

# Synthesis of $\alpha$ -Borylated Ketones by Regioselective Wacker Oxidation of Alkenylboronates

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**Supporting Information** 

**ABSTRACT:** As part of a program aimed at metal-catalyzed oxidative transformations of molecules with carbon—metalloid bonds, the synthesis of  $\alpha$ -borylated ketones is reported via regioselective TBHP-mediated Wacker-type oxidation of *N*-methyliminodiacetic acid (MIDA)-protected alkenylboronates. The observed regioselectivity correlates with the hemilabile nature of the B—N dative bond in the MIDA boronate functional group, which allows boron to guide selectivity through a neighboring group effect.



The reactivity of organoboron reagents is defined by the Lewis acidity of boron, which can attenuate the nucleophilicity of the C–B bond. Boronic esters are used as key intermediates in many fundamental synthetic processes where the nucleophilic nature of the C–B bond enables formation of various C–C, C–O, C–S, and C–N linkages. The N-methyliminodiacetic acid (MIDA) protecting group has seen widespread application as it masks boron's Lewis acidity through a dative B–N bond, forming a stabilized tetracoordinate boronate complex that tolerates a range of reaction conditions.<sup>1–14</sup>

Given our long-standing interest in the chemistry of amphoteric  $\alpha$ -boryl aldehydes, we sought to develop a route to MIDA-protected  $\alpha$ -borylated ketones. We opted to pursue oxidation of borylated alkenes. The Wacker-Tsuji oxidation is an established protocol for the oxidation of terminal alkenes to methyl ketones. Recent advances in this area have extended this oxidative catalysis to internal alkenes, although regioselectivity is often problematic.<sup>15–19</sup> We therefore sought to explore the effects of the MIDA boronate substitution in this context. A recent study from our group determined that the hemilability of the B-N bond modulates the reactivity of the boronate group in boron transfer reactions.<sup>20</sup> We were motivated to explore the role of the MIDA ligand in influencing regioselectivity, due to either the neighboring group effect as a result of the hemilabile nature of the B-N bond or the electronic direction as a result of the nucleophilic C–B bond.<sup>21,22</sup> Herein, we report the role of MIDA boronates in guiding the highly regioselective oxidation of borylated alkenes to access  $\alpha$ -borylated ketones.

To the best of our knowledge, there have been no reports wherein a metal-catalyzed oxidation has been performed on a boron-containing alkene, delivering an oxygenated end point with preservation of the C–B bond. We initially attempted the synthesis of desired  $\alpha$ -borylated ketones using PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> catalysts and molecular oxygen or TBHP as the oxidant (Table 1, entries 1–4). However, no oxidation of the alkenyl MIDA boronates was observed. We then explored TBHP-mediated Wacker-type oxidation using the Pd(Quinox)- $Cl_2$  catalyst reported by Sigman and co-workers, given its previous success with internal systems.<sup>23</sup> We were pleased to observe that, although initial conversion was low, oxidation of 1a (Table 1, entry 5) proceeded with high regioselectivity and resulted in exclusive oxidation at the benzylic position to give 2a. The remaining mass balance was unreacted starting material.

The same conditions were applied to pinacol boronic ester **1v** and trifluoroboronate **1w**; however, both compounds were incompatible with the reaction conditions. Decomposition was observed in both cases after mixing with the peroxide, which suggested that the MIDA derivative behaved as an outlier.

To rule out steric direction in the experimentally observed regioselectivity, the reaction was repeated with R groups possessing A values similar to those of the MIDA boronate, which was computed to be 2.40 kcal/mol (see Supporting Information (SI)). (E)-3-Methyl-1-phenyl-1-butene and (E)-1-*tert*-butyl-2-phenylethene were subjected to the aforementioned conditions. In the case of (E)-1-*tert*-butyl-2-phenylethene, only starting material was recovered after prolonged reaction times, with no trace of the ketone products. Oxidation of (E)-3-methyl-1-phenyl-1-butene resulted in an approximate 10:1 mixture of regioisomeric ketone products, with the major isomer identified as 3-methyl-1-phenylbutan-2-one.

The generality of the reaction was probed through a substrate scope, the results of which are displayed in Scheme 1. Alkenes substituted with aliphatic R groups (1d-f,n,p) and aromatic rings bearing electron-donating groups (1g-i) were converted to the corresponding ketones with good conversion and high selectivity. Oxidation of aliphatic alkenes was achieved at a lower

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Tab.	le 1	. Oj	ptimiza	ation	of	React	tion	Cond	itions
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[B] catalyst, oxidant solvent time, temp 2a												
entry	catalyst		additive	solvent	temperature (°C)	yield (%) <sup>b</sup>						
1	$Pd(OAc)_2$ (5 mol %)	$O_2$ (1 atm)	TFA	DMF/H <sub>2</sub> O 7:1	50	0						
2	$Pd(OAc)_2$ (5 mol %)	$O_2$ (1 atm)	CuCl <sub>2</sub>	DMF/H <sub>2</sub> O 7:1	50	0						
3	$PdCl_2$ (5 mol %)	$O_2$ (1 atm)	CuCl <sub>2</sub>	DMF/H <sub>2</sub> O 7:1	50	0						
4	$Pd(OAc)_2$ (5 mol %)	TBHP		DMF	rt	0						
5	Pd(Quinox)Cl <sub>2</sub> (5 mol %)	TBHP	AgSbF <sub>6</sub> (12.5 mol %)	$CH_2Cl_2$	rt	20 (11)						
6	$Pd(Quinox)Cl_2 (10 mol \%)$	TBHP	AgSbF <sub>6</sub> (15 mol %)	$CH_2Cl_2$	rt	65 (58)						
7	Pd(Quinox)Cl <sub>2</sub> (15 mol %)	TBHP	$AgSbF_6$ (20 mol %)	$CH_2Cl_2$	rt	75 (70)						
1		1 - (	. 16	1/	$h_{n} \rightarrow h_{n}$	11 17737379						

<sup>*a*</sup>Reactions were carried out using 0.10 mmol 1a (0.1 M) and monitored for 18 h. TBHP (70% aq) was used (12 equiv). <sup>*b*</sup>Determined by <sup>1</sup>H NMR analysis (isolated yields are given in parentheses).

Scheme 1. Substrate Scope for the Synthesis of  $\alpha$ -Borylated Ketones



<sup>*a*</sup>10 mol % of Pd(Quinox)Cl<sub>2</sub> and 12 mol % of AgSbF<sub>6</sub> were used. <sup>*b*</sup>NMR yield. <sup>*c*</sup>Decomposition observed.

10 mol % catalyst loading, likely due to decreased steric congestion in the catalyst's coordination sphere. For more hindered alkenes, a decrease in conversion, though not in selectivity, was observed. Meta-substituted phenyl rings (1h,k) showed a decrease in conversion relative to that of their para analogues. Ortho substitution (1i,m) was not tolerated. For alkenes bearing electron-deficient aromatic rings (1j–1), a decrease in conversion was also observed,<sup>24</sup> though the reaction still proceeded with high regioselectivity. For alkenes 1c,i,m,o,r,s,u, the oxidation did not proceed at all, most likely due to a high degree of steric congestion around the alkene.

Interestingly, when vinyl MIDA boronate (Scheme 1, 1q) was subjected to the TBHP-mediated Wacker-type conditions, the oxidation resulted in formation of the  $\alpha$ -boryl aldehyde (anti-Markovnikov product) with no trace of the acyl boronate (Markovnikov product). The Pd(Quinox)Cl<sub>2</sub> reportedly operates under catalyst control, yielding single regioisomeric products in electronically biased alkenes and methyl ketone products in terminal alkenes following Markovnikov's rule.<sup>23–28</sup> No aldehyde was observed when 3,3-dimethylbut-1-ene was subjected to the same reaction conditions. Additionally, oxidation of allyl MIDA boronate (Scheme 1, 1t) resulted in the Markovnikov ketone product (Scheme 1, 2t). This reversal in regioselectivity as a result of direct boronate substitution was somewhat unexpected in light of previous studies<sup>23,25,26,29</sup> but supported our initial hypothesis.

The selectivity of the TBHP-mediated Wacker oxidation of alkenyl MIDA boronates was investigated by DFT analysis at the B3LYP/Lan2DZ (IEFPCM = dichloromethane) level of theory using Gaussian 09.<sup>30</sup> Emerging from these calculations were transition states  $TS_{(Ph)}$ -I and  $TS_{(Ph)}$ -II, which correspond to the lowest-energy  $\alpha$ - and  $\beta$ -carbon addition modes of the peroxide to the coordinated alkene 1a (see Figure 1 and SI). Transition state structures in which the MIDA ligand was coordinated to the palladium center through a Pd–O interaction could not be located. The relative free energy barriers of  $TS_{(Ph)}$ -I and  $TS_{(Ph)}$ -I was favorable by 1.9 kcal/mol, respectively.  $TS_{(Ph)}$ -I was favorable by 1.9 kcal/mol relative to starting reagents and the Pd(Quinox) catalyst, which is consistent with the observed experimental  $\beta$ -selectivity.

Contributing to this energetic difference was a steric contact between the alkene and *tert*-butyl group of TBHP in TS<sub>(Ph)</sub>-II as seen by a H…H distance of 2.31 Å (Figure 1) and noncovalent interaction plots (see SI). In addition to sterics, computational analysis discerned underlying electronic factors contributing to  $\alpha$ -versus  $\beta$ -selectivity. NBO analysis revealed stabilizing donor acceptor orbital interactions amounting to 16.7 kcal/mol involving electron donation from a d-orbital of Pd and the C-Pd  $\sigma$  bond to a p-orbital of boron in TS<sub>(Ph)</sub>-I (Figure 2). Also present was a smaller in magnitude donor–acceptor  $\sigma_{\rm (C-B)} \rightarrow$  $d_{(Pd)}^*$  interaction, which provided 2.7 kcal/mol of stabilization. Similar donor-acceptor orbital interactions were not present in  $TS_{(Ph)}$ -II. Nucleophilic attack at the  $\beta$ -carbon of  $TS_{(Ph)}$ -I was also accompanied by electrons from the double bond being shuttled toward the MIDA boronate, resulting in a buildup of electron density at the  $\alpha$ -carbon. Consistent with this were the computed NBO charges of -0.778e and -0.613e at the  $\alpha$ carbon of  $TS_{(Ph)}$ -I and its precomplex ( $PC_{(Ph)}$ -I), respectively. From these results, it is apparent that the boron of MIDA contributes to the preorganization of reaction components through a stereoelectronic neighboring group effect, yielding single regioisomeric products. To eliminate the possibility that regioselectivity is attained as a result of benzylic attack of the nucleophile, calculations were carried out using vinyl MIDA boronate, and similar results were obtained (see SI).



**Figure 1.** Lowest-energy transition states for the regioselective attack of the TBHP nucleophile at the  $\alpha$ - and  $\beta$ -carbon.

Finally, to rule out a reaction pathway in which  $\alpha$ - versus  $\beta$ -regioselective addition is directed through complete decoordination of the MIDA ligand, **TS**<sub>(Ph,O)</sub>-**I** was computed to be the preferred mode of addition (Figure 3). Surprisingly, **TS**<sub>(Ph,O)</sub>-**I** 



Figure 3.  $TS_{(Ph,O)}$ -I involving regioselective direction as a result of the hemilabile nature of the MIDA B–N dative bond.

was 7.4 kcal/mol lower in energy than  $TS_{(Ph)}$ -I. The most striking feature of this structure is a cooperative H-bond bridging the TBHP, hydroxyl bound boron, and protonated N atom. The competitiveness of this addition mode, nevertheless, is unlikely given that the computed barrier for water-promoted MIDA opening of borylated alkene 1a was ~22.6 kcal/mol. This value is also consistent with the ~26.1 kcal/mol reported barrier for water-promoted MIDA opening in the absence of a proximal intramolecular donor group.<sup>31</sup>

In summary, we report a highly selective route to MIDAprotected  $\alpha$ -borylated ketones from borylated alkenes. The palladium-catalyzed TBHP-mediated Wacker oxidation of MIDA alkenylboronates is thought to proceed through the well-defined oxypalladation mechanism, previously established by Sigman and co-workers.<sup>24</sup> Computational analysis indicates



Figure 2. NBO analysis showing stabilizing donor-acceptor orbital interactions in  $TS_{(Ph)}$ -I between boron and palladium, resulting in regioselective attack of the peroxide at the  $\beta$ -carbon.

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that the high degree of regioselectivity observed in the oxidation of MIDA alkenylboronates is the result of an electronic directing effect derived from the hemilabile nature of the MIDA B–N dative bond that is intimately related to the acceptor capacity of the boron atom. Ultimately, this directing group effect guides selectivity through the donation of electron density to boron. This method was applied to a number of borylated alkenes and provides a mild and facile route to  $\alpha$ -boryl ketones. Given the demonstrated tolerance of the C–B bond, we suspect that a number of other metal-catalyzed oxidations can be performed on boron-containing alkenes. We anticipate that the MIDA boronate will have a similar directing effect in other settings.

## ASSOCIATED CONTENT

### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02234.

Experimental procedures and characterization of products, computational results (PDF)

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#### Notes

The authors declare no competing financial interest.

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