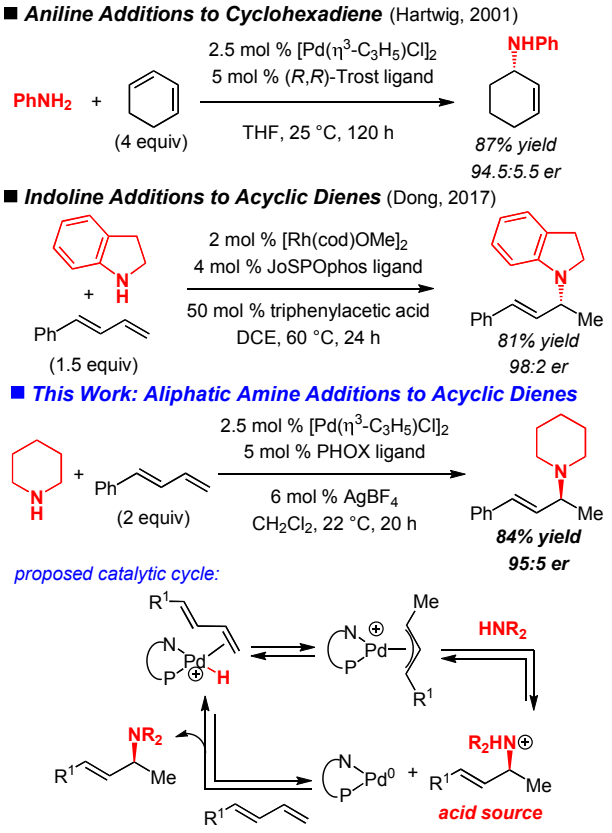
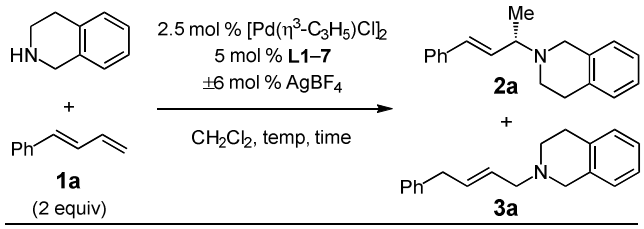
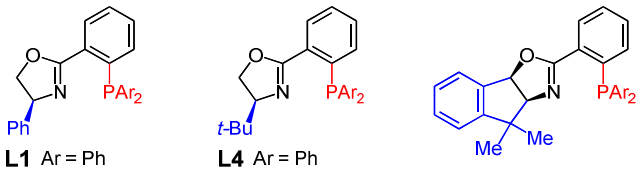


Table 1. Reaction Optimization for Addition of Tetrahydroisoquinoline to 1-Phenylbutadiene.[a]



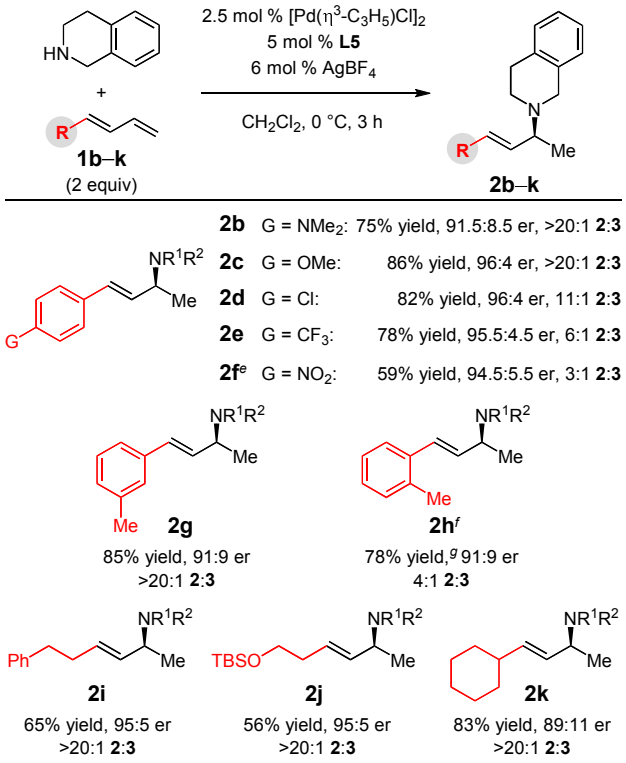


entry	ligand	$AgBF_4$ (Y/N)	temp (°C); time (h)	**2a**:**3a**[b]	yield (%)[c]	er[d]
1	**L1**	N	22; 20	8.5:1	70	81:19
2	**L1**	Y	22; 20	12:1	61[e]	85:15
3	**L2**	Y	22; 20	17:1	84	83:17
4	**L3**	Y	22; 20	>20:1	96	89:11
5	**L4**	N	22; 20	4:1	63	68:32
6	**L4**	Y	22; 20	2:1	76	92:8
7	**L5**	Y	22; 20	19:1	89	94.5:5.5
8	**L5**	Y	22; 0.5	>20:1	79	95:5
9	**L5**	Y	0; 3	>20:1	89	97:3
10	**L6**	Y	22; 20	6:1	87	94:6
11	**L7**	Y	22; 20	>20:1	64	95:5
12	**L7**	Y	30; 20	>20:1	79	94:6

[a] Reactions run with 0.2 mmol tetrahydroisoquinoline (0.8 M). See the Supporting Information for experimental details. [b] Determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [c] Isolated yield of a **2a**/**3a** mixture unless otherwise noted. [d] Enantiomeric ratio determined by HPLC analysis of purified products in comparison with authentic racemic standards. [e] Isolated yield of **2a** only.

We then turned our attention to phosphinooxazoline (PHOX) ligands, which have enjoyed a great deal of success in enantioselective allylic substitution,[18] but to the best of our knowledge have not been employed in hydrofunctionalization reactions.[14] We began by examining the Ph-substituted PHOX ligand **L1** (Table 1, entry 1). After 20 h at room temperature with 5 mol % catalyst, a mixture of desired 1,2-hydroamination product **2a** and achiral 1,4-hydroamination adduct **3a** is generated (70% yield, 8.5:1 **2a**:**3a**). The desired allylic amine is formed in 81:19 er. The addition of $AgBF_4$ to the catalyst mixture improves the product ratio and slightly increases the enantioselectivity as well (12:1 **2a**:**3a**, 85:15 er, entry 2).[19] Switching to a more electron-poor phosphine (**L2**, entry 3) improves product yield[20] and increases the proportion of **2a**[13l] (84% yield, 17:1 site-selectivity) without significant change to enantioselectivity. A bis[3,5-$(CF_3)_2$]-aryl phosphine (**L3**, entry 4) further increases yield and site-selectivity and also offers enhanced enantioselectivity (89:11 er). Similar trends in site- and enantioselectivity are observed with the *t*-Bu-substituted oxazolines (**L4**–**L5**, entries 5–7). Once more, the more electron-deficient phosphine increases site- and enantioselectivity (19:1 **2a**:**3a**, 94.5:5.5 er, entry 7) relative to the diphenylphosphino ligand (2:1 **2a**:**3a**, 92:8 er, entry 6). Ligand **L5** provides dramatically increased reactivity as well, at room temperature (entry 8) affording 79% yield of **2a** in 0.5 h. Cooling to 0 °C further enhances enantioselectivity: after 3 h, amine **2a** is delivered in 89% yield and 97:3 er. Indane-derived PHOX ligands **L6**–**L7** were also explored (entries 10–12) and lead to similar selectivity trends albeit with overall reduced reactivity. Yield could be improved if the reaction were run at 30 °C without diminishing enantioselectivity (79% yield, 94:6 er, entry 12), but a further increase negatively impacted enantioselectivity.

Table 2. Addition of Tetrahydroisoquinoline to 1-Substituted Butadienes.[a–d]

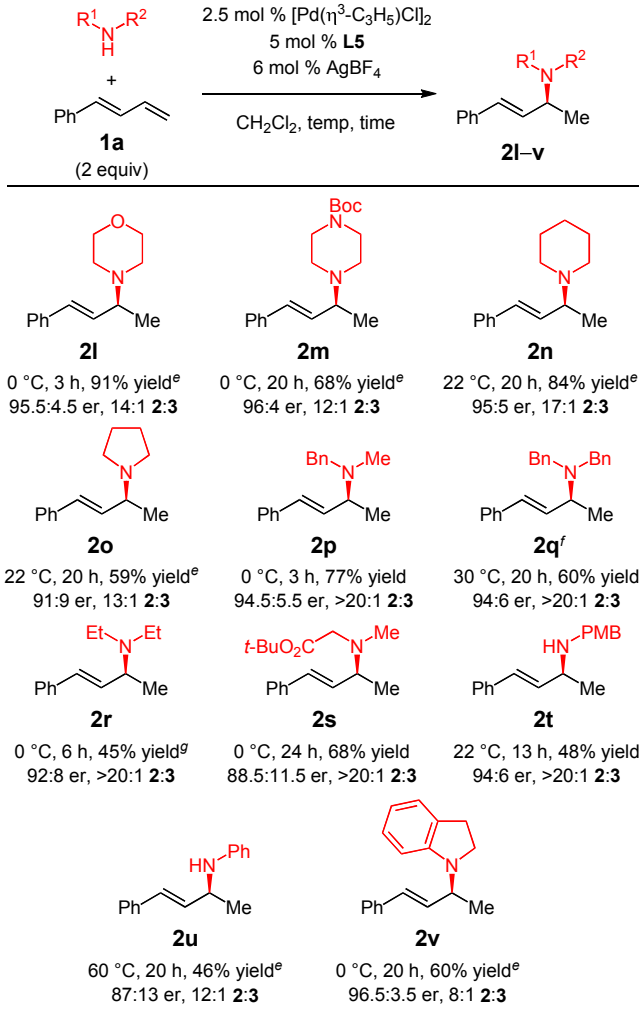


[a] See the Supporting Information for experimental details. [b] Site-isomer ratio determined by 400 MHz ^{1}H NMR spectroscopy of the unpurified mixture. [c] Isolated yield of **2** only unless otherwise noted. [d] Enantiomeric ratio determined by HPLC analysis of purified products in comparison with authentic racemic standards. [e] Reaction for 9 h. [f] Reaction at 22 °C. [g] Isolated yield of a mixture of **2** and **3**.

A number of 1-substituted dienes take part in enantioselective addition of THIQ (Table 2).[21] Electronic variation at the arene's *para*-position of aryl-substituted butadienes was investigated and proved to have a profound effect on site-selectivity (allylic amines **2b**–**f**). More electron-rich substituents lead to high selectivity for 1,2-addition product **2**.[13l] For example, dimethylamino-containing **2b** and methoxy-substituted **2c** are formed as the exclusive product of the reaction whereas nitroarene **1f** leads to a 3:1 mixture of site-isomers. In contrast, enantioselectivity is largely unchanged (91.5:8.5 to 96:4 er). In cases where a mixture is obtained, the two product isomers are separable. Methyl substitution at the *meta*-position maintains high site-selectivity (>20:1) for allylic amine **2g**. In comparison, the *ortho*-tolyl **2h** is formed with only 80% selectivity[13l] although enantioselectivi-

ty is the same in both cases (91:9 er); neither parameter in forming **2h** is improved upon cooling to 0 °C. Alkyl-substituted dienes efficiently undergo hydroamination to deliver chiral amines **2i–k** as the exclusive product in 89:11–95:5 er. In all cases, olefin migration is not observed.

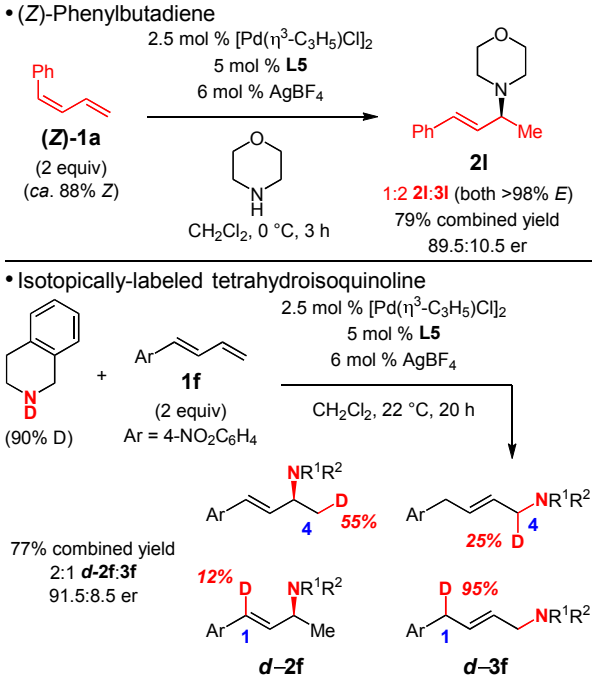
Table 3. Amine Variation in the Hydroamination of 1-Phenylbutadiene.[a–d]



[a–d] See Table 2. [e] Isolated as a mixture of **2** and **3**; see the Supporting Information. [f] Ligand **L7** used. [g] Lower yield due to product volatility.

Several aliphatic amines participate in hydroamination of phenylbutadiene **1a** with Pd—PHOX catalysts although the optimal reaction conditions vary considerably depending on the nature of the amine (Table 3). Like THIQ, cyclic amines with inductively electron-withdrawing groups (e.g., morpholine and N-Boc-protected piperazine) are able to furnish allylic amine products at 0 °C with the **L5**-derived catalyst: **2l** and **2m** are obtained with *ca.* 92% site-selectivity and 96:4 er. As the cyclic amines become more donating, higher temperature is required to promote reaction, presumably because of increasing competition with the diene for coordination to Pd.[1] Piperidine forms allylic amine **2n** in 84% yield at room temperature (95:5 er). Pyrrolidine, a challenging amine for many late transition metal catalysts, affords **2o** in 91:9 er and 59% yield. Acyclic secondary amines are also competent partners for the diene hydroamination, delivering amines **2p–s** as a single site-isomer with good enantioselectivity (88.5:11.5–94.5:5.5 er). Sterically hindered dibenzylamine affords **2q** in 94:6 er with higher efficiency with indane-derived ligand **L7** at 30 °C.[22] Primary alkyl amines undergo a single hydroamination event: secondary amine **2t** is generated in 48% yield (94:6 er). Aryl amines are also effective nucleophiles, delivering allylic amines **2u–v** in up to 96.5:3.5 er.

Scheme 2. Initial Mechanistic Investigations of Pd—PHOX-Catalyzed Diene Hydroaminations.



Initial mechanistic studies demonstrate that site-selectivity in the reaction is strongly dependent upon diene stereochemistry and isotope effects (Scheme 2). (*Z*)-Phenylbutadiene **(*Z*)-1a** (*ca.* 88% *Z*), when combined with morpholine and the Pd—**L5** complex under the optimal conditions for **(*E*)-1a** (Table 3), yields a dramatically higher proportion of the 1,4-hydroamination product (1:2 **2l**:**3l**) compared to reaction of the (*E*)-isomer, perhaps due to styrenyl olefin insertion now being significantly kinetically preferred. Both hydroamination products are formed exclusively as the (*E*)-olefin isomer, signifying that olefin isomerization is faster than amine attack in forming **2l**. Excess diene **1a** is recovered with *ca.* 82% *Z* content. Furthermore, **2l** is formed as the same enantiomer from **(*Z*)-1a** as from the (*E*)-isomer.

To determine the extent to which the diene/Pd–H insertion might be reversible, reaction of N-deuterated THIQ with diene **1f** was examined. At room temperature, the reaction of unlabeled THIQ with **1f** generates an 8:1 mixture of 1,2- and 1,4-hydroamination products with **L5**.[17] Unexpectedly, N-deuterated THIQ significantly lowers the site-selectivity to 2:1 ***d*-2f**:***d*-3f** (Scheme 2). The deuterium distribution in each product, however, demonstrates that the site of migratory insertion largely controls which product forms as indicated by the relatively smaller amount of deuterium incorporation into C1 in ***d*-2f** and C4 in ***d*-3f**. Whether this analysis extends to unlabeled amines with **L5** is ambiguous due to the isotope effect in product distribution. Recovered diene **2f** has *ca.* 12% D-incorporation into the C1 position but <2% at C4.

A Pd complex, bearing an electronically dissymmetric chi-

ral PHOX ligand, is an efficient and highly enantioselective catalyst for the intermolecular hydroamination of dienes with aliphatic amines. Diene and ligand electronics have a dramatic effect on product distribution, and a more electron deficient phosphine ligand significantly increases catalyst reactivity. Current studies are focused on further elucidating the reaction mechanism and related methods development.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for new compounds. 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 interests.

ACKNOWLEDGMENT

We are grateful to Duke University for sponsoring this research. N. J. A. was supported by NIGMS (T32GM007105–42). We thank Katherine Wilbur for experimental assistance.

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(16) Amine attack upon the original η^3-allyl Pd salt generates an ammonium salt that oxidatively protonates Pd, initiating catalysis.

(17) See the Supporting Information for details.

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(19) Other Ag salts afford greater quantities of achiral **3a** although the er of **2a** is largely invariant. Additionally, polar solvents lead to greater product yields with CH_2Cl_2 proving optimal.

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(21) 1,4-disubstituted dienes fail to generate hydroamination product. Other substitution patterns deliver 1,4-hydroamination or a complex mixture. See the Supporting Information.

(22) Product **2q** is obtained in 53% yield, 12:1 **2q**:**3q**, and 93:7 er after 17 h at 0 °C with **L5**.

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