Pd and Fe Co-Catalyzed Synthesis of Remotely Borylated Aza-Heterocycles

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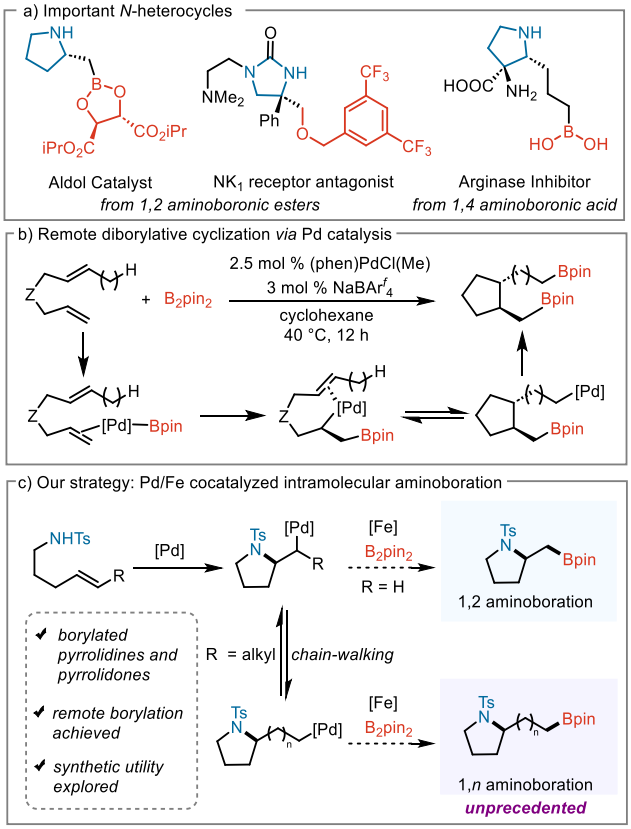
ABSTRACT: We report the intramolecular 1,*n*-aminoboration for the simultaneous synthesis of aza-heterocycles with distal carbon–boron bonds. Pd-catalyzed remote 1,*n*-aminoboration occurs with 1,2-disubstituted alkenes; upon aminopalladation of the olefin, chain-walking generates the terminal Pd-alkyl intermediate which selectively undergoes Fe-catalyzed borylation. Terminal bishomoallylic amines, amides, carbamates, and ureas afford the borylated pyrrolidines and lactams through 1,2-aminoboration. Forty-one examples of 1,*n*-borylated heterocycles are presented with yields up to 92% yield. Derivatization of the products is explored: cross-coupling, amination, and oxidation to access unnatural amino alcohols and acids.

INTRODUCTION

Nitrogen-containing heterocycles, particularly pyrrolidines, are widely prevalent in natural products, agrochemicals, and pharmaceuticals due to their biological activity.[1,2] Alkylboron reagents are versatile intermediates for synthetic chemistry and are important carboxylic acid isosteres. Methods for accessing molecules containing both of these valuable moieties are highly desirable, especially if these methods allow for the rapid synthesis of 1,*n*-borylated aza-heterocycles ($n \geq 2$) (Scheme 1a).[3] Intramolecular alkene aminoboration is a powerful and efficient strategy to simultaneously generate the aza-heterocycle and selectively install the boron handle.[4] Recently, significant advances in intramolecular aminoboration have been reported.[5] While robust, these methods require either toxic reagents (i.e. BCl_3) or pre-oxidized amine/oxime substrates and are limited to generating α-borylated *N*-heterocycles. To our knowledge, no report has been made on the remote aminoboration to synthesize distally borylated aza-heterocycles.

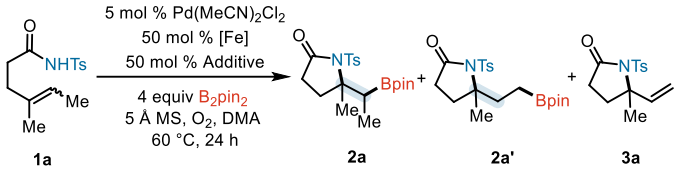
Palladium-catalyzed intramolecular aminopalladation/functionalizations are well-precedented for the generation of *N*-heterocycles and an adjacent functionality.[6] The borylation of Pd^{II}-alkyl intermediates with B_2pin_2 has attracted significant interest for the synthesis of C^{sp3}–B bonds; these reactions are generally promoted by Lewis bases.[7] Recently, Kochi reported a remote diborylation, cyclization of dienes with a cationic Pd^{II}-catalyst.[8] In this reaction, they take advantage of the chain-walking ability of Pd^{II} and find that the cationic catalyst undergoes selective transmetalation with B_2pin_2 at the least hindered, terminal Pd-alkyl intermediate (Scheme 1b). Subsequently, we reported the Markovnikov selective Pd- and Fe-cocatalyzed aminoboration of unactivated terminal alkenes. Under our conditions, the Fe catalyst serves as a halophilic Lewis acid which generates a cationic Pd-alkyl intermediate that rapidly undergoes borylation.[9] Notably, we do not observe any chain-walking under these conditions: likely due to the formation of the terminal Pd-alkyl bond upon aminopalladation.[10] Given the importance of aza-heterocycles and the synthetic versality of alkylboranes, we envisioned a reaction which utilizes Pd to promote an intramolecular aminopalladation and subsequent borylation to generate 1,2-aminoborati-

Scheme 1. Strategies for borylation via Pd catalysis



-on products. Moreover, we hypothesized that upon aminopalladation, internal alkenes may undergo isomerization to generate a terminal Pd^{II}-alkyl intermediate prior to reaction with B_2pin_2 (Scheme 1c).[11] In this context, we could use simple bishomoallylic amines to form the *N*-heterocycle and install a distal boronic ester in a single step—a remote 1,*n*-aminoboration reaction.

Table 1. Reaction development.[a]



Entry	[Fe]	Additive	Solvent	**2a'** (%)[b]	**3a** (%)[b]
1	$Fe(OTf)_2$	–	DMA[c]	36	13
2	$Fe(OTf)_2$	$^nBu_4NI$	DMA	< 1	3
3	$Fe(OTf)_2$	$^nBu_4NBr$	DMA	16	11
4	$Fe(OTf)_2$	$^nBu_4NCl$	DMA	54	45
5	$FeCl_2$	-	DMA	55	45
6	$FeCl_2$	-	Dioxane	38	< 1
7	$FeCl_2$	-	THF[d]	59	7
8	$FeCl_2$	-	DME	76 (61)[e]	3

[a]Conditions: **1a** (0.1 mmol), $Pd(MeCN)_2Cl_2$ (5 mol %), $FeCl_2$ (50 mol %), B_2pin_2 (4 equiv), 5 Å molecular sieves (MS) (40 mg), 1,2-dimethoxyethane (DME) (0.33 M), and O_2 (1 atm), 60 °C, 24 h. [b]GC yields determined using 1-methylnapthalene as an internal standard. [c]*N,N*-dimethylacetamide. (DMA) [d]Tetrahydrofuran (THF). [e]Isolated yield.

RESULTS AND DISCUSSION

We began our initial efforts towards the development of an 1,*n*-aminoboration reaction with our previously reported conditions using $Pd(MeCN)_2Cl_2$ and $Fe(OTf)_2$ as co-catalysts (Table 1, entry 1) and **1a** to promote unidirectional chain-walking. Gratifyingly, we observed a promising 36% yield of **2a'** along with 13% of aza-Wacker side product **3a**. We posit that **3a** forms after β-hydride elimination from dissociation of the [Pd]–H, rather than reinsertion into the C=C bond. Notably, 1,2-aminoboration product **2a** is not detected. Halide additives are known to help with catalyst turnover in aerobic oxidations and promote migratory insertion.[12] Therefore, we speculated that the addition of a halide source may improve reactivity and selectivity by facilitating chain-walking. Indeed, upon the addition of 50 mol % $^nBu_4NCl$ to the reaction mixture, we observed a significant increase in overall reactivity (99% combined yield of **2a'** and **3a**), unfortunately, at the expense of selectivity as **2a'** and **3a** are formed in a 1.2:1 ratio. Replacing the Fe co-catalyst with $FeCl_2$ leads to comparable reactivity. Remarkably, upon varying solvents with $FeCl_2$, we observed that ethereal solvents promote the desired aminoboration reaction over the aza-Wacker process; using DME as the solvent dramatically improves the selectivity towards the aminoboration product while maintaining the desired reactivity. Under our optimized reaction conditions, **2a'** is afforded in 76% *in situ* and 61% isolated yield as a single regioisomer. Notably, no protodeborylation is observed under the reaction conditions.

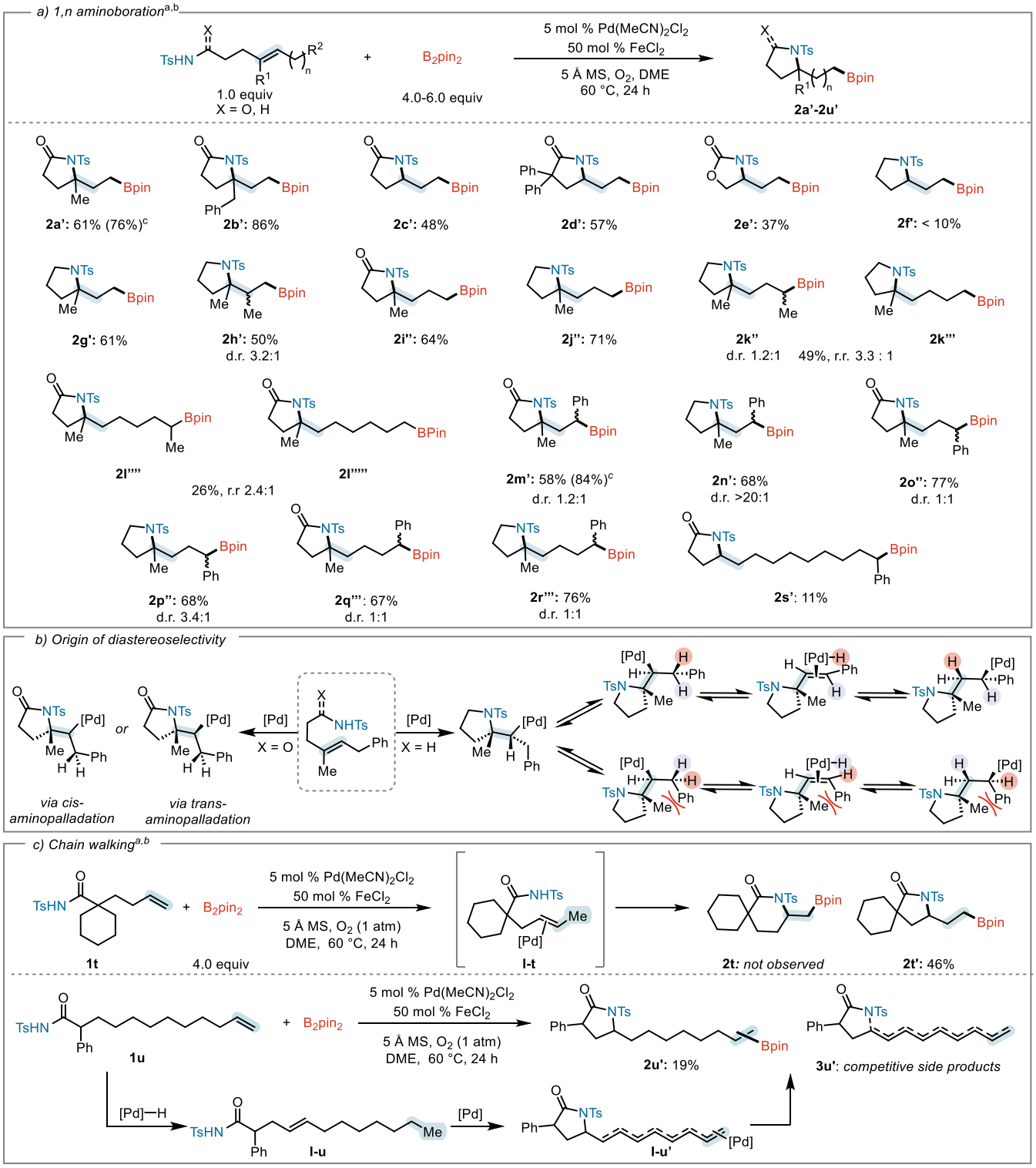
With the optimized conditions in hand, we next explored the reaction scope for the remotely borylated heterocycles (Table 2). There is a notable discrepancy between many of the *in situ* and isolated yields; we attribute this to the high affinity of alkyl organoboranes for silica gel and significantly complicating column chromatography (see SI). In general, trisubstituted alkenes display excellent reactivity and selectivity for 1,3-aminoboration, as distally borylated lactams **2a'** and **2b'** are isolated in 61 and 86% yield, respectively. 1,2-disubstituted alkenes also participate, as γ-borylated lactam **2c'** is isolated in 48% yield. Adding *gem*-diphenyl substituents on the backbone improves the reactivity and affords **2d'** in 57% yield. Other heterocycles are accessible, as oxazolidone **2e'** is obtained in 37% yield along with unreacted starting material. Unfortunately, pyrrolidine **2f'** is formed in low yield due to poor conversion and preferential formation of aza-Wacker product (**3f**) (see SI). Gratifyingly, trisubstituted alkene **1g** proves to be a superior substrate, as **2g'** is isolated in 61% yield. Moreover, despite its steric hinderance, tetrasubstituted alkene **1h** participates to afford **2h'** in 50% yield (3.2:1 d.r.).

Chain-walking can be extended to the δ-carbon to afford the 1,4-aminoboration product **2i''** in 64% yield and corresponding pyrrolidine **2j''** in 71% yield. As the alkyl chain is further extended (R^1 = ^nPr), 1,4- and 1,5-aminoboration products **2k''** and **2k'''** are both formed in 49% combined yield as 3.3:1 mixture of regioisomers. This preference for the formation of the secondary boronic ester over the primary suggests that the rate of borylation is impacted by proximity to the sterically hindered heterocycle as well as the substitution of the Pd-alkyl. Similarly, 1,6- and 1,7-aminoboration products are observed with **1l** in a modest 26% yield (2.4:1 r.r.).

Given the moderate regioselectivities observed in 1,*n*-aminoboration when $n \geq 5$, we hypothesized that selective stabilization of the Pd-alkyl intermediate, as a π-benzyl, may generate secondary benzylic boronic esters. Indeed, the distal borylation is not limited to the formation of primary alkyl boronic esters; **2m'**-**2r'''** are obtained in very good yields. Interestingly, lactam **2m'** and pyrrolidine **2n'** are formed in 58% and 68% isolated yield, respectively, with drastically different diastereoselectivites (1.2:1 and >20:1). This is despite both substrates, **1m** and **1n**, being *trans* alkenes (>20:1 *E*/*Z*). Monitoring the reaction over time, we observed no epimerization of **1m** and the diastereomeric ratio of **2m'** is constant over the course of the reaction (see SI). Combined, these results suggest that there is a lack of stereospecificity which may be caused by competing *cis*- and *trans*-aminopalladation by the *N*-tosylamide (Table 2b).[13] The less acidic **1n**, may undergo selective *cis*-aminopalladation as **2n'** is formed as a single diastereoisomer (Table 2b). Moreover, the diastereoselectivity for the pyrrolidines **2n'**, **2p''**, and **2r'''** decreases as the chain extends for increasingly distal borylation. With 1,3-aminoboration, there is a significant $A^{1,3}$-strain difference between the *E* and *Z* alkenes which inhibits the formation of the *Z* alkene, and thus Pd stays on the initial face and **2n'** is formed in high d.r. (>20:1). However, as the chain becomes longer, the strain difference decreases with each subsequent β-hydride elimination, allowing epimerization to occur, and resulting in reduced diasteroselectivities for **2p''** and **2r'''**. While aminopalladation is likely still occurring in a stereoselective fashion, Pd^{II} migrates from one face of the chain to the other during β-hydride elimination when both the *E* and *Z* alkenes are energetically accessible. Importantly, we no longer observed mixtures of regioisomers even with extended chains, as shown with lactam **2q'''** and pyrrolidine **2r'''**. Finally, we observed that up to 1,10-aminoboration is possible, as **2s'** is formed in 11% yield: with low yield resulting from competitive aza-Wacker and olefin isomerization.

Interestingly, subjecting terminal alkene **1t**, which could undergo

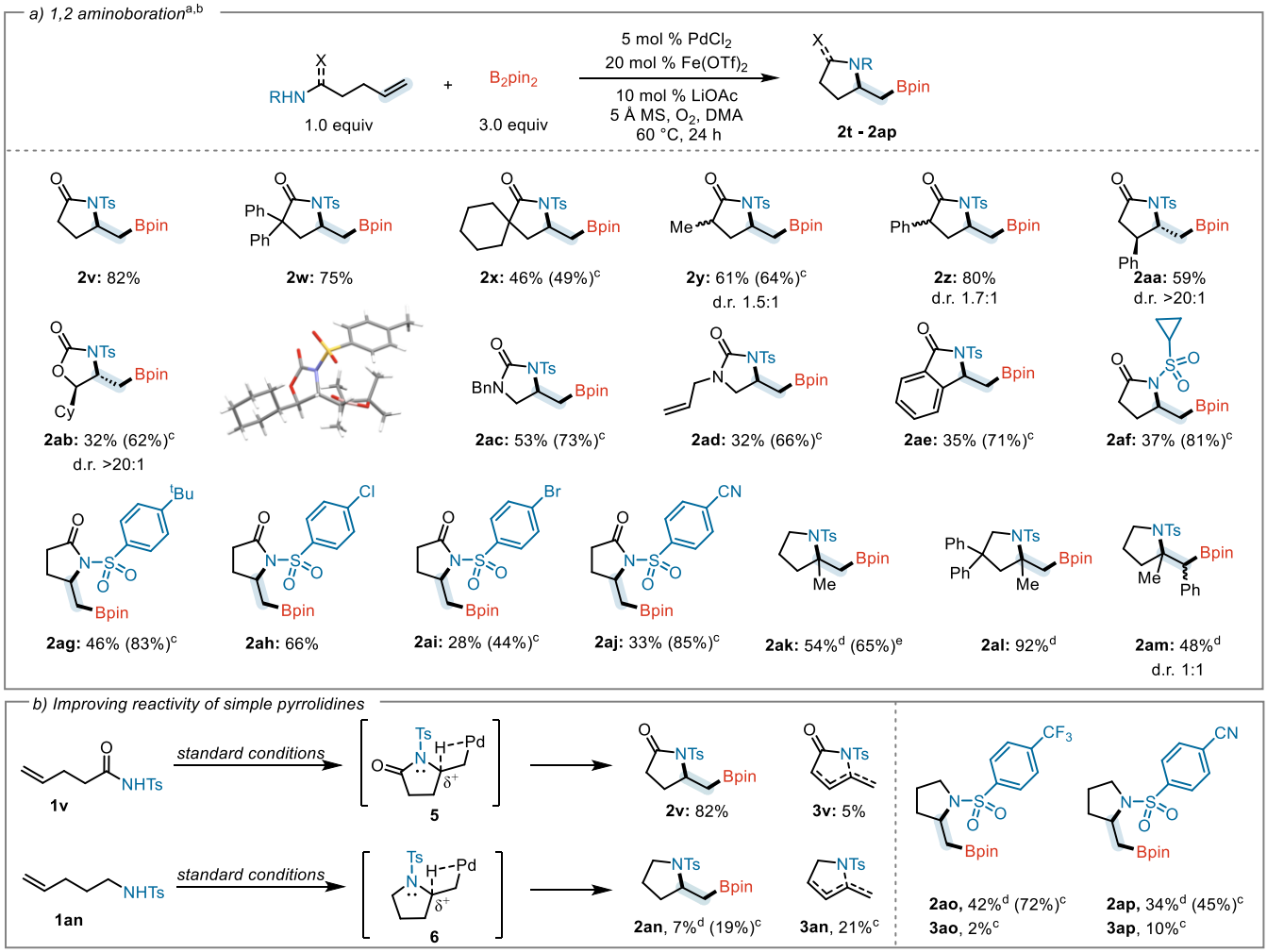
Table 2. Scope of chain walking products



[a]Isolated yields. [b]Reaction conditions: **1a-1u** (0.1-0.2 mmol), $Pd(MeCN)_2Cl_2$, (5 mol %), $FeCl_2$ (50 mol %), B_2pin_2 (4-6 equiv), 5 Å MS (40 mg), DME (0.33 M), and O_2 (1 atm), 60 °C, 24 h. [c]GC yield determined by comparison to an internal standard.

intramolecular 1,2-aminoboration to afford the six membered γ-lactam, leads to the exclusive formation of distally borylated δ-lacam. **2t'** in 46% yield instead. We hypothesized that this formation is due to olefin isomerization of the internal alkene (**I-t**), followed by the Pd catalyzed 1,3-aminoboration to afford the five-membered δ-lactam **2t'**. This result indicates that there is a significant kinetic preference for 5-membered ring formation under these conditions, which necessitates olefin isomerization. In an extreme example of this, when dodec-11-enamide **1u** is subjected to the reaction conditions, only the five-membered aminoboration products (**2u'**) are

Table 3. Scope of borylated lactams and pyrrolidines

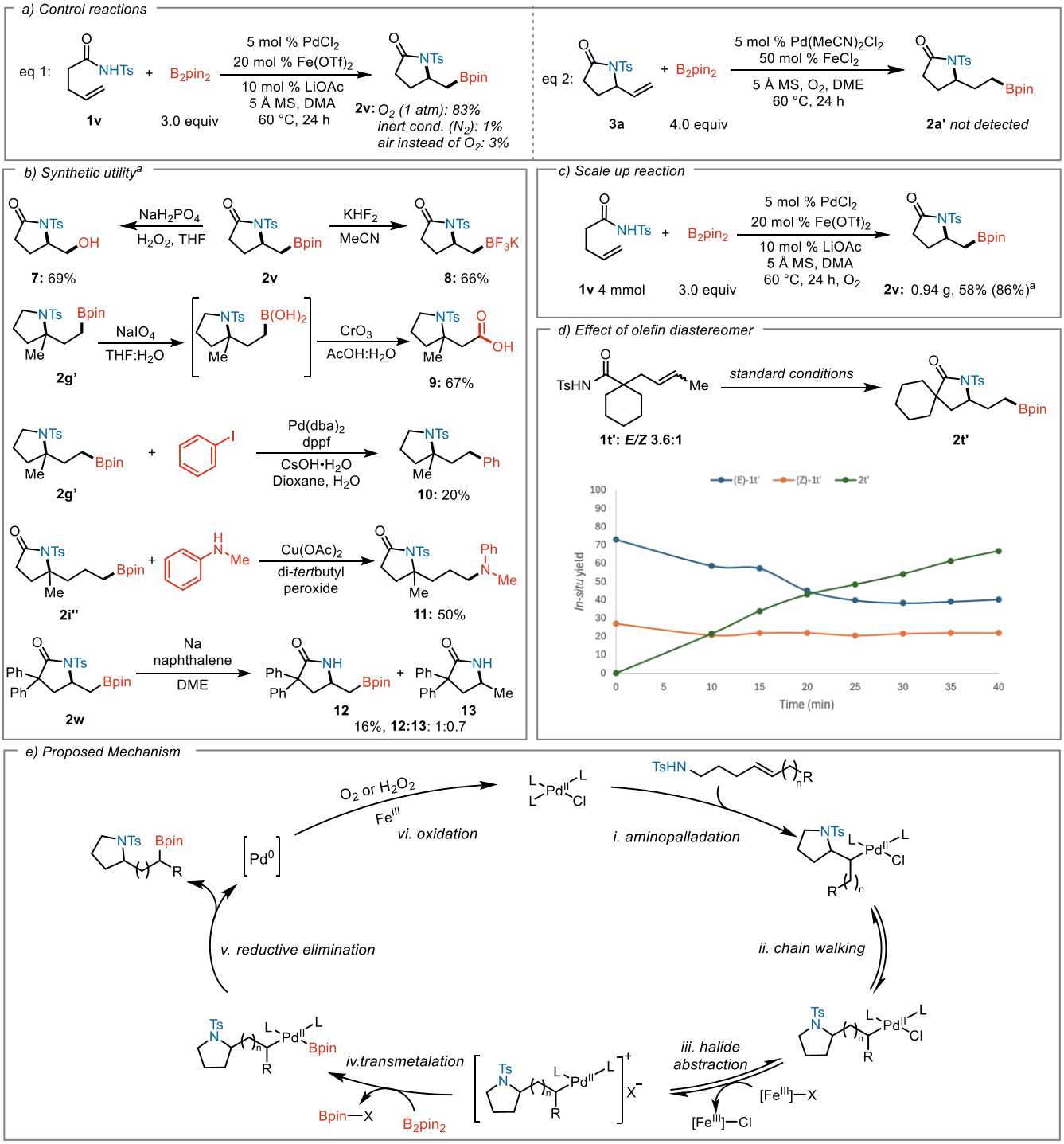


[a]Isolated yields. [b]Reaction conditions: **1v-1aj** (0.2 mmol), $PdCl_2$ (5 mol %), $Fe(OTf)_2$ (20 mol %), LiOAc (10 mol %), B_2pin_2 (3 equiv), 5 Å MS (40 mg), DMA (0.33 M), and O_2 (1 atm), 60 °C, 24 h. [c] ^{1}H NMR or GC yield determined by comparison to an internal standard. [d]**1ak-1ap** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (5 mol %), $Fe(OTf)_2$ (50 mol %), B_2pin_2 (4 equiv), benzoquinone (20 mol %), 5 Å MS (40 mg), 1:1 DMA:PhMe (0.33 M), and O_2 (1 atm), 80 °C, 24 h. [e]**1ak** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (5 mol %), $Fe(OTf)_2$ (50 mol %), B_2pin_2 (4 equiv), 5 Å MS (40 mg), 1:1 DMA:PhMe (0.33 M), and O_2 (1 atm), 80 °C, 24 h.

observed in 19% yield as a mixture of regioisomers. Aza-Wacker and olefin isomerization products (**3u'**) are also formed over the course of the reaction.

With the success of terminal olefins in our reaction conditions and given the synthetic utility of α-borylated heterocycles, we sought to further expand our scope to achieve 1,2-aminoboration (Table 3). Under slightly modified conditions (see SI), namely using $Fe(OTf)_2$ as the Lewis acid additive and catalytic amounts of base (LiOAc or K_2CO_3), a variety of α-borylated *N*-heterocycles are generated. Simple lactam **2v** can be obtained in an excellent 82% yield. Substitution along the carbon backbone is well tolerated; α,α-disubstituted amides readily participate in the reaction and afford **2w** and spirocyclic **2x** in 75% and 46% yield, respectively. Moreover, mono-substituted substrates afford 61% yield of **2y** and 80% yield of **2z**, with modest diastereoselectivities (1.5-1.7 d.r.). Substituents β to the carbonyl have been reported to improve the diastereoselectivity in comparison to α, as they are directly adjacent to the newly formed stereocenter.[14] Indeed, **2aa** and **2ab** are formed with significantly improved diastereoselectivities (>20:1). Of note, trans-diastereomer **2ab** forms exclusively, as confirmed by x-ray crystallography. Interestingly, analogues of urea, which are biologically prevalent motifs[2d] undergo the desired aminoboration in good yields (**2ac-2ad**) and provide access to diverse heterocycles. Moreover, the borylated isoindolinone derivative **2ae** can be formed in a synthetically useful 35% isolated yield (71% *in situ*). Various substituents on the sulfonamide protecting group are tolerated (**2af-2aj**). The low yield for **2ai** is attributed to low conversion of the starting material, likely due to a decreased rate of aminopalladation with this weaker nucleophile.[15] Tosyl-protected bishomoallylic amines containing 1,1-disubstiuted alkenes, which upon aminopalladation lack a β-hydrogen, proved again to be superior substrates. For example, **2ak** which forms a tetrasubstituted carbon, is afforded in 54% yield. Increasing the Thorpe-Ingold effect on the olefin backbone yields **2al** in an excellent 92% isolated yield. The more hindered, trisubstituted internal olefin affords **2am** in 48% yield and 1:1 d.r. In addition to being under modified reaction conditions, this loss in selectivity suggests that

Table 4. Mechanistic Insights and synthetic utility of 1,*n*-aminoboration products



[a]See SI for detailed reaction conditions. [b]*In-situ* yield determined in comparison to internal standard.

the more hindered alkene is undergoing competitive *cis* and *trans*-aminopalladation. Simple pyrrolidine **1an** performed poorly in the aminoboration reaction: only 19% *in situ* yield of **2an** is observed along with significant aza-Wacker and olefin isomerization side products (21% combined yield). Comparing the chemoselectivity between pyrrolidines and lactams, we hypothesized that transition state **5** is higher in energy than **6**, due to it being a more electron-deficient tosylamide rather than a tosylamine. This slows β-hydride elimination relative to borylation. With tosylamine **1an**, the δ^+ charge formed during β-hydride elimination is better stabilized in **6**, thus β-hydride elimination is now faster relative to borylation. We hypothesized that a more electron-deficient protecting group should improve chemoselectivity. Indeed, replacing the tosyl protecting group with *para*-trifluoromethylbenzenesulfonamide (**1ao**) or *para*-cyanobenzenesulfonamide (**1ap**) dramatically improves the product selectivity: **2ao** and **2ap** are formed in 72% (42%) and 45% (34%) *in situ* (isolated) yield, respectively. With these substrates, less than 10% aza-Wacker or olefin isomerization products (**3ao** and

3ap) are observed. Unfortunately, a similar strategy proved unsuccessful in the 1,3-aminoboration with **1f** derivatives (see SI). Moreover, other protecting groups, e.g. benzamide, lead to considerably decreased yields along with unreacted starting material for 1,*n*-aminoboration (see SI).[16]

Our substrate scope demonstrates good functional group tolerance, as aryl halides (**2ah** and **2ai**), nitriles (**2aj** and **2am**), trifluoromethyl groups (**2al**), and pendant olefins (**2ad**) are tolerated. To further explore the functional group tolerance of this aminoboration we conducted a robustness screen.[17] Various heteroatom-containing functionalities such as carbazole, benzamide, acetanilide, benzonitrile, benzofuran, benzothiophene, and alkyl chloride were tolerated under the reaction conditions; basic nitrogens, alkynes, and oxygen-sensitive functionalities were less stable (see SI).

Control reactions showed that 1 atm O_2 is essential to promote catalyst turnover, as reactions ran under N_2 or air only afford trace amounts of the aminoboration product (eq 1, Table 4a). Moreover, to confirm that the reaction is not proceeding through hydroboration of the aza-Wacker product, we subjected **3a** to the reaction conditions with B_2pin_2; product **2a'** was not observed (eq 2, Table 4a).

We also demonstrated the synthetic utility of the aminoboration products by derivatization of the alkyl boronic esters (Table 4b). The corresponding amino alcohol **7** can be obtained in good yields over two steps without purification of the borylated intermediate **2v**. The boronic ester motif can be transformed to the bench stable BF_3K salt **8** in 66% yield. Deprotection of the boronic ester **2g'** and subsequent oxidation affords the unnatural amino acid derivative **9** in 67% yield. Moreover, it can undergo Suzuki-Miyaura cross-coupling to obtain **10** in synthetically useful yields. Cu-catalyzed amination of 1,4-aminoboration product **2i''** affords 1,4-diamine **11** in 50% yield. Finally, we demonstrate that sodium naphthalene successfully removes the tosyl-protecting group to afford **12** and **13** in 16% combined yield under reported conditions.[18] Additional attempts for deprotection are summarized in the SI. The aminoboration reaction can also be scaled up to obtain 0.94 g of the borylated lactam **2v** (Table 4c).

As some of our starting materials are a mixture of *E/Z* olefin isomers, we were interested in determining the impact of diastereomeric ratio on reactivity. We subjected internal olefin **1t'** (*E/Z* 3.6:1) to our reaction conditions (Table 4d), and monitored the consumption of the diastereomers relative to product formation. Interestingly, we observed the (*E*)-olefin reacting rapidly, while the (*Z*)-olefin remains unreacted after 40 minutes. This indicates that under our conditions, the *E* isomer undergoes faster aminopalladation.

From our observations and previous mechanistic investigations [9], we propose the following mechanism: (*i.*) Pd^{II} undergoes aminopalladation with the internal bishomoallylic amine, (*ii.*) followed by rapid chain-walking to generate the distal Pd-alkyl species by a series of β-hydride elimination/re-insertion process.[19, 20] Then, (*iii.*) Lewis acid-catalyzed halide abstraction by Fe^{III} leads to the cationic Pd-alkyl species, which can (*iv.*) undergo borylation to afford the Pd-boryl species. Upon (*v.*) reductive elimination, the distally borylated heterocycle is generated and, finally, (*vi.*) Pd^0 is oxidized by O_2 and/or Fe^{III} to regenerate Pd^{II} (Table 4e).

Given the importance of 5-membered aza-heretocycles, we have developed an aerobic Pd-catalyzed method for the formation of distally and proximally borylated *N*-heterocycles directly from bishomoallylic amines. A variety of 1,*n*-borylated lactam and pyrrolidine derivatives are readily formed in good to excellent yields utilizing the chain-walking capability of Pd^{II}. The synthetic versatility of our products is demonstrated. With the excellent selectivity observed for borylation of primary alkyl-palladium intermediates *via* chainwalking, our future efforts will focus on the development of additional remote nucleoboration reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental Procedures, Characterization Data, Annotated NMR spectra (PDF)

MNova FID Files (zip file)

This material is available free of charge via the Internet at http://pubs.acs.org.

Accession Codes

CCDC 2327006 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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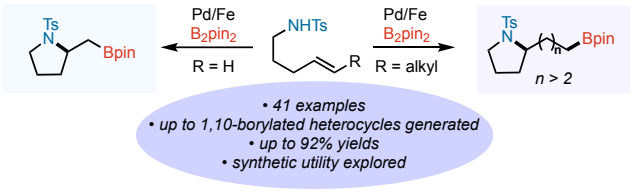

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