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Oxyboration with and without a Catalyst: Borylated Isoxazoles via B−O σ-Bond Addition

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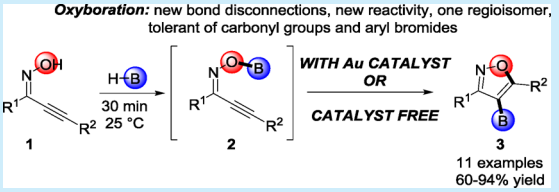
Supporting Information

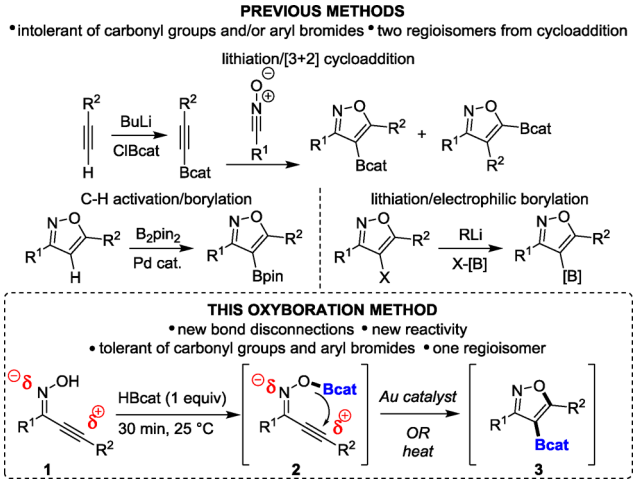
ABSTRACT: Herein we report an oxyboration reaction with activated substrates that employs B−O σ bond additions to C−C π bonds to form borylated isoxazoles, which are potential building blocks for drug discovery. Although this reaction can be effectively catalyzed by gold, it is the first example of uncatalyzed oxyboration of C−C π bonds by B−O σ bonds—and only the second example that is catalyzed. This oxyboration reaction is tolerant of groups incompatible with alternative lithiation/borylation and palladium-catalyzed C−H activation/borylation technologies for the synthesis of borylated isoxazoles.



Isoxazoles[1] exhibit a wide variety of biological activities, including analgesic,[2] antibiotic,[3] antidepressant,[4] and anticancer[5] activities. Consequently, borylated isoxazoles are valuable bench-stable building blocks for drug discovery.[6] Oxyboration reactions that proceed through the addition of B−O σ bonds to C−C π bonds would be an attractive route to these and other building blocks by transforming easily formed B−O σ bonds into more difficult to form B−C σ bonds. Yet the addition of B−O σ bonds to C−C multiple bonds had remained elusive for 65 years[7] until our first report in 2014.[8a] We herein report catalyzed and uncatalyzed oxyboration routes to borylated isoxazoles. This is the first report of an *uncatalyzed* oxyboration of C−C π bonds with B−O σ bonds. This oxyboration method is tolerant of a wide variety of functional groups and produces exclusively the 4-borylated regioisomer, which establishes the generality of oxyboration strategies[8] to generate borylated heterocycles for drug discovery. Specifically, compounds of this type may currently be accessed through the [3 + 2] cycloaddition reaction of nitrile oxides and alkynylboronates as shown in Scheme 1. However, this method can produce two regioisomers, and the alkynylboronate synthesis involves a lithiation step.[9] Alternatively, the Pd(0)-catalyzed Miyaura borylation[10] and lithiation/electrophilic borylation[11] have been used for the synthesis of borylated heterocycles, but as with lithiation/cycloaddition, aryl bromides and electrophilic functional groups are reactive under these conditions.

Inspired by previous reports from Perumal[12] and Ueda,[13] who demonstrated analogous Au-catalyzed rearrangements of oximes to form 4-substituted isoxazoles without boron, we considered that analogous routes to borylated isoxazoles may be assessable through oxyboration. We hypothesized that this gold-catalyzed oxyboration reaction could proceed through carbophilic Lewis acid activation of the C−C π bond, a mechanistically distinct route to B−Element addition reactions.[8] The oxyboration reaction developed here is an operationally simple one-pot procedure from oximes and requires no isolation of reaction intermediates (Scheme 1).

Scheme 1. Comparison of Previous Methods and New Oxyboration Method for the Synthesis of 4-Borylated Isoxazoles



The reaction was developed through optimization studies with model substrate **1a**. We first investigated a series of Au catalysts through varying the oxidation state and counterion (Table 1, entries 1−5). The catalyst IPrAuTFA proved an optimal balance of counterion coordinating ability.[14] The catalyst IPrAuOAc, with the more strongly coordinating acetate ion,[14b] did not lead to any detectable product formation. A control reaction with catalytic NaTFA (entry 6) in place of IPrAuTFA showed no product, confirming a key role for the gold. Control experiments with IPrAuCl (no product formation) and separately with AgTFA (30% ^{1}H NMR yield of product vs 90% under identical conditions but with IPrAuTFA) confirmed the catalytic activity was optimal with

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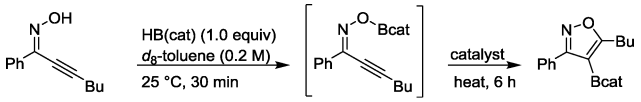
Table 1. Selected Data from Optimization Study[a]



1a **2a** **3a**

entry	catalyst	temp (°C)	cat. loading (% mol)	yield[b]
1	AuCl	50	2.5	0
2	$AuCl_3$	50	2.5	0
3	IPrAuOAc	50	2.5	0
4	IPrAuOTs	50	2.5	34
5	IPrAuTFA	50	2.5	90
6	NaTFA	50	2.5	0
7	None	50	0	0
8	IPrAuCl	50	2.5	0
9	AgTFA	50	2.5	48
10	IPrAuTFA	50	1.0	85[c]
11	IPrAuTFA	50	5.0	90
12	IPrAuTFA	50	10	92
13	IPrAuTFA	25	10	89[d]

[a]Reactions were carried out on a 0.10 mmol scale. [b]Yields were determined by the ERECTIC method using mesitylene as ^{1}H NMR external standard. [c]23 h. [d]22 h.

IPrAuTFA and not its synthetic precursors (entries 7–9). A survey of catalyst loading and reaction temperature (entries 10–13) determined the optimal loading to be 2.5 mol %, resulting in full conversion (90% ^{1}H NMR yield) after 6 h at 50 °C.

Interestingly, oxyboration of **1a** could be carried out under catalyst-free conditions, albeit with higher temperatures and longer reaction times. Specifically, heating **1a** to 110 °C for 17 h afforded **3a** in 58% ^{1}H NMR yield (Table 2). Similarly,

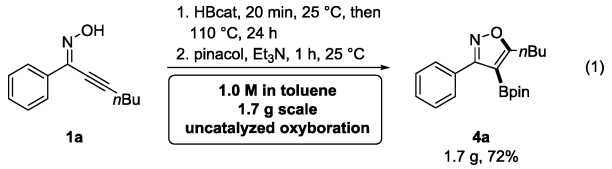
Table 2. Initial Reaction Development with and without Catalyst

	R^1/R^2	IPrAuTFA 6 h, 50 °C	uncat. 6 h, 50 °C	uncat. 17 h, 110 °C
1a	Ph/Bu	90%	<1%	58%
1c	4-BrC_6H_4/*n*-Bu	93%	4%	89%
1f	Ph/TMS	87%	<1%	<1%

cyclization of **1c** under catalyst-free conditions of 110 °C for 17 h produced **3c** in 89% ^{1}H NMR yield. We hypothesize that the Michael-acceptor/polar character of the starting materials enables this catalyst-free oxyboration through lowering the barrier of cyclization (Scheme 1); alternatively, the nucleophilic nitrogen lone pair[15] of the hydroxylimine may coordinate and activate the boron. Identification of this class of activated substrates thus provides access to catalyst-free reactivity that was not possible within our earlier reported oxyboration substrates.[8] In contrast to the reactivity exhibited by **1a** and **1c**, when silylated **1f** was used as the substrate for catalyst-free oxyboration, only B–O σ-bond formation was observed (boric ester **2f**), and no cyclized products were formed even after an extended time of heating at 110 °C. This lack of reactivity possibly derives from the steric hindrance and the electron-donating ability of the trimethylsilyl group[16] adjacent to the alkyne carbon, which may alter the polarization of the alkyne, rendering it less susceptible to nucleophilic attack. Because of its reduced temperatures, shorter reaction times, and action with the silylated substrate, the metal-catalyzed route was selected for further isolation.

This oxyboration method provided a new set of bond disconnections to access previously unreported isoxazole pinacol boronic esters **4a–4k** (except **4f**[9]), which are isolable by silica gel chromatography and are bench-stable building blocks for a variety of downstream reactions[6a,b] as shown in Scheme 2. The numbers in parentheses denote the ^{1}H NMR spectroscopy yield of catechol boronic ester **3** relative to an external standard. The numbers outside the parentheses in the first row denote the isolated yield of bench-stable pinacol boronic ester **4**.[17] The numbers outside the parentheses in the second row correspond to the reaction time of the uncatalyzed oxyboration when run at 110 °C. After completion of the catalytic reaction, PPh_3 was employed to quench the active catalyst IPrAuTFA by trapping it as the catalytically inactive $[IPrAuPPh_3]^+$.[18]

We herein compare the catalyzed reaction yields with those obtained through the uncatalyzed method for each substrate. To permit direct comparison, both reactions were performed at 0.2 M in substrate. The lengthy reaction times for the uncatalyzed reaction were reduced at higher concentration in substrate upon scale-up (eq 1). With the exception of silylated



1a **4a** 1.7 g, 72% (1)

1f, all substrates showed uncatalyzed reactivity at longer reaction times. Bulky substituents such as *tert*-butyl and trimethylsilyl, however, only produced very low ^{1}H NMR yield (24% for **3d** and <1% for **3f**), with the starting materials remaining. Thus, they required catalysis for synthetically useful product formation. The electron-poor *p*-CF_3 substrate and 3-furyl substrate required a rather lengthy 18–21 d to reach full conversion at 110 °C. In many cases, the cost benefit of obtaining the product under catalyst-free conditions may be desired in exchange for elevated temperatures and marginally longer reaction times, most notably with **4c**, **4e**, **4h**, **4i**, **4k**, reactions which achieved similar ^{1}H NMR yields to the catalyzed reactions in 20–65 h.

Interestingly, substrates that exhibited slow conversions under the catalyzed conditions for apparent electronic reasons (rather than steric reasons) such as **1i** and **1k** were the faster converting substrates under the uncatalyzed conditions; it may be that the electronics that favor π Lewis acid catalysis through gold–alkyne binding disfavor cyclization in the absence of a catalyst. This orthogonality in electronic and steric substrate reactivity highlights the complementarity provided by the catalyzed and uncatalyzed methods. Both the metal-catalyzed and the uncatalyzed oxyboration reactions are tolerant of functional groups that would otherwise be sensitive to alternative borylation methods. For example, aryl bromide **1c** smoothly undergoes oxyboration to produce borylated isoxazole **3c** (93% ^{1}H NMR yield, 65% isolated yield of **4c** with a catalyst; 91% ^{1}H NMR yield without a catalyst). This substrate would be sensitive to a lithiation/borylation sequence[11,19] because of competitive lithium/halogen exchange,[20] and to an alternative palladium-catalyzed borylation[10] because of competitive oxidative addition of the aryl–bromide

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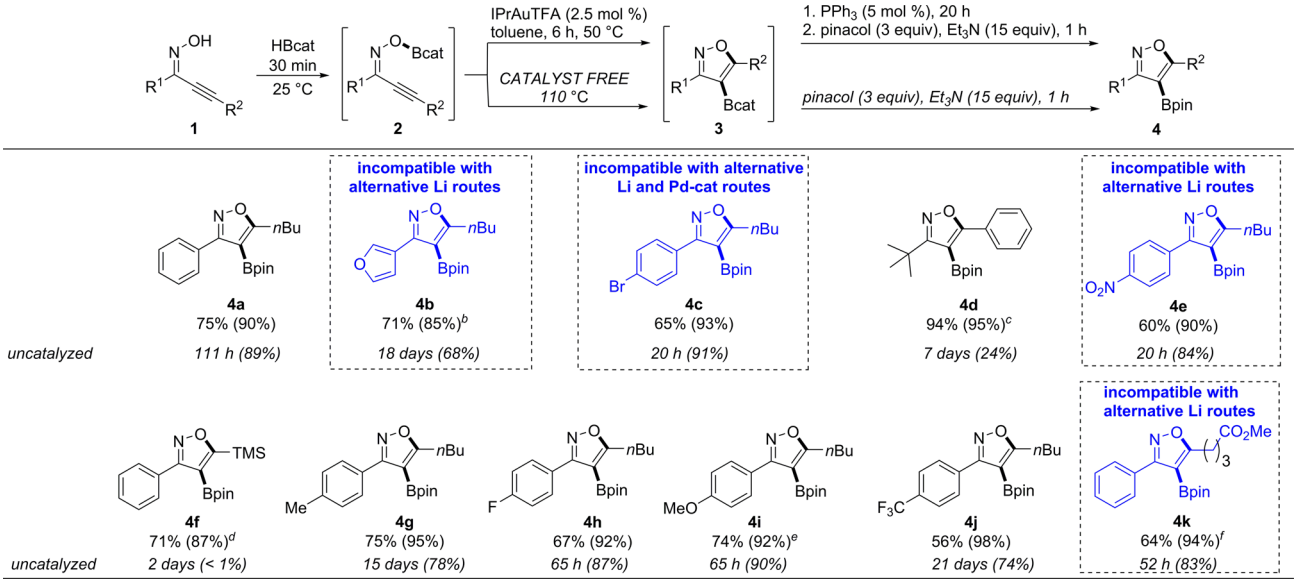
Scheme 2. Reaction Substrate Scope[a]



[a]Substrates shown in blue are incompatible with alternative routes. All substrates give exclusively 4-borylated regioisomer. Isolated yield of **4** (^{1}H NMR yield of **3**). *Uncatalyzed: Reaction time (^{1}H NMR yield of 3).* [b]50 °C, 24 h. [c]110 °C, 4 h. [d]90 °C 24 h. [e]60 °C 24 h [f]50 °C, 8h

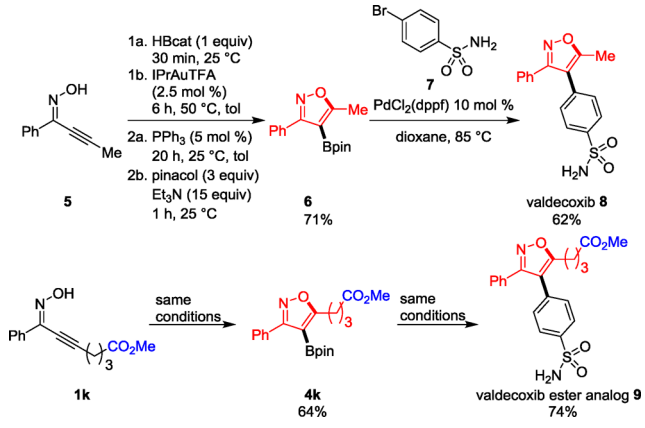
bond. The nitro group in **1e** and the ester group in **1k** are similarly tolerated, producing oxyboration product **3e** in 90% ^{1}H NMR yield (60% isolated yield of **4e**) and **3k** in 94% ^{1}H NMR yield (64% isolated yield of **4k**) under catalysis whereas these groups are intolerant of alternative lithiation techniques.[11] Furan-substituted **4b** demonstrates the complementary bond disconnections enabled by oxyboration to avoid competitive *ortho*-borylation of the furan ring[21] which would compete under alternative lithiation/borylation strategies (85% ^{1}H NMR yield of **3b**; 71% isolated yield of **4b**).

In addition, heteroaryl (**4b**), aliphatic (**4d**), electron-poor aryl (**4e**, **4j**, and **4k**), silyl (**4f**), and electron-rich aryl (**4g** and **4i**) are all compatible with the reaction conditions. Some substrates required a higher reaction temperature and/or longer reaction time to achieve full conversion under catalytic conditions, while no reaction was observed when the same conditions were applied in the absence of an Au catalyst. Oxyboration products **3d** and **3f** required 110 °C for 4 h and 90 °C for 24 h, respectively, which may be caused by the steric hindrance of the *tert*-butyl and the silyl groups. Electron-rich aryl **3i** and heteroaryl **3b** required heating at 60 °C for 24 h and 50 °C for 24 h, respectively, which may be attributed to the electron-donating ability of these substituents to reduce the electrophilicity of boron.

We proposed that a plausible catalytic cycle for the gold catalyzed oxyboration reaction could be similar to our previously published proposed mechanism for alkoxyboration,[8a] which highlights the activation of the C−C π bond by the carbophilic Lewis acid catalyst.[22] Investigation of the proposed mechanism for both the catalyzed and uncatalyzed oxyboration reactions are currently underway in our laboratory.

Synthetic Utility. The utility of the oxyboration reaction to generate building blocks for pharmaceutical targets was showcased through the synthesis of valdecoxib, a nonsteroidal anti-inflammatory drug (NSAID),[23] and its analog. Our synthetic route is shown in Scheme 3. Under standard catalytic conditions, bench-stable pinacol boronate building blocks **6** and **4k** were generated from oximes **5** and **1k** in 71% and 64%

Scheme 3. Oxyboration Synthesis of Valdecoxib



isolated yields, respectively. Suzuki cross-coupling of these borylated isoxazoles with *p*-bromobenzenesulfonamide **7** afforded valdecoxib **8** and valdecoxib ester analog **9** in 62% and 74% isolated yields, respectively. This synthesis provides the key substituted organoboron building block **6** in higher isolated yield, compared to the competing route with [3 + 2] cycloaddition of nitrile oxides and alkylboronates, which formed the same organoboron **6** in only 54% isolated yield in a route employed in a previously reported synthesis of valdecoxib.[9]

Additionally, the application of oxyboration to the synthesis of ester-containing valdecoxib analog **9** showcases the utility of the functional group tolerance of this oxyboration method. Previously reported syntheses of valdecoxib from academic[9,11] and industrial[23] laboratories involve lithiation steps that are not compatible with ester functional groups. These applications demonstrate the versatility and efficiency of the oxyboration reaction for the construction of pharmaceutical targets.

Access to a cost-effective uncatalyzed version of the reaction is particularly desirable on scale, wherein the cost of the catalyst may become a significant consideration that outweighs time

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considerations. The uncatalyzed oxyboration reaction scales well. Compound **1a** was successfully converted to 1.7 g of pinacol boronate **4a** on a 7.3 mmol scale under catalyst-free conditions in 24 h with 1.0 M in **1a** (eq 1, vide supra). The reaction time was reduced significantly when the starting material concentration was increased to the widely employed concentration in the chemical industry. This convenient scalability demonstrates that quantities of these heterocyclic boronic acid building blocks that are sufficient for multistep downstream synthesis may be prepared by this oxyboration method.

In conclusion, we have developed a method for preparing 4-borylated isoxazoles via oxyboration. This reaction proceeds with catalytic gold(I), or for many substrates without an added catalyst in the first reported uncatalyzed oxyboration reaction of C−C multiple bonds with B−O σ bonds. The reaction conditions are sufficiently mild to form functionalized borylated isoxazoles in good yields and in exclusively one regioisomer. The utility and functional group compatibility of this method were highlighted in the synthesis of valdecoxib and a valdecoxib ester analog and an effective scale-up reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03530.

Full experimental procedures, characterization data and ^{1}H and ^{13}NMR spectra (PDF)

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Notes

The authors declare the following competing financial interest(s): Provisional patent application (no. 62/198,410) has been filed by the University of California..

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