Communication

Synthesis and Applications of Un-quaternized C-bound Boron Enolates

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Synthesis and Applications of Un-quaternized C-bound Boron Enolates

Elvis Wang Hei Ng, Kam-Hung Low‡ and Pauline Chiu*

Department of Chemistry, and the State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, P. R. China

Supporting Information Placeholder

ABSTRACT: A general and facile method to prepare un-quaternized C-bound boron enolates by a ligand-controlled O-to-C isomerization is reported. Using this protocol, C-bound pinacolboron enolates have been isolated in pure form for the first time, and have been fully characterized by NMR spectroscopy and X-ray crystallography. In contrast to the general perception, such C-boron enolates are stable without coordinative saturation at the boron. Moreover, C-boron enolates present reactivities that are distinct from the O-boron enolates, and their applications in C–O and C–C bond formations are demonstrated.

Boron enolates are well-known reactive intermediates that have been prepared and used in numerous applications, particularly for aldol reactions[1] in total syntheses. Despite their wide use in organic synthesis, the fact that there are two isomeric forms has been largely disregarded (Fig. 1). In practice, the term "boron enolate" has almost always been used in reference to the O-bound isomer (O-boron enolate). The C-bound isomer (C-boron enolate, or α-borylcarbonyl), on the other hand, has received much less attention.[2] Being potentially chiral and amphoteric, C-boron enolates could be expected to exhibit a reactivity profile different from that of O-boron enolates.

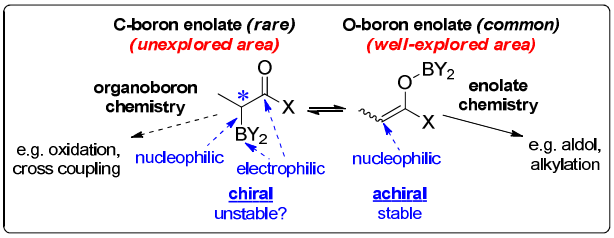


Figure 1. Comparison of the O-bound and C-bound isomers of boron enolates.

However, to synthesize C-boron enolates has been a challenge. Traditionally, this has been attributed to their tendency towards isomerization to the O-boron enolates,[3] thermodynamically driven by the formation of a strong B–O bond, and kinetically facilitated by an empty p orbital on boron. Therefore, a major strategy to generate C-boron enolates has been to stabilize the boron by quaternization (Fig. 2).[2] This has led to elegant work culminating in the successful preparation and isolation of a number of stable C-boron enolates[4] whose carbonyl functionality can be chemically manipulated, making them versatile precursors for the synthesis of various borylated compounds.[5]

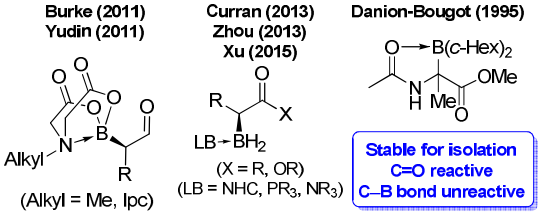


Figure 2. Representative examples of isolated C-boron enolates stabilized by boron quaternization.

Although there is a generally perceived instability of un-quarternized C-boron enolates, recent computational studies have indicated that the stability is highly dependent on the nature of the carbonyl group and the boryl group.[6] While C-boron enolates of aldehydes were predicted to be thermodynamically unstable compared to their O-bound isomers, C-boron enolates of esters with electron rich boryl group in particular, were predicted to be stable even without boron quaternization or intramolecular coordination. Nevertheless, this has yet to be experimentally verified.

Two reports of C-boron enolates without apparent boron quaternization have appeared (Fig. 3).[7] Abiko *et al* have reported C-boron enolates as a minor component in equilibrium with their O-boron enolates, in an enolboration of a hindered ester. Marder's group has also observed C-boron enolates in a Pt catalyzed diborylation reaction. In this case, however, stablization by intramolecular coordination between the β-boryl group and the carbonyl oxygen cannot be ruled out,[8] and later commentary has suggested that it may be critical for stability.[2] Therefore, it was still not clear whether un-quaternized C-boron enolates without extra stabilization by intramolecular coordination can be thermodynamically favored over the O-boron enolates. Furthermore, neither of these C-boron enolates had been isolated, or explicitly engaged in further reactions.

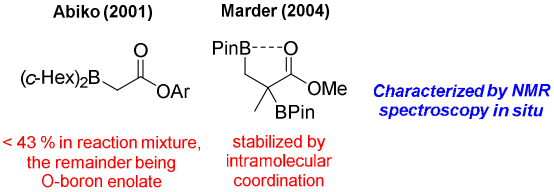


Figure 3. C-boron enolates without boron quaternization.

There is also another challenge, namely the lack of control over the O/C isomerization of boron enolates.[9] All isomerizations

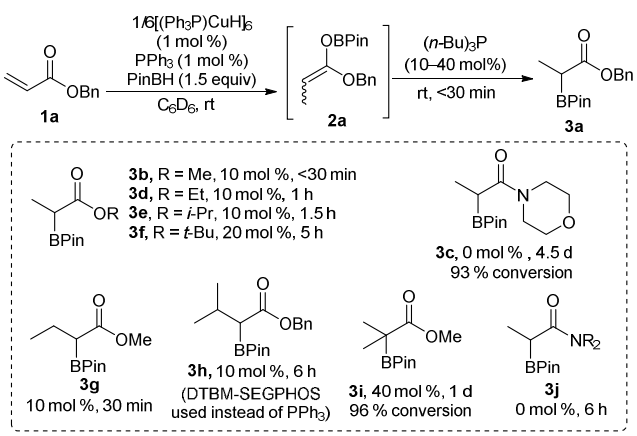
reported to-date were presumed to occur via uncatalyzed 1,3-boryl shifts.[2, 3, 6b] As a result, the formation of O- or C-boron enolates has been dependent largely on the substrate structure, and the selective formation of O- and C-boron enolates from the same substrate has not yet been demonstrated.[10]

Herein we report the facile preparation of un-quaternized C-boron enolates, via a copper-catalyzed O-to-C isomerization; moreover, we also demonstrate their applications in organic synthesis.

Catalyzed by copper hydride,[11,12] and with pinacolborane as the stoichiometric reductant, benzyl acrylate **1a** was reduced as expected to O-boron enolate **2a**. Upon the addition of a catalytic amount of phosphine or NHC, we discovered that an O-to-C isomerization occurred to generate a new species, C-boron enolate **3a** (Scheme 1). The process was monitored by ^{1}H NMR spectroscopy, and both the O-boron enolate **2a**, and then the C-boron enolate **3a** after isomerization, were characterized by *in situ* ^{1}H and ^{13}C NMR spectroscopy. The rate of the isomerization correlated roughly with the nucleophilicity of the ligands, in the following order of efficiency: IPr > $(n\text{-Bu})_3$P > $(c\text{-Hex})_3$P > $PhMe_2P$ > $Ph_2MeP \approx (EtO)_3P \approx (t\text{-Bu})_3P > Ph_3P \approx$ none. In most of our studies, the readily available and inexpensive $(n\text{-Bu})_3$P was routinely used.

To ascertain the structure of the new species, the more volatile C-boron enolate, **3b,** was synthesized and isolated in a pure state by vacuum distillation. Although **3b** is very moisture sensitive and undergoes protodeboronation in minutes when exposed to air, it is stable at room temperature under argon for weeks without appreciable decomposition. The ^{1}H and ^{11}B NMR spectra of C-boron enolate **3b** are consistent with the proposed structure. The ^{11}B NMR signal at δ 32.5 ppm was typical of a tricoordinate BPin moiety (cf. *n*-BuBPin, δ 37 ppm) and inconsistent with that of an ate-type boron complex. This is corroborated by the carbonyl group resonating at δ 174.9 ppm in the ^{13}C NMR spectrum, diagnostic of a typical ester carbonyl without strong coordination (cf. methyl propionate, δ 173.9 ppm). Finally, the absence of any stabilization by quaternization is unequivocally confirmed by X-ray crystallographic analysis of **3c** (Fig. 4),[13] a particularly crystalline C-boron enolate derived from 4-acryloylmorpholine. The planarity of the boron centre, together with the observation that the carbonyl oxygen and the BPin moiety were actually diametrically opposed, showed that these C-boron enolates are indeed stable even without stabilization by extra coordination. We rationalized that the diminished Lewis acidity of BPin (compared to BR_2) invited less electron donation from the enolate oxygen to the boron centre and resulted in less preference for the O-bound isomer.[6a]

Scheme 1. Generation of C-boron enolates 3



The scope of this O-to-C isomerization is quite broad (Scheme 1). Primary, secondary and tertiary esters, as well as α,α-disubstituted and β,β-disubstituted esters investigated were cleanly and quantitatively converted to their corresponding C-boron enolates using this protocol, where the rate of the isomerization decreases with increasing steric encumbrance. Amides undergo O-to-C isomerization even more readily than esters, and do not even require particularly nucleophilic phosphine to induce the isomerization. This can be attributed to the greater resonance delocalization of amides compared to esters, resulting in stabilization of the carbonyl group and therefore a higher preference for C-boron enolate formation.[14] Consistent with this trend, attempts to generate C-boron enolates from O-boron enolates of ketones were unsuccessful.[15]

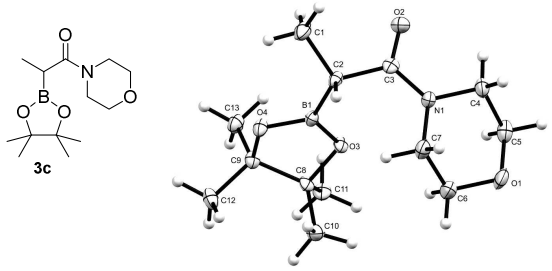
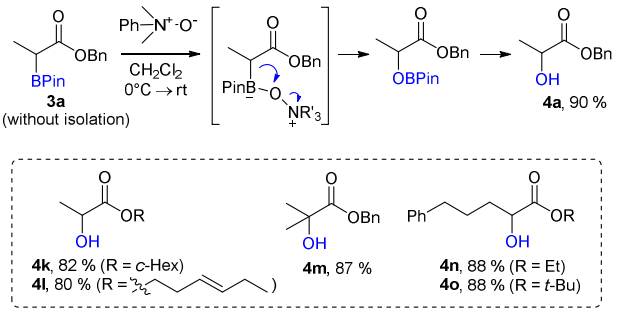


Figure 4. X-ray crystallographic structure of C-boron enolate **3c** (ORTEP representation, 50% probability ellipsoids).

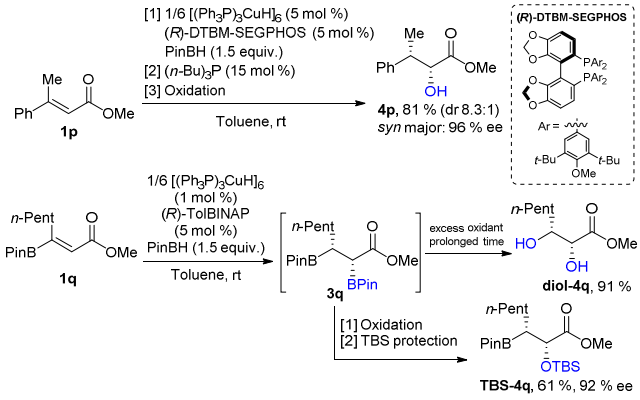
The lack of boron quaternization in these C-boron enolates confers reactivity to their C–B bonds that distinguishes them from other known, quaternized C-boron enolates (Fig. 2), whose boryl groups are protected and therefore unreactive. Although C-boron enolates **3** are quite prone to protodeboronation because of the lability of the enolate, the C–B bond can be transformed *in situ* to a C–O bond by an anhydrous oxidation (Scheme 2). In the event, treatment of **3a** with trimethylamine *N*-oxide[16] resulted in ~ 40% yield of **4a**,[17] but employing *N*,*N*-dimethylaniline *N*-oxide[18] with a better amine leaving group successfully oxidized a range of C-boron enolates to afford α-hydroxyesters **4a**, **4k-o** in very good yields (Scheme 2).

Scheme 2. Oxidation of C-boron enolates 3



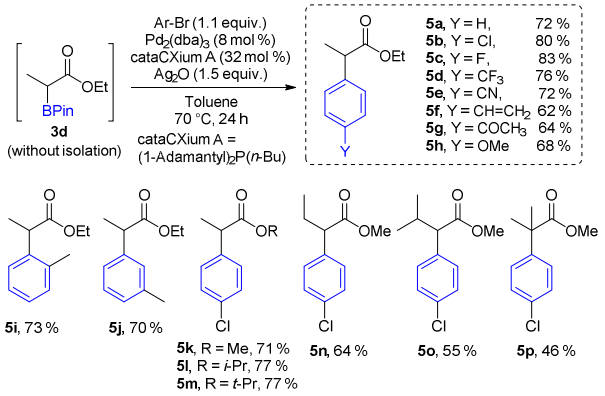
Furthermore, sequencing an asymmetric reduction using chiral phosphine-ligated copper hydride to generate the O-boron enolate enantioselectively,[19] a diastereoselective O-to-C isomerization, and finally a stereospecific oxidation using *N*,*N*-dimethylaniline *N*-oxide – converted **1p** and **1q** to alcohols **4p** and **4q** bearing two new stereogenic centers, with good diastereoselectivities and in high ee (Scheme 3).[20,21] Notably, the oxidation of C-boron enolate **3q** demonstrates the selective functionalization of the two secondary -BPin groups. Alternatively, the use of an excess of the amine oxide and extended reaction time oxidized **3q** in one step to the chiral **diol-4q**.

Scheme 3. Asymmetric reduction, diastereoselective isomerization and stereospecific oxidation sequence.



The synthetic potential of un-quaternized C-boron enolates is further demonstrated by enabling C–C bond formation from the C–B bond via a Suzuki–Miyaura cross coupling under anhydrous conditions (Scheme 4).[22] Our studies found that the phosphines used to induce O-to-C isomerization were detrimental to the subsequent palladium-catalyzed coupling. But by employing IPr, which can be used at as low as 1 mol % to induce the isomerization, C-boron enolate **3d** thus obtained was successfully coupled with various aryl bromides, catalyzed by a palladium-cataCXium A complex, to afford **5a-p** in good yields. The cross coupling reaction, as well as the oxidation, has also been performed using isolated C-boron enolate **3b**,[17] which confirmed that the Suzuki coupling indeed proceeded via the C-boron enolate, and not via the O-boron enolate in a Curtin-Hammett scenario.

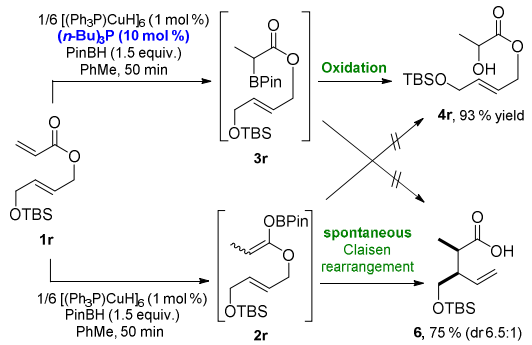
Scheme 4. Suzuki-Miyaura Coupling of C-boron enolates 3



The reactivity of the un-quaternized C-boron enolate is also notably distinct from that of O-boron enolate. For example, an aldol reaction occurred for O-boron enolate **2d** with an aldehyde,[23] but did not occur for its C-boron enolate counterpart, **3d**.[17] Moreover, whereas C-boron enolates **3** underwent oxidation and cross coupling reactions as shown in Schemes 2 and 4, under the same conditions, O-boron enolates **2** provided little or none of the C–O, C–C coupled products.[17]

In fact, by a judicious choice of reaction conditions, the extent of O-to-C isomerization of the boron enolates can be controlled, allowing the reactivity of either the O-bound or C-bound isomer to be exploited as desired (Scheme 5). In the absence of additional phosphine, reductively generated O-boron enolate **2r** spontaneously underwent Ireland-type Claisen rearrangement[24] to afford carboxylic acid **6** in good yield.[25] On the other hand, by introducing 10 mol % of $(n\text{-Bu})_3$P to promote the isomerization, the reaction was intercepted to form exclusively C-boron enolate **3r,** which did not undergo the Claisen rearrangement, but rather, provided lactate **4r** in excellent yield upon further oxidation.

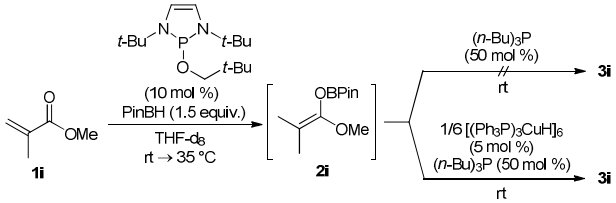
Scheme 5. Manipulation of reaction conditions to control the formation of O-boron enolate and C-boron enolate.



Although it appears at first glance that free phosphine or free NHC could be directly promoting the isomerization, this is in fact not the case. When $(IPr)Cu(OAc)_2$ – a well-characterized and robust copper complex that does not dissociate and release unligated NHC – was used to generate the copper hydride catalyst in the reaction,[26] a very fast O-to-C isomerization of **2f** to **3f** still occurred, even at a catalyst loading level as low as 0.5 mol%.[17] This led us to surmise that NHC or nucleophilic phosphines may not be promoting the isomerization directly as nucleophilic catalysts, but rather as ligands to copper, which has always been present in the reaction as a result of the reduction conditions.

To further examine the involvement of copper in the mechanism of isomerization, O-boron enolate **2i** was generated by an alternative route in the absence of copper (Scheme 6).[27] Whereas the treatment of **2i** thus generated with $P(n\text{-Bu})_3$ alone did not see any O-to-C isomerization, the introduction of $[(Ph_3P)CuH]_6$ and $P(n\text{-Bu})_3$ induced isomerization to **3i**, indicating that copper does play a key role in the isomerization. These observations allude to a mechanism that involves a metal, in contrast to previous proposals and calculations that explored uncatalyzed, direct 1,3-boryl shifts to account for C-boron enolate formation.[6b,7b]

Scheme 6. O-to-C isomerization of O-boron enolate 2i



Our observations, taken together with literature reports that pinacol boronic esters undergo B → Cu transmetallation in the presence of copper,[28] led us to hypothesize that the isomerization proceeds via the intermediacy of copper enolates. Presumably, in the presence of copper, boron enolates can undergo a B → Cu transmetallation to form the corresponding copper enolates, where they equilibrate via O/C as well as *E*/*Z* isomerizations.[29] Phosphines or NHC presumably act as ligands on copper to modify the relative stabilities of O-bound and C-bound copper enolates, and thereby affect the isomerization efficiency.[30] In fact, *E*/*Z* isomerization of O-boron enolates was invariably observed alongside the O-to-C isomerization, and the *E*/*Z* isomerization was also promoted by the presence of phosphines. Mechanistic studies are currently underway in our laboratory to elucidate more details of this isomerization mechanism.

In summary, we have described a general synthesis of un-quaternized C-boron enolates by a copper-catalyzed O-to-C

isomerization of the corresponding boron enolates, and the synthetic applications of these C-boron enolates have been demonstrated in subsequent C–O and C–C bond forming reactions. Further applications of these species in organic synthesis are anticipated. We envisage that this unusual O-to-C isomerization could occur in other reaction contexts (e.g. conjugate borylation) where similar O-boron enolates have been implicated as intermediates.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures and spectra (PDF)
Crystallographic data of **3c** (CIF)

AUTHOR INFORMATION

Corresponding Author

pchiu@hku.hk

Author Contributions

‡ Author responsible for X-ray diffraction analysis.

Notes

The authors declare no competing financial interests.

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(10) Marder has reported that the ligand on the Pt catalyst has some effect on the selectivity between O- vs C-boron enolate formation (see ref 7b). However, a follow-up computational study by the same group considered an uncatalyzed 1,3-boryl shift as the isomerization mechanism (see ref 6b), which did not account for the ligand effect. Despite the insights from these works, controlled formation of either isomer from the same substrate with high selectivity remained to be demonstrated.

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(20) Alcohol **4q** is not stable for isolation and was therefore protected as the TBS ether **TBS-4q** before isolation.

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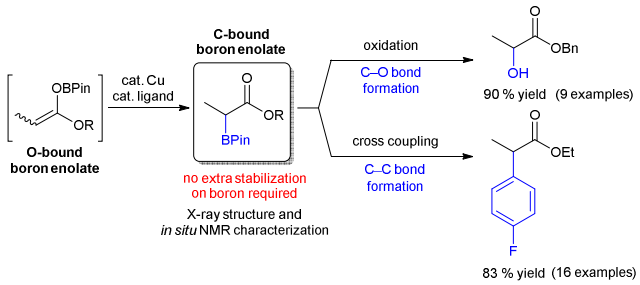
C-bound
boron enolate
OBPin
OR
O-bound
boron enolate
cat. Cu
cat. ligand
O
OR
BPin
no extra stabilization
on boron required
X-ray structure and
in situ NMR characterization
oxidation
C–O bond
formation
cross coupling
C–C bond
formation
O
OBn
OH
90 % yield (9 examples)
O
OEt
F
83 % yield (16 examples)