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Nickel-Catalyzed 1,1-Aminoborylation of Unactivated Terminal Alkenes

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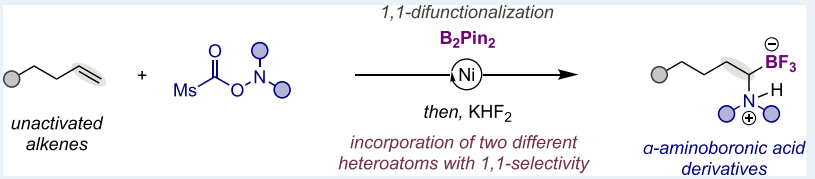
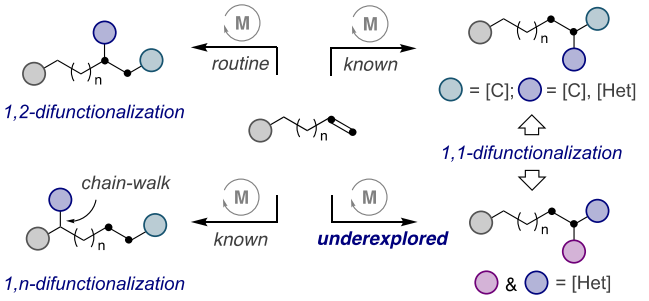


ABSTRACT: Herein, we disclose a Ni-catalyzed 1,1-difunctionalization of unactivated terminal alkenes that enables the incorporation of two different heteroatom motifs across an olefin backbone, thus streamlining the access to α-aminoboronic acid derivatives from simple precursors. The method is characterized by its simplicity and generality across a wide number of coupling counterparts.

KEYWORDS: *nickel, unactivated alkenes, aminoborylation, chain walking, site selectivity*

Recent years have witnessed an emerging demand for catalytic techniques that harness the potential of unactivated olefins as vehicles to generate sp^3-hybridized backbones.[1] In this context, 1,2-difunctionalization of olefins and chain-walking reactions have offered innovative pathways for rapidly and reliably forging sp^3 architectures, thus representing a powerful alternative to canonical cross-coupling reactions requiring prefunctionalization at the targeted sp^3 site (Scheme 1).[2,3] In contrast, the utilization of unactivated olefins as adaptive synthons in catalytic 1,1-difunctionalization events has received much less attention. Such techniques not only offer a nonclassical site-selectivity pattern in the olefin functionalization arena but also provide a palette of conceptually new tactics for our ever-growing synthetic arsenal.[4] Despite the elegant advances realized in C−C[5,6] and C−heteroatom bond-forming reactions,[7−10] the incorporation of two different heteroatom motifs across the olefin backbone with a 1,1-site-selectivity pattern still remains an underexplored, yet desirable, endeavor (Scheme 1).[11,12]

Scheme 1. Catalytic Functionalization of Olefins



α-Aminoboronic acids have gained considerable momentum as bioisosteres of natural amino acids.[13] Not surprisingly, these compounds have found a considerable echo in drug discovery as molecular probes[14] and enzyme inhibitors, such as bortezomib or vaborbactam, among others.[15−18] Consequently, chemists have been challenged to design new catalytic routes that complement traditional Matteson homologations requiring cryogenic conditions[19] or multistep synthetic sequences.[20] While significant progress has been made by utilizing alkynes[21] and well-defined vinyl boronates as precursors,[22,23] we anticipated that a generic platform aimed at streamlining the synthesis of α-aminoboronic acids from a 1,1-difunctionalization of simple and widely available unactivated olefins might represent an attractive scenario. As part of our interest in Ni-catalyzed chain walking,[24] we expected that a protocol consisting of a [1,2]-nickel migration might translocate the metal center adjacent to a boron atom prior to C−N bond formation (Scheme 2, II).[25,26] At the outset of our investigations, however, it was not clear whether it would be possible to overcome the inherent propensity of unactivated olefins for triggering catalytic 1,2-difunctionalization and to avoid parasitic chain-walking

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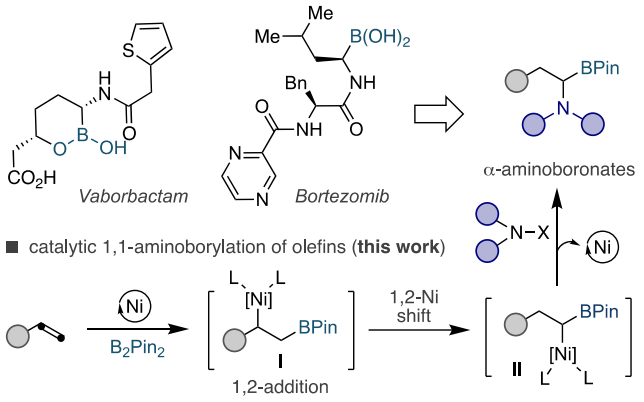
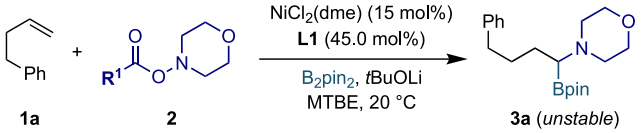
Scheme 2. 1,1-Aminoborylation of Unactivated Olefins



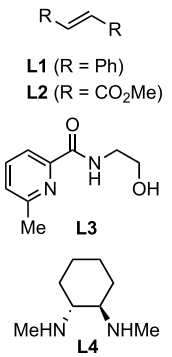
reactions that might enable bond formation at remote, previously unfunctionalized sp^3 reaction sites. Herein, we report the successful implementation of this goal, culminating in a protocol that gives access to a wide variety of α-aminoboronic acid derivatives possessing basic amine functions—an elusive motif when preparing 1,1-aminoboranes—from simple unactivated olefin precursors via an unorthodox 1,1-difunctionalization event (Scheme 2, bottom).

We started our investigations by examining the reaction of 4-phenyl-1-butene (**1a**) with a series of N,O-electrophiles and B_2Pin_2 (Table 1).[27] After some experimentation,[28] a protocol

Table 1. Optimization of Reaction Conditions[a]



entry	deviation standard conditions	3a (%)[b]
1	none (R^1 = mesityl)	76 (68)[c]
2	without **L1**	55
3	**L2** instead of **L1**	30
4	**L3** instead of **L1**	6[d]
5	**L4** instead of **L1**	11[d]
6	$NiCl_2$(dme) (10 mol%)	68
7	using $Ni(cod)_2$ as catalyst	6
8	using *t*BuONa instead of *t*BuOLi	6
9	T = 40 °C	1
10	using 1,4-dioxane as solvent	60
11	R^1 = Ph	23
12	R^1 = *m,m*-$(OMe)_2C_6H_3$	58



[a]Conditions unless specified otherwise: **1a** (0.20 mmol), **2a** (R^1 = mesityl; 0.30 mmol), $NiCl_2$(dme) (15 mol %), **L1** (45 mol %), B_2Pin_2 (0.34 mmol), *t*BuOLi (0.30 mmol), MTBE (0.6 M), 20 °C for 18 h; then **2a** (0.20 mmol), B_2Pin_2 (0.24 mmol), and *t*BuOLi (0.20 mmol), 18 h. [b]GC yields using *n*-decane (1.0 equiv) as an internal standard. [c]Isolated yield of the corresponding trifluoroborate salt upon treatment with KHF_2 in AcOH (**4a**). [d]**L4** (18 mol %).

consisting of **2a**, $NiCl_2$(glyme), **L1**, *t*BuOLi, and *tert*-butyl methyl ether (MTBE) afforded the best results (entry 1). Although the instability of **3a** precluded its isolation in pure form, simple exposure to KHF_2 in AcOH delivered the corresponding α-aminotrifluoroborate **4a** in 68% isolated yield.[29−31] The N,O-electrophile played an important role on reactivity, with sterically congested arenes possessing electron-donating groups providing the best results (entries 1, 11, and 12).[32] As expected, the solvent, temperature, nickel precatalyst, base, and concentration had a non-negligible impact on the reaction outcome (entries 6−10). As for related Ni-catalyzed chain-walking reactions, we anticipated significant differences depending on the ligand employed.[8,9,24] As shown in entries 2−5, this turned out to be the case. Intriguingly, however, ligands previously described to efficiently enable 1,1-difunctionalization[33] failed to provide significant amounts of **3a**, whereas the utilization of electron-deficient olefin ligands provided the best results.[34−36] Tentatively, this observation suggests that the presence of the latter might facilitate a final sp^3 C−N bond reductive elimination en route to **3a**.

Next, we turned our attention to exploring the generality of our 1,1-aminoborylation by evaluating a wide variety of N−O electrophilic counterparts. As shown in Scheme 3, the presence of morpholine (**4a**), thiomorpholine (**4c**), piperidine, and piperazine (**4b**,**d**−**g**) did not interfere with productive sp^3 C−B/C−N bond formation. Moreover, the reaction could be extended to seven-membered rings (**4h**,**i**), albeit in slightly lower yields. Notably, even noncyclic secondary amines (**4j**,**k**) could be employed as substrates. Importantly, our 1,1-aminoborylation could be applied across a wide range of unactivated olefins. Indeed, the method showed an excellent chemoselectivity pattern, and esters (**4o**−**q**), amides (**4v**,**w**) or acetals (**4ab**,**ac**,**ae**) could all be well-accommodated. While the presence of arenes or strongly coordinating groups in the vicinity might compromise the 1,1-site selectivity via translocation of the nickel catalyst throughout the side chain,[3] this was not the case; under the limits of detection, no sp^3 C−N bond formation was observed adjacent to an arene (**4r**−**t**) or an amide (**4v**,**w**) via chain walking at remote sp^3 C−H sites.[37] Equally interesting was the observation that our method tolerated the presence of nitrogen-containing heterocycles (**4y**−**aa**) and advanced synthetic intermediates (**4ae**−**ah**), thus leaving ample room for diversification.[38] Although one might argue that low yields are generally achieved in our catalytic 1,1-aminoborylation, these results should be interpreted against the challenge that is addressed; indeed, a close look into the literature data reveals that the majority of modern synthetic routes aimed at preparing 1,1-aminoboranes requires the inclusion of nonparticularly basic, yet more coordinating, nitrogen-containing amide backbones.[20,23,39,40] In contrast, the preparation of 1,1-aminoboranes possessing a rather basic amine function still remains a challenging synthetic endeavor. Therefore, our method might represent a new entry point for accessing elusive amino acid isosteres that might find application in medicinal chemistry settings.

Encouraged by the results compiled in Scheme 3, we focused our attention on exploring the synthetic applicability of our Ni-catalyzed 1,1-aminoborylation of unactivated olefins. As shown in Scheme 4, simple exposure of **4a** to hexamethyldisiloxane (HMDSO) gave access to **5a** in quantitative yield.[41] Subsequently, we turned our attention to the venerable Matteson homologation as a vehicle to generate β-aminoboronic esters from the corresponding α-substituted congeners. While this reaction proved particularly recalcitrant under numerous reaction conditions, a cocktail consisting of CH_2I_2, $ZnCl_2$, and *n*-BuLi gave access to the targeted homologated product.[42] Although the fragility of the latter defied all our attempts at experimental characterization due to the instability of the resulting alkyl boron fragment in the presence of a basic amino function at the vicinity, oxidative treatment with $NaBO_3$

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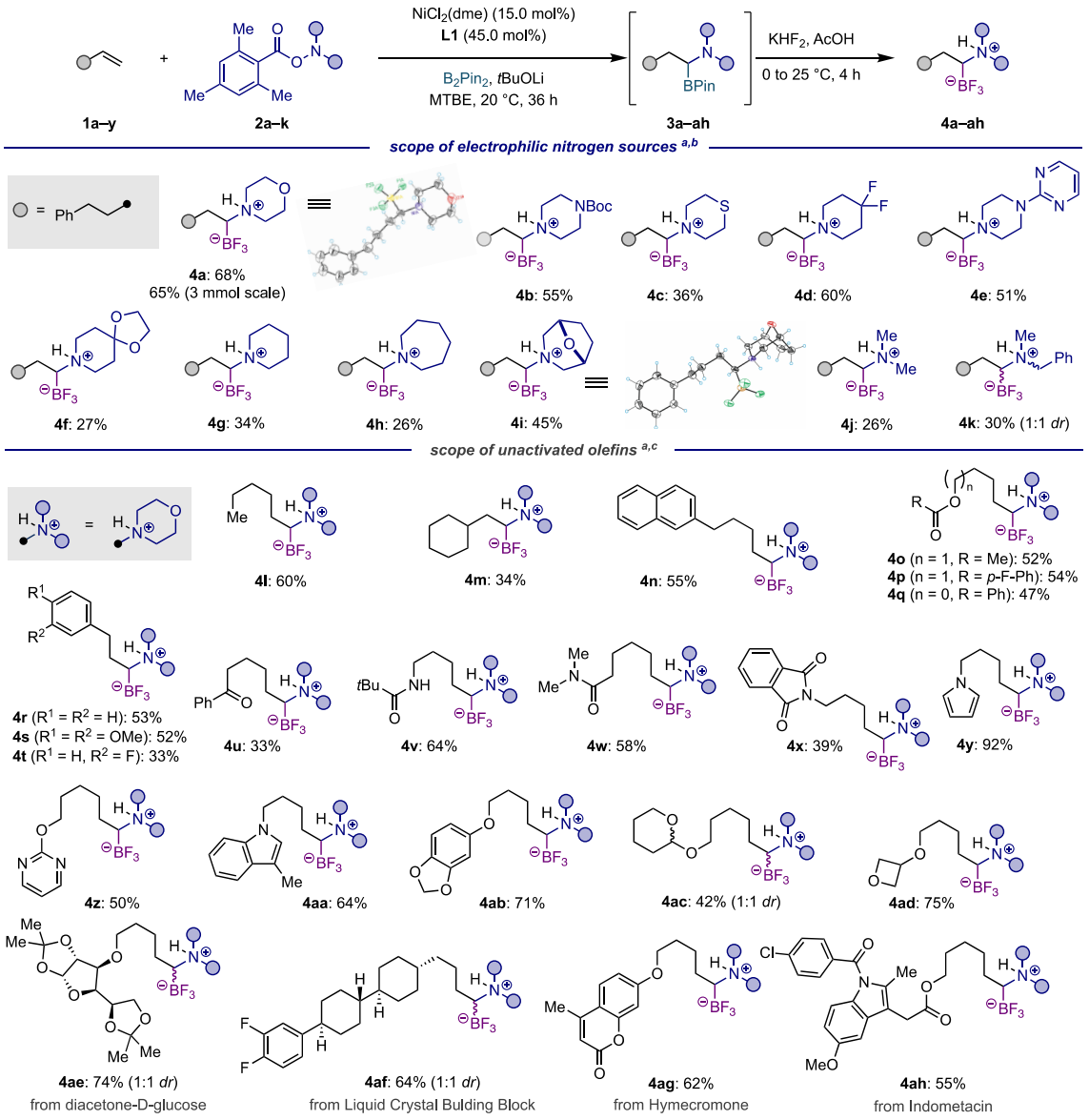
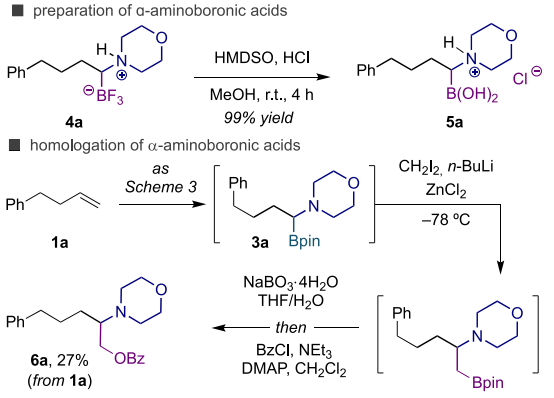
Scheme 3. Nickel-Catalyzed 1,1-Aminoborylation of Unactivated Primary Alkenes



[a]As for Table 1 (entry 1), then add KHF_2 (20 equiv) in AcOH for 4 h. Isolated yields, average of two different independent runs. [b]Using **1a** (0.2 mmol). [c]Using **2a** (2.5 equiv).

Scheme 4. Synthetic Applicability



followed by protection of the primary alcohol delivered **6a** in 27% yield over four synthetic steps.[28]

In summary, we have reported a catalytic 1,1-difunctionalization of terminal olefins to generate α-aminotrifluoroboronic salts. This reaction offers the possibility to utilize simple olefin feedstocks to rapidly and reliably generate bioisosteres of amino acids, thus complementing existing techniques for their preparation. Further investigations on the diversification of the obtained zwitterionic species are ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c00888.

Crystallographic data for **4a** (CCDC-2243931) (CIF)

Crystallographic data for **4i** (CCDC-2243932) (CIF)

Experimental procedures and spectral and crystallographic data (PDF)

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Author Contributions

L.T. and R.R.A.F. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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ACS Catal. 2023, 13, 5538−5543

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