**Low-Valent Tungsten Catalysis Enables Site-Selective Isomerization—Hydroboration of Unactivated Alkenes**

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**Supporting Information Placeholder**

**ABSTRACT:** A tungsten-catalyzed hydroboration of unactivated alkenes at distal C(sp^3^)–H bonds aided by native directing groups is described herein. The method is characterized by its simplicity, exquisite regio- and chemoselectivity and wide substrate scope, offering a complementary site-selectivity pattern to other metal-catalyzed borylation reactions and chain-walking protocols.

Chain-walking has emerged as a powerful strategy for forging C–C bonds at remote C(sp^3^) sites by controlled migration of the metal catalyst through a hydrocarbon side chain. At present, these protocols can promote functionalization at either the terminal position of the alkyl chain or adjacent to a stabilizing group (Scheme 1a, *paths a & b*). Despite recent advances, several challenges remain to be addressed. Among them, expanding the scope of chain-walking reactions beyond C–C bond-formation and achieving tunable selectivity to target previously inaccessible C(sp^3^)–H sites would be worthwhile endeavors for chemical innovation.

**Scheme 1. Olefin Functionalization via Chain-Walking.**

- **a** catalytic chain-walking reactions with unactivated alkenes
  - [G] = aryI, BX₃, C(=O)R
  - α-selectivity
  - linear selectivity
- **b** this work: control chain-walking site-selectivity with native DG
  - DG = directing group
  - chelation-controlled
  - β-selective

Elegant work by Chirik and others has shown the ability of Co catalysts to trigger chain-walking borylation of unactivated alkenes for forging C(sp^3^)–B bonds at terminal primary sites or α- to arenes or alkyl boronates. Although Koh recently leveraged the stabilizing features of π-benzyl intermediates (*path b*, [G] = aryl) to promote a homobenzylic protoborylation, the means to enable C–B bond-formation through alkylmetal stabilization at less-activated sp^3^ sites via chain-walking still remains elusive. Based on recent findings by our group, we wondered whether we could enable a W-catalyzed C(sp^3^)–B bond-formation controlled by native directing groups at C(sp^3^)–H sites that are beyond reach in conventional chain-walking events (Scheme 1b).

**Table 1. Optimization of the Reaction Conditions.**

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from standard conditions</th>
<th>2a (%)</th>
<th>2a (r.r.)*d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>93 (91)(c)</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>2</td>
<td>W(CO)₅ or W(n₅-mes)(CO)₅ (5 mol%)</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>PCy₃ (5 mol%)</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>IPr•HCl and KOH·Bu (5 mol%)</td>
<td>&lt;5</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>HBpin (2 equiv)</td>
<td>46</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>6</td>
<td>2-MeTHF as solvent</td>
<td>62</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>7</td>
<td>1,4-dioxane as solvent</td>
<td>65</td>
<td>40:1</td>
</tr>
<tr>
<td>8</td>
<td>Et₂O as solvent</td>
<td>68</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>9</td>
<td>PhMe as solvent</td>
<td>25</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>10</td>
<td>THF (0.10 M)</td>
<td>62</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>11</td>
<td>450-Watt UV lamp at rt</td>
<td>5 (4:2)</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

*a 1a (0.20 mmol), W(MeCN)₅(CO)₅ (5 mol%), HBpin (0.80 mmol), THF (0.67 M), 40 °C, 20 h. b Yields determined by GC using decane as internal standard. c Isolated yield. d Regioisomeric ratio (r.r.) calculated by LCMS or GCMS between β and γ/δ.

Specifically, we believed that the ability of low-valent W catalysts to adopt multiple coordination geometries combined with their high Lewis acidity when compared to later transition metals, would be particularly critical for success. We anticipated that such a technology would not...
only expand the boundaries of chain-walking reactions by offering a complementary site-selectivity profile, but also stimulate the adoption of low-valent W catalysts in alkene functionalization.\(^7\) As part of our interest in alkene functionalization and chain-walking reactions,\(^8\) we describe the successful implementation of this goal, culminating in the development of the first W-catalyzed hydroboration of alkenes.\(^9\)

We began our work by evaluating the catalytic borylation of 1a (Table 1). After some experimentation,\(^1\) a protocol employing commercially available W(MeCN)\(_3\)(CO)\(_3\) and HBpin provided the best results, delivering 2a as a single \(\beta\)-regioisomer in 91% isolated yield. As expected, the nature of the catalyst and lability of the ligands had a non-negligible impact on reactivity. Indeed, only traces of 2a were observed when changing the three weakly coordi-

![Table 2. Site-Selective \(sp^1\) C–H Borylation of Unactivated Alkenes Aided by Native Directing Groups.\(^a\)](image)

<table>
<thead>
<tr>
<th>R(^2)</th>
<th>R(^3)</th>
<th>R(^4)</th>
<th>Bpin</th>
<th>HBpin</th>
<th>N-aryl amides</th>
<th>tertiary amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a–x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>O</td>
<td>BH</td>
<td>[X-ray]</td>
<td>2a</td>
<td>single regioisomer</td>
</tr>
<tr>
<td>2a</td>
<td>91% (X = H)</td>
<td>2d</td>
<td>81% (X = Br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>87% (X = F)</td>
<td>2e</td>
<td>85% (X = OMe)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>85% (X = Cl)</td>
<td>2f</td>
<td>65% (X = CO(_2)Et)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2g</td>
<td>75%(^b)</td>
<td>2h</td>
<td>65%(^c)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>(\alpha)-branched amides</th>
<th>N-alkyl amides</th>
<th>1,2-dienes</th>
<th>carboxylic-acid-directed</th>
<th>internal alkene</th>
</tr>
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<tbody>
<tr>
<td>2m</td>
<td>93%, R = Me</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2n</td>
<td>81%, R = Bn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2o</td>
<td>76%, R = Ph</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2p</td>
<td>57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2q</td>
<td>91% (R = t-Bu)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2r</td>
<td>51% (R = n-Bu)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2s</td>
<td>82% (R = Bn)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2u</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2v</td>
<td>52%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2w</td>
<td>81%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2x</td>
<td>55%(^b)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions as in Table 1, entry 1; Isolated yields. \(^b\) Isolated as the aliphatic alcohol following treatment with H\(_2\)O\(_2\), aq. NaOH. \(^c\) HBpin (5 equiv). All depicted X-ray structures have hydrogen atoms omitted for clarity.

Next, we turned our attention to exploring the generality of our protocol. As shown in Table 2, a variety of \(N\)-aryl secondary amides could be employed as substrates, and the \(C(sp^2)\)–H borylation could be conducted in the presence of aryl fluorides, chlorides, bromides, and iodides (2b–d, 2g). Importantly, no borylation or reduction at the C(\(sp^2\))–halide bond was detected in the crude reaction mixtures. This finding is particularly important, showing a complementary selectivity pattern to that observed for other low-valent transition metals that would otherwise result in functionalization at the C(\(sp^2\)) site. Likewise, functional groups prone to reduction, such as esters (2f,
or the presence of an arylboronate (2h) did not interfere with the efficacy of the sp² β-borylation event. The reaction could be extended to tertiary amides (2i–l) and N-alkyl secondary amides (2q–t). The former observation is particularly interesting, as it does not only expand the range of amides that can be utilized, but also suggests that binding of the substrate to the tungsten catalyst does not require the presence of a (deprotonatable) N–H bond. In addition, it is worth noting the reaction en route to 2i could be easily scaled up to 5 mmol scale without an erosion in yield. The preparation of 2j–p illustrates that substrates containing N-heterocycles—particularly prevalent motifs in natural products and advanced synthetic intermediates—can easily be accessed under our protocol. The chemoselectivity of our reaction is further illustrated by the successful preparation of 2u and 2v possessing additional alkynes on the side chain. Under the limits of detection, diene substrates (2u, 2v) underwent monofunctionalization without additional borylation or competitive isomerization occurring at the second alkene. As shown for 2w, the reaction could be similarly applied to internal alkynes, albeit in moderate yields. Although esters (2v) or ketones were not competent as directing groups, a free carboxylic acid delivered 2w as single regioisomer. Particularly noteworthy is the ability to easily access α-branched products 2m–p in good yields and excellent diastereoselectivities (>20:1).

**Scheme 2. Preservation of an α-Stereocenter.**

The anti-stereochemistry of substrates containing an α-substituent was unequivocally confirmed by X-ray crystallography of the aliphatic alcohol derived from the stereoretentive oxidation of 2n. More importantly, 2m could be obtained in high yield as a single enantiomer and diastereoisomer when starting from enantiopure 1m (>99% ee) (Scheme 2). This finding has important mechanistic implications. Specifically, it suggests that alkene isomerization stops at the β,γ-position, as formation of a conjugated α,β-unsaturated amide would ablate the α-stereocenter in 2m. This observation was further corroborated by the successful preparation of α,α-gem-dimethyl substituted 2p in good yield and as single regioisomer despite the proximal steric hindrance.

**Scheme 3. Expansion of the Coupling Partner Scope.**

- **utilization of żγ-unsaturated secondary amides**
  - W(MeCN)₃(CO)₂ (10 mol%) + PCy₃ (15 mol%) + CuF₂ (50 mol%) + MeTHF, 100 ºC, 20 h

- **sp² β–C–H silylation of secondary amides**
  - W(MeCN)₃(CO)₂ (10 mol%) + CuF₂ (50 mol%) + Et₂SiBpin, CsF (1.5 equiv) + MeTHF, 100 ºC, 20 h

- **sp² α–C–H germylation of secondary amides**
  - W(MeCN)₃(CO)₂ (5 mol%) + HGeEt₃ (2.0 equiv) + THF, 40 ºC, 20 h

While aliphatic amides possessing a pendant alken at the δ,ε-position resulted in trace amounts of the targeted sp² β-borylation under the optimized reaction conditions, a protocol based on CuF₂ and Bpin₂ delivered 2x in moderate yield, but as a single regioisomer (Scheme 3). In line with these results, we wondered whether our protocol could be extended to other C–heteroatom bond-forming reactions. Gratifyingly, this was indeed the case, and an analogous silylation event could be conducted under otherwise identical reaction conditions (3a). Intriguingly, a hydrogermylation could also be implemented in an unoptimized 27% yield. This reaction gave rise to 3b with an unexpected α-selectivity pattern, the identity of which was unambiguously determined by X-ray diffraction. While the origin of such regioselectivity remains unclear, it suggests that boranes may react differently with low-valent tungsten catalyst when compared to other main group metal hydrides, thus setting the basis for enabling future catalytic endeavours.

**Scheme 4. Expansion of the Coupling Partner Scope.**

- accessing quaternary organoboranes
  - W(MeCN)₃(CO)₂ (7.5 mol%) + HBpin (8 equiv) + THF, 100 ºC, 20 h

- product diversification via organotrifluoroborates
  - 3j + KF₂B

Although β-branched γ,δ-unsaturated secondary amides showed poor yields under our optimized reaction conditions, an increase in the amount of HBpin at elevated temperatures enabled the formation of quaternary organoboranes (Scheme 4). Interestingly, a close inspection of the
NMR data revealed *in situ* reduction of the carbonyl group under the reaction conditions, with 3e being produced in modest 40% yield. Notably, 2j can readily be converted to 3d by reaction with KHF₂, providing an additional handle for further manipulation via cross-coupling reactions. 3d could then be further derivatized via 1,2-boronoate rearrangement, affording 3e in 96% yield without competitive addition of the Grignard reagent to the carbonyl.

**Scheme 5. Deuteron Labelling Studies.**

Next, we turned our attention to studying the mechanism of our C(sp³) β-borylation. *A priori*, one might expect that both 1,2- and 1,3-hydride shift might come into play for the initial alkene isomerization. To this end, we conducted the borylation of 1a and 1i with DBpin. Deuterium incorporation at the γ-position was anticipated for a pathway consisting of 1,3-hydride shift; on the contrary, labelling at the terminal δ sp³ site would indicate a mechanism via 1,2-hydride shift. As shown in Scheme 5, exclusive deuterium incorporation into the γ-position was observed in 2a-d and 2i-d, thus strongly supporting the notion that alkene isomerization proceeds via 1,3-hydride shift. Conducting the reaction without HBpin corroborated previous findings that showed the ability of W(0) to promote isomerization via 1,3-H shift without external hydride sources. In addition, the lack of deuterium incorporation at the β-C(sp³) site argues against a 1,1-hydroboration of a Fischer-type W-carbene. Although other scenarios might be conceivable, we currently propose a pathway consisting of coordination of W(0) to both carbonyl group and the alkene (1) followed by allylic sp³ C–H oxidative addition (II). Re-insertion of the metal hydride to the π-allyl moiety would formally result in an olefin isomerization, thus setting the stage for an oxidative addition of H–Bpin to W(0) intermediate III (Scheme 6). Subsequently, exo-hydride insertion to the β,γ-alkene might form IV which ultimately undergoes C–B reductive elimination to afford the final sp³ β-borylation while regenerating the propagating W(0) catalyst. From intermediate III, the isomerized alkene 1ab is able to reversibly dissociate, as free 1ab can be detected by *in situ* ¹H NMR.

**Scheme 6. Proposed Mechanism.**

In conclusion, we have developed a protocol that illustrates the unique properties of the W(0)/W(II) redox cycle to address site-selectivity issues that have remained challenging for other transition metals in the chain-walking arena. Our sp³ β-borylation is distinguished by its simplicity, mild conditions, and broad scope. This includes challenging functional group combinations, while exhibiting an exquisite chemo-, regio- and diastereoselectivity profile, thus offering a complementary technique in our synthetic repertoire for forging sp³ C–B linkages.

**ASSOCIATED CONTENT**

**Supporting Information.**

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectral and crystallographic data (PDF)

Crystallographic data for 2b (.cif)
Crystallographic data for 2j (.cif)
Crystallographic data for 2u (.cif)
Crystallographic data for 3b (.cif)

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**Author Contributions**

§T.C. Jankins and R. Martin-Montero contributed equally to this work.

**Note**

The authors declare no competing financial interest.

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REFERENCES


11. To the best of our knowledge, W-catalyzed hydrofunctionalization has not been reported to date. For a recent perspective, see: Bage, A.D.; Nicholson, K.; Hunt, T.A.; Langer, T.; Thomas, S.P. The Hidden Role of Boranes and Borohydrides in Hydrofunctionalization. ACS Catal. 2020, 10, 13479-13486.

12. For details, see Supporting Information.

13. The remaining mass balance corresponds to recovered starting material and a mixture of internal alkenes and reduced byproducts. See Supporting Information for details.


15. Tentatively we believe that the CuF₂/B₃P₂ system may proceed through a mechanistically distinct pathway involving 1,4-protoproborylation of an in situ generated α,β-unsaturated amide.


19. Computational work has shown that H–X (X = Si, Sn, Ge) oxidative addition to W(0) is slightly endergonic but kinetically accessible (ref. 7a), which is consistent with our inability to detect W–hydrides by \( ^1 \)H NMR spectroscopy either under our optimized reaction conditions or by reacting W(MeCN)\(_3\)(CO)\(_3\) with large excess of HBpin.