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Palladium and Iron Cocatalyzed Aerobic Alkene Aminoboration

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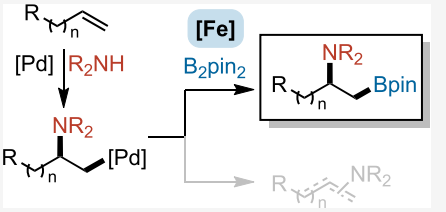
ABSTRACT: Aminoboration of simple alkenes with nitrogen nucleophiles remains an unsolved problem in synthetic chemistry; this transformation can be catalyzed by palladium *via* aminopalladation followed by transmetalation with a diboron reagent. However, this catalytic process faces inherent challenges with instability of the alkylpalladium(II) intermediate toward *β*-hydride elimination. Herein, we report a palladium/iron cocatalyzed aminoboration, which enables this transformation. We demonstrate these conditions on a variety of alkenes and norbornenes with an array of common nitrogen nucleophiles. In the developed strategy, the iron cocatalyst is crucial to achieving the desired reactivity by serving as a halophilic Lewis acid to release the transmetalation-active cationic alkylpalladium intermediate. Furthermore, it serves as a redox shuttle in the regeneration of the Pd(II) catalyst by reactivation of nanoparticulate palladium.



INTRODUCTION

Alkene difunctionalizations are straightforward approaches to install two functional groups across a carbon−carbon double bond, delivering valuable compounds from easily accessible starting materials in a single step.[1−4] Two common and versatile functionalities in organic chemistry are amines and boronic acids and their ester analogues. Amines and their derivatives are featured prominently in natural products, pharmaceuticals, agrochemicals, and organic materials.[5,6] Boronic acids and esters have found widespread use in synthetic chemistry[7−10] and are key pharmacophores in a number of pharmaceuticals.[11−13] Therefore, alkene aminoboration, which incorporates both valuable functional groups in a single step, is a particularly desirable transformation. One approach is the Cu-catalyzed umpolung aminoboration (Scheme 1a).[14−22] These transformations occur through migratory insertion of a Cu−boryl intermediate into an alkene to form a stable Cu−alkyl species (**1**),[23] which then undergoes oxidative functionalization with an electrophilic amine. This methodology necessitates the presynthesis of *O*-benzoylhydroxylamine(s) (R_2N−OBz) and is limited to the formation of tertiary aliphatic amines (**2**). A generalized aminoboration strategy utilizing commercially available nitrogen nucleophiles (R_2N−H) directly is a desirable and complementary methodology.

Known for their versatile reactivity, Pd catalysts are excellent at constructing C−N bonds *via* aminopalladation of alkenes.[24−26] Moreover, as in the Miyaura borylation, Pd(II)−C intermediates are known to undergo transmetalation with diboron reagents, e.g., bis(pinacolato)diboron (B_2pin_2).[27,28] Combining these two steps: (i) aminopalladation of an alkene and (ii) interception of the resulting Pd(II)−C^{alkyl} intermediate (**4**) with B_2pin_2 would afford the 1,2-aminoboration product upon reductive elimination. However, this requires the transient intermediate **4** to undergo intermolecular transmetalation faster than intramolecular *β*-hydride elimination (Scheme 1c) and is especially challenging as *β*-hydride elimination from **4** is known to be rapid.[1] To date, Pd-catalyzed aminoboration has been achieved by use of a directing group on the alkene.[29,30] The metalacyclic intermediate (**3**) formed upon aminopalladation is stabilized by 8-aminoquinoline (AQ), inhibiting *β*-hydride elimination relative to transmetalation (Scheme 1b).[29] Developing strategies for aminoboration of directing-group-free alkenes with R_2N−H remains an unsolved challenge.[31]

RESULTS AND DISCUSSION

Reaction Development. Initial experiments explored the Pd-catalyzed aminoboration of terminal, unactivated homoallylbenzene (**5**) with phthalimide (PhthNH) and B_2pin_2 using O_2 as the oxidant (Table 1). In the absence of any additive, neither aminoboration product **6** nor aza-Wacker product **7** is observed (entry 1). As Lewis bases are conventional additives used to promote transmetalation with diboron reagents,[32] we examined a series of these reported Lewis bases. Unfortunately, they are ineffective at aminoboration, giving <1% yield of **6** (entries 2−6).

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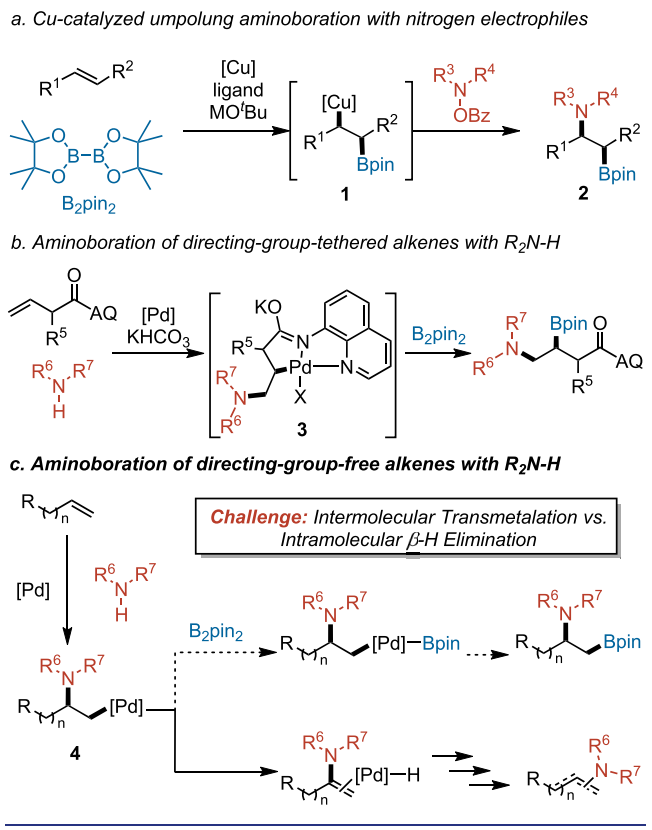
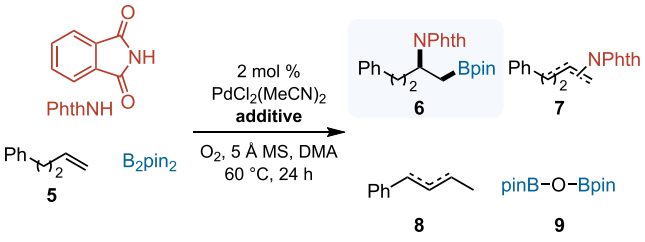
Scheme 1. Transition-Metal-Catalyzed Intermolecular Alkene Aminoboration



Consequently, an alternative strategy was required. In a recent report focused on Pd-catalyzed remote diboration by Kochi and co-workers, a cationic Pd(II) species is the active catalyst which was generated *in situ* by the addition of $NaBAr_4^F$.[33] Similarly, halophilic Lewis acids have also been proposed to promote transmetalation in Pd-catalyzed cross-coupling reactions.[34,35] Inspired by these elegant strategies, various Lewis acidic additives[36] were screened in the presence of $PdCl_2(MeCN)_2$ (entries 7−14). The desired product **6** is observed with $Cu(OTf)_2$ and $Fe(OTf)_3$ in 24 and 12% yield, respectively, along with substantial aza-Wacker product (**7**), alkene isomerization (**8**), and $O(Bpin)_2$ (**9**), a byproduct formed by the Pd-catalyzed oxidation of B_2pin_2[37] (entries 7 and 8). To our delight, $Fe(OTf)_2$ affords **6** in 62% under the same conditions (entry 9). Other Lewis acids were less effective (entries 10−14). Additionally, no conversion was observed when Brønsted acid additives were added, implying that halophilicity of the additive is important in promoting aminoboration (entries 15−17). After screening other reaction parameters (the Supporting Information, Tables S2−S10), aminoboration **6** is formed in 72% isolated (81% *in situ*) yield using 2 mol % $PdCl_2(MeCN)_2$, 50 mol % $Fe(OTf)_2$, 10 mol % benzoquinone (BQ), 1.0 equiv of PhthNH (0.25 mmol), 4.0 equiv of **5**, and 4.0 equiv of B_2pin_2 under an O_2 atmosphere at 40 °C (entry 18). We hypothesize that BQ serves as a co-oxidant for Pd(0), as less **9** is observed in its presence. Notably, we do not observe mixtures of regioisomers under the reaction conditions.

Scope of Aminoboration of Terminal Alkenes. Under the optimized conditions, a wide variety of terminal alkenes participate in the reaction to afford the 1,2-aminoboration products in good to excellent yields (Table 2). The reaction

Table 1. Selected Additive Screening of the Pd-Catalyzed Aminoboration of Homoallylbenzene[a]



entry	additive (mol %)	**6** (%)[b]	**7** (%)[b]
1	—	<1	<1
2	KO^{t}Bu (100)	<1	<1
3	KOAc (100)	<1	<1
4	K_3PO_4 (100)	<1	<1
5	K_2CO_3 (100)	<1	<1
6	NaF (100)	<1	<1
7	$Cu(OTf)_2$ (50)	24	28
8	$Fe(OTf)_3$ (50)	12	13
9	$Fe(OTf)_2$ (50)	62	25
10	$Mg(OTf)_2$ (50)	<1	<1
11	$Sc(OTf)_3$ (50)	<1	<1
12	$Zn(OTf)_2$ (50)	<1	<1
13	AgOTf (50)	<1	<1
14	$NaBAr_4^F$ (100)	<1	<1
15	Benzoic acid (50)	<1	<1
16	AcOH (50)	<1	<1
17	TfOH (50)	<1	<1
18	$Fe(OTf)_2$ (50), BQ (10)	81 (72)[c,d]	19

[a]Reaction conditions: PhthNH (0.25 mmol), **5** (2.0 equiv), B_2pin_2 (4.0 equiv), $PdCl_2(MeCN)_2$ (2.0 mol %), additive, 5 Å molecular sieves (125 mg), *N*,*N*-dimethylacetamide (DMA) (0.75 mL, 0.33 M), and O_2 balloon, 60 °C, 24 h. [b]GC yields using 1-methylnaphthalene as an internal standard. [c]Reaction was carried out with 10 mol % BQ and 4.0 equiv of **5** at 40 °C for 72 h. See the Supporting Information for detailed reaction conditions. [d]Isolated yield is given in parentheses.

conditions are scalable as **6** is isolated in 67% yield (1.4 g) on a 5.0 mmol scale. A variety of substitutions on the aryl ring are well tolerated, including electron-donating and electron-withdrawing groups (**10**−**16**, 41−64%). Notably, both aryl chlorides and bromides remain intact over the course of the reaction, affording **12** and **16** in 60 and 54% yields, respectively; no protodehalogenation or cross-coupling products are observed. Both bishomoallylbenzene and simple aliphatic alkenes, such as octene, dodecene, and allylcyclohexane, form **17**−**20** in good yields (62−63%). Increasing the steric hindrance proximal to the alkene does impact the reactivity, as vinylcyclohexane requires an elevated reaction temperature (60 °C) to afford **21** in 50% yield and the bulky *tert*-butylethylene delivers only trace product **22** (<5%).

Functional groups proximal to the alkene are generally tolerated. To our delight, allyl acetate, an excellent oxidant for Pd(0), undergoes the aminoboration to afford **23** in 60% yield with no observed allylation products.[38] Additionally, benzyl ethers and benzoyl groups are well tolerated as **24** and **25** are isolated in 47 and 65% yields, respectively. While styrene is readily aminoborylated (**26**) in 52% yield, allyl benzene is a poor substrate, forming **27** in 25% yield along with extensive alkene isomerization.

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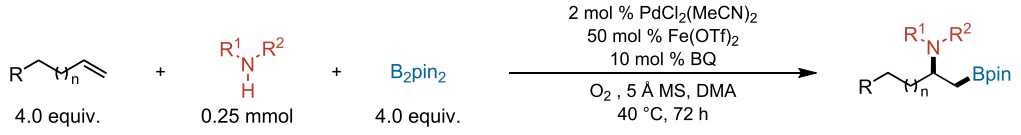
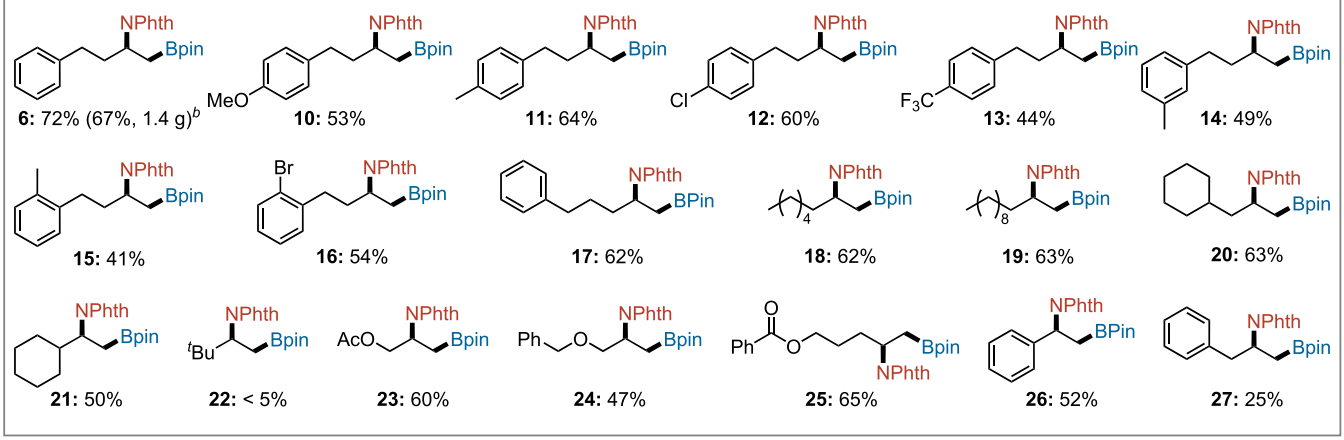
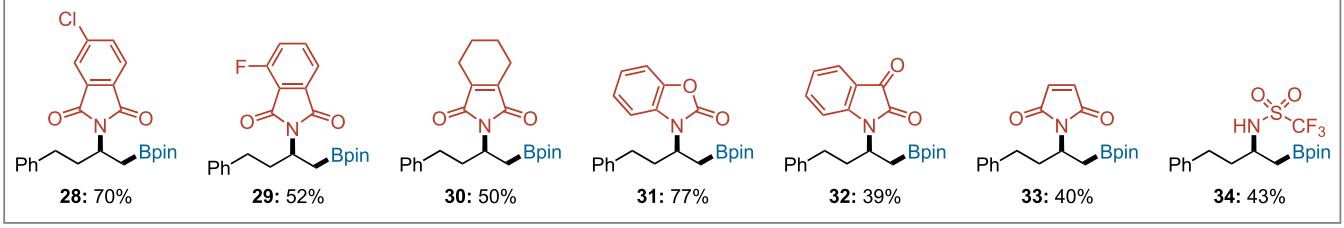
Table 2. Scope of Pd/Fe Cocatalyzed Aminoboration of Simple Alkenes[a,b,c]



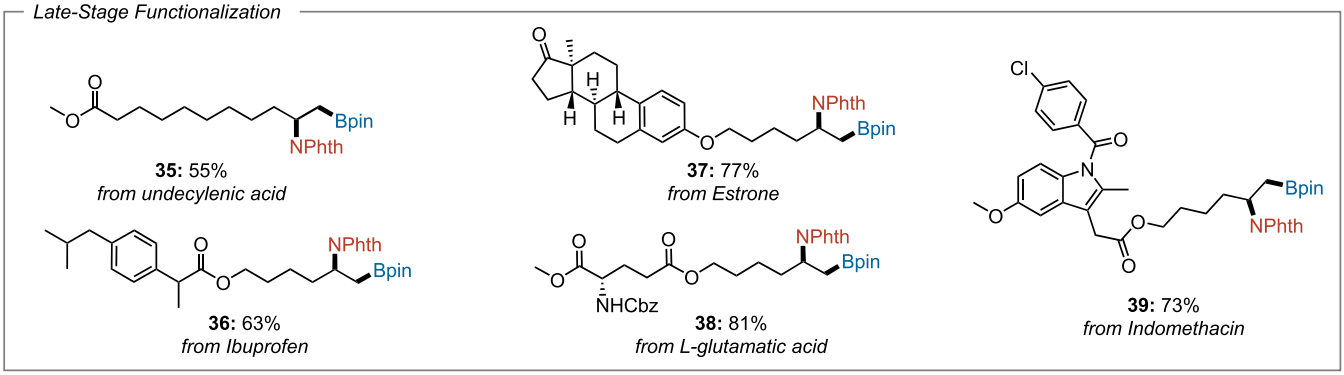
Terminal Alkenes



Nitrogen Nucleophiles



Late-Stage Functionalization



[a]See the Supporting Information for detailed reaction conditions. Isolated yields are indicated. [b]5 mmol of PhthNH. [c]The d.r. is indistinguishable by ^{1}H NMR; we presume that the products form as a 1:1 mixture of diastereoisomers.

Delightfully, other nucleophiles are also tolerated in the aminoboration of homoallylbenzene: phthalimide derivatives undergo the aminoboration and form **28**–**30** in good yields (50–70%). Benzoxazolinone reacts efficiently and **31** is isolated in 77% yield. Further, isatin, maleimide, and trifluoromethanesulfonamide are suitable nucleophiles and deliver aminoboration products **32**–**34** in modest yields (39–43%).

We also tested the compatibility of these conditions with bioactive motifs: **35**–**39** are formed in good to excellent yields (55–81%) with excellent chemoselectivity. Nitrogen-containing functionalities, such as α-amino acids and indole heterocycles, are stable under the reaction conditions (**38** and **39**). Finally, robustness screens[39] were performed, and a variety of additional functionalities, *e.g.*, benzofuran, benzothiophene, *N*-phenylacetamide, and alkyl chloride, are tolerated and remain intact under optimized conditions (the Supporting Information, Figure S2).

Scope of Aminoboration of Norbornene (NBE). Next, we investigated the aminoboration of internal alkenes. Simple 1,2-disubstituted alkenes, such as 2-octene and cyclooctene, show poor reactivity (the Supporting Information, Figure S3). In contrast, NBE is an excellent coupling partner[40,41] and affords aminoboration product **40** in 88% isolated yield under slightly modified reaction conditions. Notably, **40** forms in near quantitative 99% isolated yield (1.8 g) on a 5.0 mmol scale. Given the promising results with different R_2N–H sources with homoallylbenzene, we then explored the scope of nitrogen nucleophiles in the aminoboration of NBE (Table 3). In addition to PhthNH, a variety of substituted phthalimide

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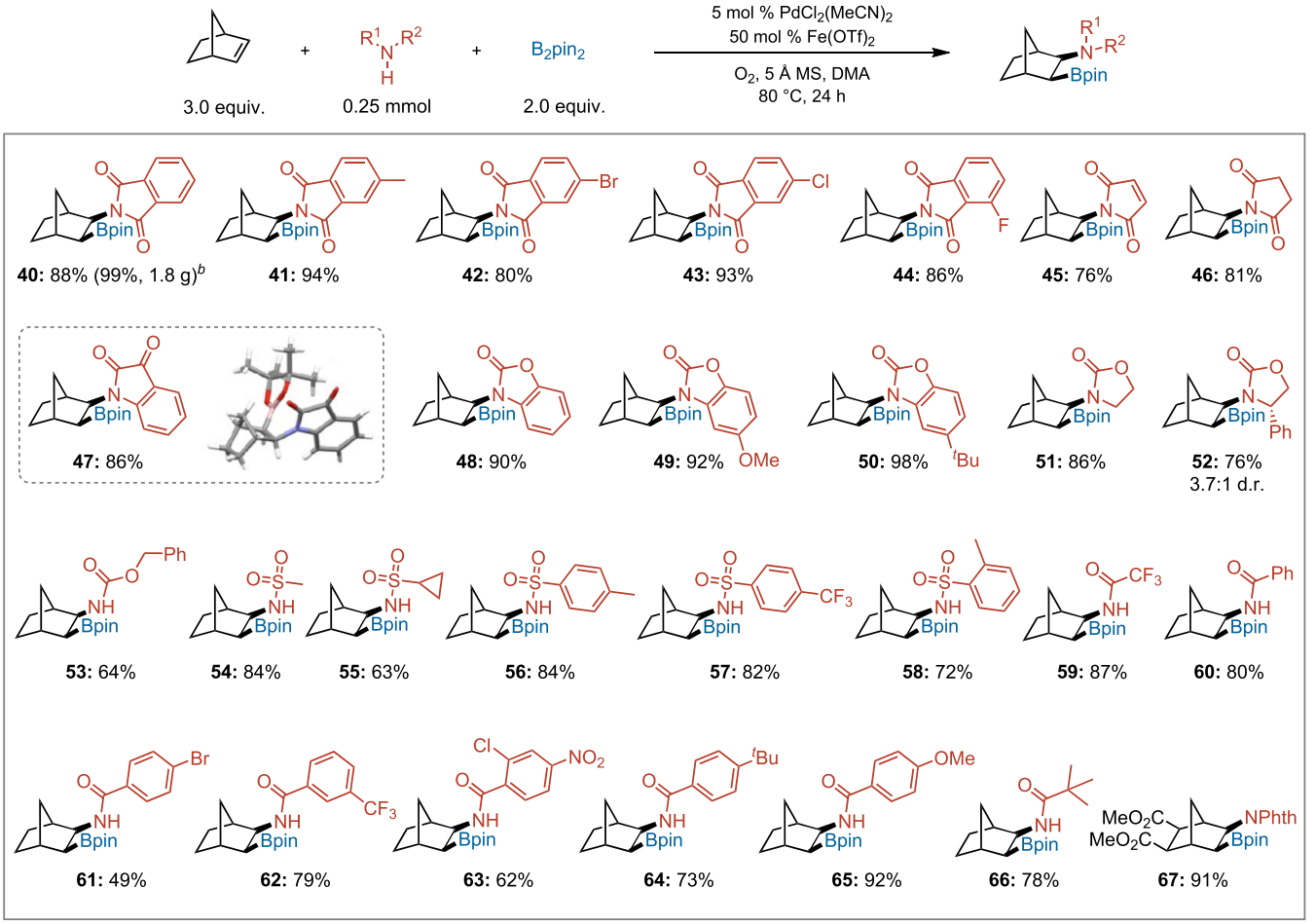
Table 3. Scope of Pd/Fe Cocatalyzed Aminoboration of Norbornene[a,b]



[a]See the Supporting Information for detailed reaction conditions. Isolated yields are indicated. [b]5.0 mmol of PhthNH.

derivatives participate in the reaction to afford **41**–**44** in good to excellent yields (80–94%). Other imides are also tolerated, including maleimide and succinimide, delivering **45** and **46** in 76 and 81% yields, respectively. Isatin reacts efficiently, giving **47** in 86% yield. Single-crystal X-ray diffraction analysis of **47** confirms that the *cis-exo*-diastereoisomer is formed selectively, consistent with a *cis*-aminopalladation on the *exo*-face of NBE.[42] Aminoboration with benzoxazolinone derivatives also proceed smoothly affording **48**–**50** in excellent yields (90–98%). Likewise, oxazolidinone is an excellent nucleophile, as **51** is isolated in 86% yield. (*S*)-4-phenyl-2-oxazolidinone gives 76% yield of aminoboration product **52**, with a modest d.r. of 3.7:1, indicating that steric encumbrance proximal to the nucleophile moderately decreases the yield. Benzyl carbamate, a readily deprotected ammonia surrogate, also participates, affording **53** in 64% isolated yield. Aliphatic sulfonamides, including methanesulfonamide and cyclopropanesulfonamide, afford **54** and **55** in 84 and 63% yields, respectively. Finally, aryl sulfonamide derivatives bearing both electron-rich, electron-deficient, and potential steric encumbrance are well tolerated, affording **56**–**58** in very good yields (72–84%).

In most aminopalladation reports, imides, sulfonamides, and carbamate derivatives are competent classes of nucleophiles described to undergo aminopalladation. Limited examples describing intermolecular aminopalladation with less acidic amide nucleophiles have been reported.[43,44] The successful incorporation of diverse amides *via* aminopalladation remains a synthetic challenge. To our delight, however, primary amides are competent nucleophiles under our aminoboration reaction conditions. Electron-deficient trifluoroacetamide and benzamides participate and deliver **59**–**63** in modest to great yields (49–87%). Electron-rich benzamides, including *p*-^{t}Bu and *p*-OMe-benzamide, also participate, giving **64** and **65** in 73 and 92% yields, respectively. Trimethylacetamide, a primary alkyl amide, also performs well under our conditions, affording **66** in 78% yield. Finally, symmetric dimethyl ester-functionalized NBE participates in the reaction delivering **67** in 91% yield.

Mechanistic Investigations. With scope in hand, we then began mechanistic investigations to elucidate the role of the Fe cocatalyst. It has been reported that metal triflate salts can serve to generate triflic acid (TfOH) *in situ*, which is subsequently responsible for Brønsted acid catalysis.[45,46] As such, we sought to determine if Fe is the active catalyst or if it is generating TfOH *in situ*. Over a range of concentrations (0.5–10.0 mol %), TfOH does not promote the aminoboration reaction in the absence of $Fe(OTf)_2$ (Scheme 2**a**). Furthermore, the use of 2,6-di-*tert*-butylpyridine as a proton scavenger has no significant impact on the efficiency of the reaction, giving **6** in 66% *in situ* GC yield (Scheme 2**b**). In combination, these data support Fe being the active cocatalyst in this system.

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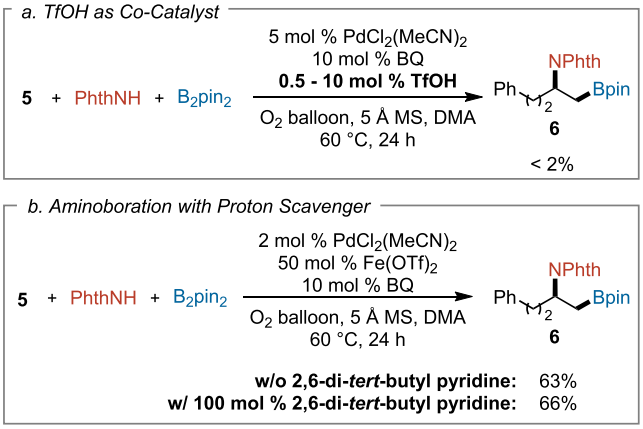
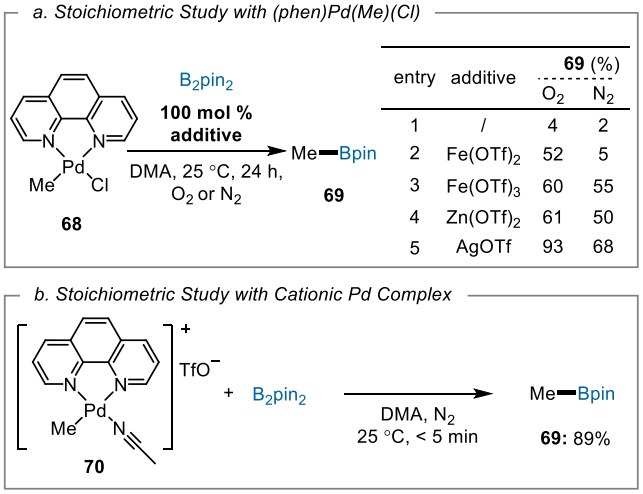
Scheme 2. Possibility of TfOH Catalysis[a]



[a]See the Supporting Information for detailed reaction conditions. GC yields using 1-methylnaphthalene as an internal standard.

Given that Fe is likely the active cocatalyst, we hoped to elucidate its role in the aminoboration reaction. We hypothesized that it may promote the transmetalation between the Pd(II)−C^{alkyl} formed upon aminopalladation and B_2pin_2.[34,35] To isolate this step from the rest of the catalytic cycle, we investigated the reaction of (phen)Pd(Me)(Cl) (**68**) with B_2pin_2 as a model system.[33] As seen in Scheme 3**a**, when

Scheme 3. Stoichiometric Borylation[a]



entry	additive	69 (%) O_2	69 (%) N_2
1	/	4	2
2	$Fe(OTf)_2$	52	5
3	$Fe(OTf)_3$	60	55
4	$Zn(OTf)_2$	61	50
5	AgOTf	93	68

[a]See the Supporting Information for detailed reaction conditions. GC yields using 1-methylnaphthalene as an internal standard.

68 is combined with B_2pin_2 in the absence of an additive, trace Me−Bpin (**69**) is observed (<5% GC yield, entry 1). As we hypothesized, $Fe(OTf)_2$ can facilitate this reaction under an oxygen atmosphere, affording **69** in 52% *in situ* yield. However, only 5% of Me−Bpin is observed if the reaction is carried out under N_2 (entry 2). Interestingly, $Fe(OTf)_3$ and $Zn(OTf)_2$ can promote the reaction between **68** and B_2pin_2, delivering product **69** in comparable yields under O_2 and N_2 (entries 3 and 4). Moreover, under our aerobic conditions with $Fe(OTf)_2$, we observe the slow formation of $[Fe^{3+}]$ by *in situ* EPR spectroscopy (Supporting Information, Figure S6). As such, we speculated that $[Fe^{3+}]$ acts as a halophilic Lewis acid and abstracts the chloride (Cl^-) to liberate a reactive cationic complex prior to transmetalation. Supporting this, when AgOTf, a source of Ag^+ ions that can irreversibly remove Cl^-, is used as the additive, 93 and 68% yields of **69** are obtained under O_2 or N_2, respectively. Likewise, when a cationic Pd(II) complex, $[(phen)Pd(Me)(MeCN)]^+[OTf]^-$ (**70**), is directly combined with B_2pin_2 in DMA, an 89% *in situ* GC yield of **69** is observed after 5 min (Scheme 3**b**).

We then sought to understand the apparent contradiction that $Fe(OTf)_3$ is an inferior cocatalyst in the aminoboration reaction (Table 1, entries 12 and 13 and Supporting Information, Table S16), yet $[Fe^{3+}]$ is required to promote transmetalation. This suggests that the $[Fe^{3+}]$ complex, formed *in situ* from $Fe(OTf)_2$ and O_2, has reactivity distinct from that of $Fe(OTf)_3$. We monitored the reaction between homoallylbenzene (**5**), 4-chlorophthalimide (**71**), and B_2pin_2 in the presence of $Fe(OTf)_2$ or $Fe(OTf)_3$ (Scheme 4**a**). $Fe(OTf)_2$ is faster and more selective than $Fe(OTf)_3$. **28** forms in 34% *in situ* yield with 3.4:1 of **28**:**72** after 9 hours with $Fe(OTf)_2$, while $Fe(OTf)_3$ affords **28** in 19% *in situ* yield (1.7:1 **28**:**72**). A substantially higher consumption of B_2pin_2 is observed with $Fe(OTf)_3$ *vs* $Fe(OTf)_2$: 48 and 83% B_2pin_2 remain after 9 hours, respectively. While we are unable to characterize all boron-containing side products, it is worth noting that a higher amount of $O(Bpin)_2$ (**9**, 7% yield) is observed with $Fe(OTf)_3$ *vs* 1% with $Fe(OTf)_2$.

Considering these results, we propose that nonselective Cl^- abstraction occurs with increased concentrations of $Fe(OTf)_3$, which promotes side reactions by generation of a cationic $[Pd(II)]^+$ species prior to aminopalladation (the Supporting Information, Figure S9). Indeed, the cationic Pd precursor, $Pd(MeCN)_4(OTf)_2$, is an inferior catalyst and favors the formation of the aza-Wacker product **7** (8% yield, 0.75:1 **6**:**7**, the Supporting Information, Table S19, entry 12) in the absence of an Fe cocatalyst. Similarly, in the presence of $Fe(OTf)_2$, $Pd(MeCN)_4(OTf)_2$ favors the aza-Wacker product, delivering **7** in 25% along with 10% of **6** (0.4:1 **6**:**7**) (Scheme 4**b**).

Based on these observations, we hypothesize that the equilibrium between the stable Pd(II)−Cl (**II**, Scheme 5) and the active $[Pd(II)]^+$ (**III**, Scheme 5) is crucial for selective aminoboration.[35] To verify this, we investigated the aminoboration of homoallylbenzene **5** with $Pd(MeCN)_4(OTf)_2$ in the presence of $^nBu_4NCl$ (0−10 mol %); the reactivity and selectivity are restored, affording **6** in 66% yield (3:1 **6**:**7**) with 4 mol % added Cl^-.[47,48] Higher loadings of Cl^- (≥10 mol%) are beneficial with respect to selectivity but have deleterious effects on the conversion to **6** and **7**, suggesting that excess Cl^-, relative to Pd, inhibits the reaction (Scheme 4b and Supporting Information, Table S19).

Redox-inactive Lewis acids, such as $Zn(OTf)_2$, promote borylation in the stoichiometric investigations (entry 4, Scheme 3a), but redox-active Fe is required to facilitate turnover, suggesting that it may have an additional role in the catalytic cycle. While optimizing the aminoboration reaction, we noted that increasing the loading of $PdCl_2(MeCN)_2$ above 2 mol % leads to significantly lower yields of **6** (the Supporting Information, Table S4). Further, the addition of Hg^0 decreased conversion to 2% yield of **6** (the Supporting Information, Figure S7). Both of these observations are consistent with the formation of Pd nanoparticles (Pd NPs).[49,50] Indeed, Pd NPs are observed by transmission electron microscopy (TEM) imaging of the reaction mixture (Scheme 4c, and the Supporting Information, Figure S8).

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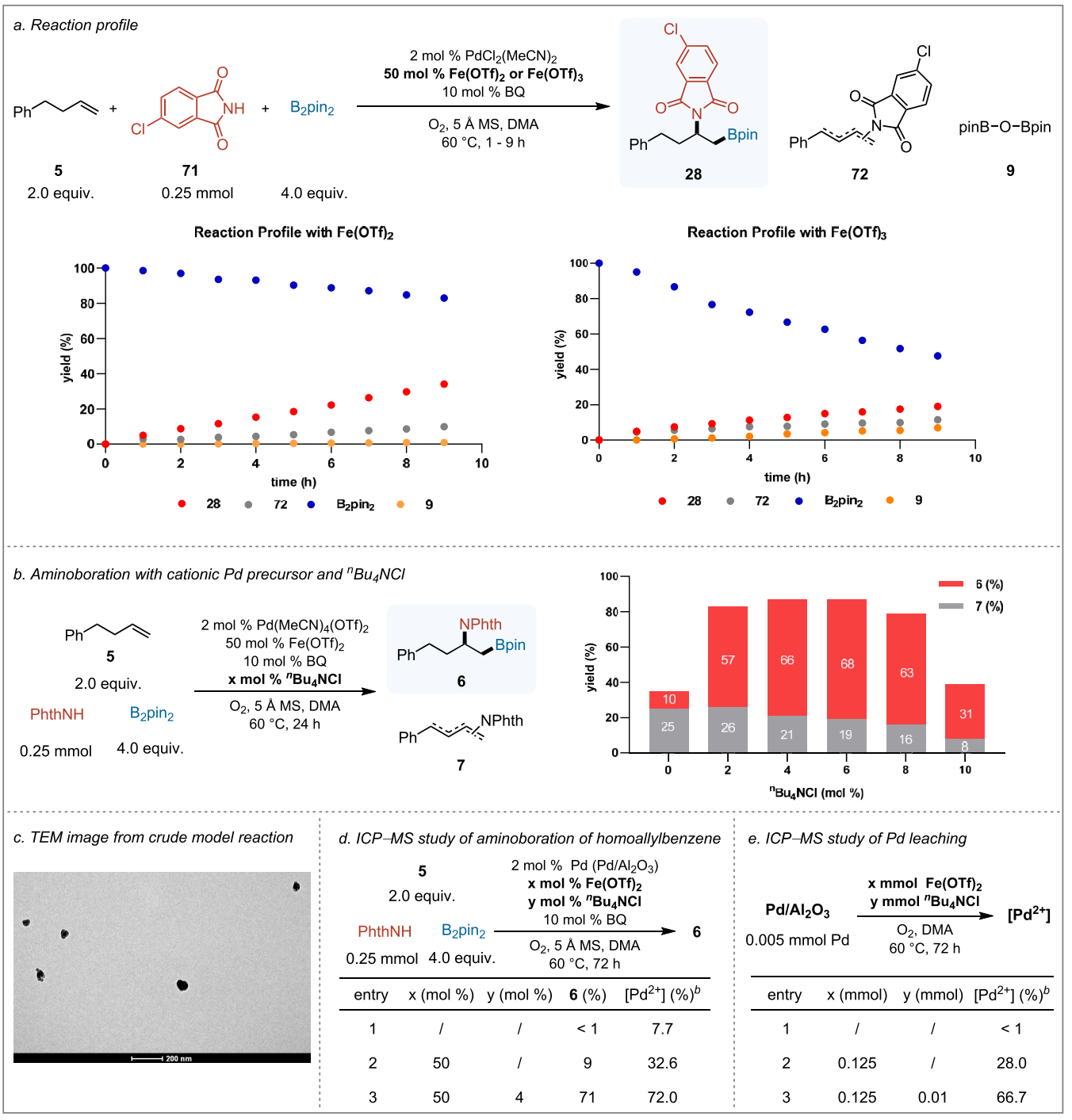
Scheme 4. Mechanistic Investigations[a,b]



entry	x (mol %)	y (mol %)	**6** (%)	$[Pd^{2+}]$ (%)[b]
1	/	/	< 1	7.7
2	50	/	9	32.6
3	50	4	71	72.0

entry	x (mmol)	y (mmol)	$[Pd^{2+}]$ (%)[b]
1	/	/	< 1
2	0.125	/	28.0
3	0.125	0.01	66.7

[a]See the Supporting Information for detailed reaction conditions. [b]$[Pd^{2+}]$ represents the Pd content in supernatant, which was determined by ICP-MS.

We hypothesized that the redox activity of the Fe cocatalyst may be its distinguishing feature and that it serves as a redox shuttle between O_2 and the Pd NPs. To test this, we used Pd/Al_2O_3 as a nanoparticulate catalyst. In the presence of $Fe(OTf)_2$ and Bu_4NCl, this heterogenous Pd(0) source catalyzes the aminoboration reaction of homoallylbenzene to afford **6** in 71% *in situ* yield (Scheme 4**d**, entry 3). In the absence of $Fe(OTf)_2$, <1% of **6** is observed (Scheme 4**d**, entry 1). There are two plausible scenarios for this Fe-catalyzed oxidation of Pd/Al_2O_3: (i) the Fe may be serving to break up the Pd NPs and form homogeneous/colloidal Pd(II) complexes *or* (ii) the Fe may be oxidizing the surface of the Pd NPs and promoting heterogeneous catalysis. As seen in Scheme 4**d**, to distinguish between these two scenarios, Pd content of the solid phase *vs* the supernatant was determined *via* inductively coupled plasma mass spectrometry (ICP-MS) in the aminoboration of homoallylbenzene (for further details, see the Supporting Information, Tables S20−S23). In the absence of the Fe cocatalyst and Bu_4NCl, 92.3% of the palladium remains in the solid phase. In the presence of 50 mol

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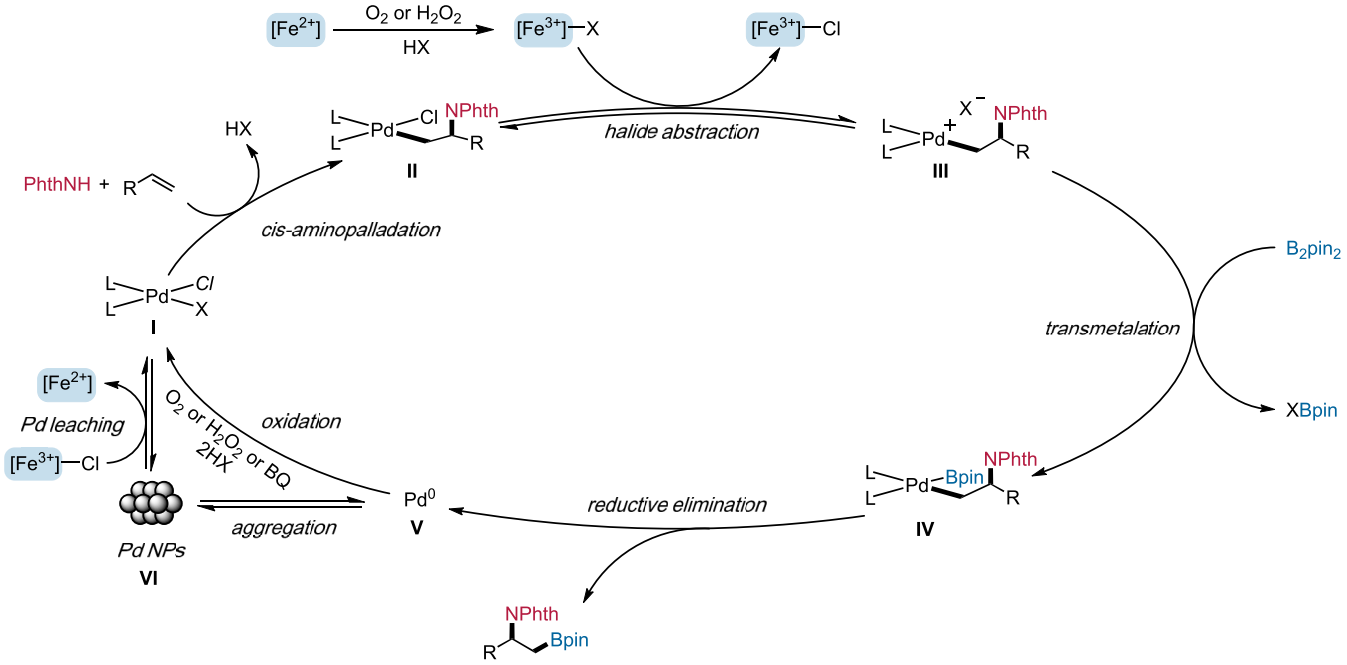
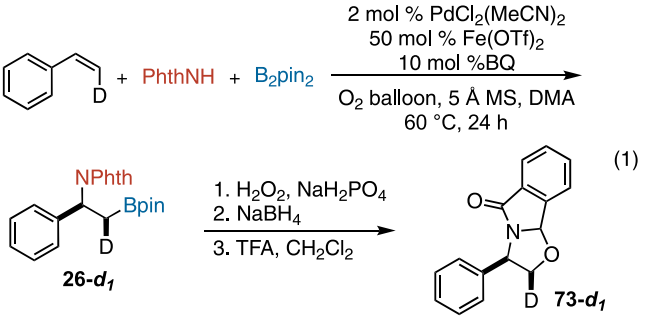
Scheme 5. Proposed Mechanism for Pd/Fe Cocatalyzed Aminoboration of Nitrogen Nucleophiles, Directing-Group-Free Alkenes and B_2pin_2



% $Fe(OTf)_2$, 32.6% of Pd is in the supernatant; this is consistent with the Fe catalyst acting as an electron transfer mediator and leaching Pd from the NPs. Furthermore, when Bu_4NCl is added, 72.0% of Pd is found in solution (Scheme 4d, entry 3), suggesting that Cl^- facilitates this process. Control experiments, shown in Scheme 4**e**, support the [Fe]/Cl^--mediated leaching of Pd from Pd NPs.[51]

With the role of the Fe cocatalyst elucidated, we finally wanted to determine the mechanism of aminopalladation. The *cis* relationship between the NPhth and Bpin in **40**−**67** is consistent with *cis*-aminopalladation and a stereoretentive borylation. To determine if the terminal alkenes also proceed through a *cis*-aminopalladation, *cis*-deuterostyrene was subjected to the aminoboration conditions to afford **26-*d*$_1$**. The Bpin of **26-*d*$_1$** was then oxidized with H_2O_2; a subsequent reduction/cyclization sequence afforded **73-*d*$_1$** as a single diastereoisomer (eq 1). NOESY experiments of **73** and **73-*d*$_1$** confirm the *cis* relationship between the deuterium and phenyl ring, consistent with *cis*-aminopalladation (for further details, see the Supporting Information, Section 5.11).



(1)

Given our investigations, we propose the following mechanism (Scheme 5): (i) ligand exchange to the Pd(II) catalyst **I** followed by (ii) *cis*-aminopalladation of the alkene, affords **II**, (iii) halide abstraction by [Fe^{3+}] generates **III**, which (iv) undergoes transmetalation with B_2pin_2 generating **IV** and, finally, (v) reductive elimination produces the aminoboration product and **V**. The Pd(0) (**V**) then either undergoes direct oxidation to **I** or aggregates to form Pd NPs (**VI**), which are then oxidatively leached by Fe and Cl^- to regenerate **I**.

CONCLUSIONS

In summary, we have developed a cooperative Pd/Fe catalytic system to realize the directing-group-free aminoboration of terminal alkenes and norbornenes with common nitrogen nucleophiles and B_2pin_2. The Fe cocatalyst plays two crucial roles in the reaction serving as (i) a halophilic Lewis acid to deliver the cationic Pd intermediate prior to transmetalation and (ii) a redox shuttle, which leaches active Pd(II) from Pd NPs. The impact of the results presented herein will likely go beyond the aminoboration reaction. This novel Lewis acid-promoted transmetalation between Pd−alkyl intermediates and B_2pin_2 is likely to impact other borylation methodologies. Further, the ability of Fe cocatalysts to reactivate Pd NPs under aerobic conditions may have implications for other Pd-catalyzed aerobic oxidations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c05790.

Additional optimization and mechanistic studies data; experimental procedures; characterization data; and annotated NMR spectra (PDF)

MNova FID Files (ZIP)

Accession Codes

CCDC 2221987 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Jensen, K. H.; Sigman, M. S. Mechanistic Approaches to Palladium-Catalyzed Alkene Difunctionalization Reactions. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088.

(2) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981−3019.

(3) Yin, G.; Mu, X.; Liu, G. Palladium(II)-Catalyzed Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center. *Acc. Chem. Res.* **2016**, *49*, 2413−2423.

(4) Dorn, S. K.; Brown, M. K. Cooperative Pd/Cu Catalysis for Alkene Arylboration: Opportunities for Divergent Reactivity. *ACS Catal.* **2022**, *12*, 2058−2063.

(5) Hili, R.; Yudin, A. K. Making Carbon-Nitrogen Bonds in Biological and Chemical Synthesis. *Nat Chem Biol* **2006**, *2*, 284−287.

(6) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; John Wiley & Sons, Inc: Weinheim, 2008.

(7) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457−2483.

(8) Lennox, A. J. J.; Lloyd-Jones, G. C. Selection of Boron Reagents for Suzuki−Miyaura Coupling. *Chem. Soc. Rev.* **2014**, *43*, 412−443.

(9) Leonori, D.; Aggarwal, V. K. Stereospecific Couplings of Secondary and Tertiary Boronic Esters. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082−1096.

(10) Zhang, C.; Hu, W.; Morken, J. P. α-Boryl Organometallic Reagents in Catalytic Asymmetric Synthesis. *ACS Catal.* **2021**, *11*, 10660−10680.

(11) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, 1. repr.; Hall, D. G., Ed.; WILEY-VCH: Weinheim, 2006.

(12) Trippier, P. C.; McGuigan, C. Boronic Acids in Medicinal Chemistry: Anticancer, Antibacterial and Antiviral Applications. *Med. Chem. Commun.* **2010**, *1*, 183−198.

(13) Li, X.; Hall, D. G. Synthesis and Applications of β-Aminoalkylboronic Acid Derivatives. *Adv. Synth. Catal.* **2021**, *363*, 2209−2223.

(14) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. Regioselective and Stereospecific Copper-Catalyzed Aminoboration of Styrenes with Bis(Pinacolato)Diboron and *O*-Benzoyl-*N*,*N*-Dialkylhydroxylamines. *J. Am. Chem. Soc.* **2013**, *135*, 4934−4937.

(15) Sakae, R.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Stereoselective Aminoboration of Bicyclic Alkenes. *Angew. Chem., Int. Ed.* **2015**, *127*, 623−627.

(16) Sakae, R.; Hirano, K.; Miura, M. Ligand-Controlled Regiodivergent Cu-Catalyzed Aminoboration of Unactivated Terminal Alkenes. *J. Am. Chem. Soc.* **2015**, *137*, 6460−6463.

(17) Kato, K.; Hirano, K.; Miura, M. Synthesis of β-Boryl-α-Aminosilanes by Copper-Catalyzed Aminoboration of Vinylsilanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14400−14404.

(18) Kato, K.; Hirano, K.; Miura, M. Copper-Catalyzed Regio- and Enantioselective Aminoboration of Unactivated Terminal Alkenes. *Chem. - Eur. J.* **2018**, *24*, 5775−5778.

(19) Nishino, S.; Nishii, Y.; Hirano, K. *Anti* -Selective Synthesis of β-Boryl-α-Amino Acid Derivatives by Cu-Catalysed Borylamination of α,β-Unsaturated Esters. *Chem. Sci.* **2022**, *13*, 14387−14394.

(20) Whyte, A.; Torelli, A.; Mirabi, B.; Zhang, A.; Lautens, M. Copper-Catalyzed Borylative Difunctionalization of π-Systems. *ACS Catal.* **2020**, *10*, 11578−11622.

(21) Hirano, K.; Miura, M. Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of *N* -Containing Molecules from Alkenes and Alkynes. *J. Am. Chem. Soc.* **2022**, *144*, 648−661.

(22) Hirano, K. Copper-Catalyzed Electrophilic Amination: An Umpolung Strategy for New C−N Bond Formations. *Bull. Chem. Soc. Jpn.* **2023**, *96*, 198−207.

(23) Tobisch, S. Copper-Catalysed Aminoboration of Vinylarenes with Hydroxylamine Esters-A Computational Mechanistic Study. *Chem. - Eur. J.* **2017**, *23*, 17800−17809.

(24) Kotov, V.; Scarborough, C. C.; Stahl, S. S. Palladium-Catalyzed Aerobic Oxidative Amination of Alkenes: Development of Intra- and Intermolecular Aza-Wacker Reactions. *Inorg. Chem.* **2007**, *46*, 1910−1923.

(25) Kohler, D. G.; Gockel, S. N.; Kennemur, J. L.; Waller, P. J.; Hull, K. L. Palladium-Catalysed Anti-Markovnikov Selective Oxidative Amination. *Nat. Chem.* **2018**, *10*, 333−340.
(26) Bhatt, S.; Wang, Y.-N.; Pham, H. T. P.; Hull, K. L. Palladium-Catalyzed Oxidative Amination of α-Olefins with Indoles. *Org. Lett.* **2022**, *24*, 5746−5750.
(27) Ishiyama, T.; Murata, M.; Miyaura, N. Palladium(0)-Catalyzed Cross-Coupling Reaction of Alkoxydiboron with Haloarenes: A Direct Procedure for Arylboronic Esters. *J. Org. Chem.* **1995**, *60*, 7508−7510.
(28) Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. Palladium-Catalyzed Cross-Coupling Reaction of Bis(Pinacolato)Diboron with 1-Alkenyl Halides or Triflates: Convenient Synthesis of Unsymmetrical 1,3-Dienes via the Borylation-Coupling Sequence. *J. Am. Chem. Soc.* **2002**, *124*, 8001−8006.
(29) Liu, Z.; Ni, H.-Q.; Zeng, T.; Engle, K. M. Catalytic Carbo- and Aminoboration of Alkenyl Carbonyl Compounds via Five- and Six-Membered Palladacycles. *J. Am. Chem. Soc.* **2018**, *140*, 3223−3227.
(30) Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. Palladium-Catalyzed Amide-Directed Enantioselective Carboboration of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *ACS Catal.* **2019**, *9*, 6502−6509.
(31) Yang, C.-H.; Zhang, Y.-S.; Fan, W.-W.; Liu, G.-Q.; Li, Y.-M. Intramolecular Aminoboration of Unfunctionalized Olefins. *Angew. Chem., Int. Ed.* **2015**, *54*, 12636−12639.
(32) Westcott, S. A.; Fernández, E. Singular Metal Activation of Diboron Compounds. In *Advances in Organometallic Chemistry*; Elsevier, 2015; Vol. *63*, pp 39−89.
(33) Kanno, S.; Kakiuchi, F.; Kochi, T. Palladium-Catalyzed Remote Diborylative Cyclization of Dienes with Diborons *via* Chain Walking. *J. Am. Chem. Soc.* **2021**, *143*, 19275−19281.
(34) García-Melchor, M.; Fuentes, B.; Lledós, A.; Casares, J. A.; Ujaque, G.; Espinet, P. Cationic Intermediates in the Pd-Catalyzed Negishi Coupling. Kinetic and Density Functional Theory Study of Alternative Transmetalation Pathways in the Me−Me Coupling of $ZnMe_2$ and *Trans* -$[PdMeCl(PMePh_2)_2]$. *J. Am. Chem. Soc.* **2011**, *133*, 13519−13526.
(35) Niwa, T.; Uetake, Y.; Isoda, M.; Takimoto, T.; Nakaoka, M.; Hashizume, D.; Sakurai, H.; Hosoya, T. Lewis Acid-Mediated Suzuki−Miyaura Cross-Coupling Reaction. *Nat Catal* **2021**, *4*, 1080−1088.
(36) Wang, D.; Stahl, S. S. Pd-Catalyzed Aerobic Oxidative Biaryl Coupling: Non-Redox Cocatalysis by $Cu(OTf)_2$ and Discovery of $Fe(OTf)_3$ as a Highly Effective Cocatalyst. *J. Am. Chem. Soc.* **2017**, *139*, 5704−5707.
(37) Ojha, D. P.; Gadde, K.; Prabhu, K. R. Generation of Hydrogen from Water: A Pd-Catalyzed Reduction of Water Using Diboron Reagent at Ambient Conditions. *Org. Lett.* **2016**, *18*, 5062−5065.
(38) Trost, B. M.; Van Vranken, D. L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395−422.
(39) Collins, K. D.; Glorius, F. A Robustness Screen for the Rapid Assessment of Chemical Reactions. *Nat. Chem.* **2013**, *5*, 597−601.
(40) Sanford, M. Lurasidone: In the Treatment of Schizophrenia. *CNS Drugs* **2013**, *27*, 67−80.
(41) Hickey, S. M.; Ashton, T. D.; White, J. M.; Li, J.; Nation, R. L.; Yu, H. Y.; Elliott, A. G.; Butler, M. S.; Huang, J. X.; Cooper, M. A.; Pfeffer, F. M. Synthesis of Norbornane Bisether Antibiotics via Silver-Mediated Alkylation. *RSC Adv.* **2015**, *5*, 28582−28596.
(42) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. Aerobic Oxidative Amination of Unactivated Alkenes Catalyzed by Palladium. *J. Am. Chem. Soc.* **2005**, *127*, 2868−2869.
(43) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. Formation of Enamides via Palladium(II)-Catalyzed Vinyl Transfer from Vinyl Ethers to Nitrogen Nucleophiles. *Org. Lett.* **2004**, *6*, 1845−1848.
(44) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. Hydrogen-Bond-Directed Highly Stereoselective Synthesis of Z-Enamides via Pd-Catalyzed Oxidative Amidation of Conjugated Olefins. *J. Am. Chem. Soc.* **2006**, *128*, 12954−12962.
(45) Dang, T. T.; Boeck, F.; Hintermann, L. Hidden Brønsted Acid Catalysis: Pathways of Accidental or Deliberate Generation of Triflic Acid from Metal Triflates. *J. Org. Chem.* **2011**, *76*, 9353−9361.
(46) Ludwig, J. R.; Watson, R. B.; Nasrallah, D. J.; Gianino, J. B.; Zimmerman, P. M.; Wiscons, R. A.; Schindler, C. S. Interrupted Carbonyl-Olefin Metathesis via Oxygen Atom Transfer. *Science* **2018**, *361*, 1363−1369.
(47) Wang, Z.; Zhang, Z.; Lu, X. Effect of Halide Ligands on the Reactivity of Carbon−Palladium Bonds: Implications for Designing Catalytic Reactions. *Organometallics* **2000**, *19*, 775−780.
(48) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. Role of Halide Ions in Divalent Palladium-Mediated Reactions: Competition between β-Heteroatom Elimination and β-Hydride Elimination of a Carbon−Palladium Bond. *Organometallics* **2001**, *20*, 3724−3728.
(49) Deraedt, C.; Astruc, D. "Homeopathic" Palladium Nanoparticle Catalysis of Cross Carbon−Carbon Coupling Reactions. *Acc. Chem. Res.* **2014**, *47*, 494−503.
(50) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118*, 2636−2679.
(51) Ding, Y.; Zheng, H.; Li, J.; Zhang, S.; Liu, B.; Ekberg, C. An Efficient Leaching of Palladium from Spent Catalysts through Oxidation with Fe(III). *Materials* **2019**, *12*, 1205.

https://doi.org/10.1021/jacs.3c05790
J. Am. Chem. Soc. 2023, 145, 18939−18947