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Catalytic Conjunctive Coupling of Carboxylic Acid Derivatives with 9-BBN-Derived Ate Complexes

Chunyin Law, Yan Meng, Seung Moh Koo, and James P. Morken*^[a]

Dedicated to Professor Amir Hoveyda on the occasion of his 60th birthday.

Abstract: β -Boryl carbonyl compounds are produced by a Nicatalyzed cross-coupling of vinylboron "ate" complexes and acid chloride or acid anhydride electrophiles. Reactions are efficient, being complete in as little as two minutes, and apply to a broad range of substrates.

Organoboron compounds can be prepared by transition-metalcatalyzed conjunctive cross-coupling reactions between alkenylboron-derived "ate" complexes and organic electrophiles (eq. 1). ^{1,2,3} These reactions can be accomplished in an enantioselective and diastereoselective fashion, but so far have been restricted to hydrocarbon (aryl, alkenyl, alkyl) electrophiles. To extend conjunctive coupling reactions to the preparation of alternatively functionalized motifs, we considered the use of carbonyl-derived electrophiles. Herein, we describe a process that employs carboxylic acid derivatives as the electrophile in conjunctive couplings and produces β -boryl carbonyls as the reaction product.⁴ Considering the synthesis utility of β -boryl carbonyls, compounds that are generally prepared by boron conjugate addition⁵, the alternate route to these materials that is presented herein may have value.



This work: Carbonyl Electrophiles



Scheme 1. Catalytic Synthesis of β-Boryl Carbonyls by Conjunctive Coupling.

Our preliminary direction in developing a conjunctive-coupling reaction with carbonyl electrophiles was largely inspired by the

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body of work by Rovis⁶, Gong⁷, Weix⁸, Reisman⁹, Doyle¹⁰, and Yamamoto¹¹ who determined that Ni complexes could undergo oxidative addition with activated carboxylic acid derivatives thereby enabling either catalytic cross-coupling with nucleophiles or, in the presence of stoichiometric reductant, catalytic crosselectrophile coupling. Importantly, ¹³C labeling experiments conducted by Rovis and Coates ¹² established that (bipyridine)Ni(acyl) complexes were prone to undergo direct transmetalation reaction with alkylzinc reagents; this observation provided optimism that such a system might facilitate catalytic acyl conjunctive coupling reactions, as well.

To develop the conjunctive coupling between carbonyl electrophiles and boron "ate" complexes, we investigated the reaction between butanoyl chloride and various *in situ*-generated vinylboron ate complexes. Whereas preliminary experiments with pinacolatoboron-derived reagents were not fruitful, use of 9-BBN borate complex **1** as a coupling partner furnished the coupling product: as depicted in Table 1, it was observed that after one hour of reaction in the presence of 5 mol% NiBr₂•glyme and 6 mol% bipyridine (**L1**), followed by oxidation, β -hydroxy carbonyl **2** could be obtained in 65% yield (Table1, entry 1). Importantly, under these conditions, background reaction between the acid chloride and the "ate" complex was minimal. Extensive ligand **Table 1.** Effect of Ligand on Conjunctive Coupling with Acid Chloride Electrophiles.^[a]

| | ligand |
|--|--|
| $Ph \xrightarrow{9-BBN} HF \xrightarrow{Li} hen \xrightarrow{Li} 1 \xrightarrow{Li} f^{(i)} \xrightarrow{15\% \text{ NiBr}_2 \circ \text{glyme}} f^{(i)} \xrightarrow{6\% \text{ ligand}} OH O \xrightarrow{0} Ph \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} Ph \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} \xrightarrow{0} \xrightarrow{0}$ | $Z = \frac{1}{2} = $ |
| | LET Z A OMA |

| Entry | R | Time | Temp (°C) | Ligand | Yield (%) |
|-------|--------|-------|-----------|--------|-----------|
| 1 | propyl | 1 h | 22 | L1 | 65 |
| 2 | propyl | 1 h | 22 | none | <5 |
| 3 | propyl | 1 h | 40 | L1 | 48 |
| 4 | propyl | 1 h | 22 | L2 | 72 |
| 5 | Ph | 1 h | 22 | L1 | 40 |
| 6 | Ph | 1 h | 22 | L3 | 75 |
| 7 | propyl | 1 h | 22 | L3 | 78 |
| 8 | propyl | 2 min | 22 | L3 | 75 |
| 9 | propyl | 1 h | 22 | L4 | 32 |
| 10 | propyl | 1 h | 22 | L5 | 40 |

[a] See text and Supporting Information for experimental details. Yields refer to isolated yield of purified material and are an average of two experiments.

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analysis (see Supporting Information) revealed that the most generally applicable reaction conditions employ 5,5'bis(trifluoromethyl)-2,2'-bipyridine (L3) as the ligand (Table 1, entry 7). While the more readily available ligand bipyridine (L1) operates effectively with aliphatic acid chloride electrophiles, markedly diminished yield was obtained when this ligand was employed with aromatic acid chloride electrophiles. Thus, ligand L3 was employed for subsequent studies. It was determined that reactions in the presence of L3 can proceed with very good efficiency, achieving complete conversion of the probe reaction within two minutes at room temperature (entry 8).

To survey the scope of this reaction, a range of 9-BBN derived borate complexes were prepared by hydroboration ¹³ of the corresponding alkenes in THF, followed by addition of vinyllithium.¹⁴ The so-formed "ate" complex was treated with premixed NiBr₂•glyme and L3 in the presence of acid chloride electrophiles, followed by stirring at room temperature for 1 h and oxidative workup. As seen in Table 2, the reaction with aliphatic unbranched (i.e., **3**, **6**, **8**) and branched (**4**, **5**, **7**) acyl chlorides afforded products in good yields, although only moderate yield was observed when the sterically demanding pivaloyl chloride (**7**)





was employed in the reaction. Acyl chloride derived from TBSprotected lithocholic acid (20) was also subjected to the reaction conditions and afforded the desired product in reasonable yield. Regarding the functional group tolerance with respect to aroyl chloride electrophiles, whereas benzoyl chloride (10) as well as substrates bearing electron-donating substituents in the paraposition (11, 14) resulted in good yields, diminished yield was observed with an electron-withdrawing group (13) in the same position. Migrating groups derived from various alkenes were also examined in the reaction. Secondary migrating groups such as cyclohexyl group (16) provided the desired product in reasonable yield with no observation of byproducts derived from the migration of the bicyclooctyl ligand of 9-BBN.¹⁵ Migrating groups with appended alkene (21), and acetal (22), as well as silvl ether (18) were also tolerated. It was also shown that the 9-BBN borate complex derived from Ph-9-BBN (prepared from phenylmagnesium bromide and 9-BBN-OMe) can be employed in the reaction to give the corresponding product (23) in good yield. Lastly, under the current reaction conditions, propenyllithiumderived 'ate' complexes have not furnished coupling products.

The compatibility of other classes of acyl electrophiles in conjunctive cross-coupling was also explored. When anhydrides were subjected to the coupling under the conditions of Table 2, only trace quantities of coupled product were observed. We reasoned that the oxidative addition of Ni to less electrophilic anhydrides may be less facile as compared to the reaction with acid chloride counterparts¹⁶, and this process might be facilitated with a more electron-rich metal center. In line with this hypothesis, the use of unsubstituted bipyridine (L1) in place of the bis(trifluoromethyl) version resulted in a much more efficient coupling (Scheme 2). Of note, this reaction extended to a mixed anhydride with coupling occurring with the less hindered carbonyl (inset, Scheme 2).¹⁷



Scheme 2. Ni-Catalyzed Conjunctive Coupling with Anhydride Electrophiles.

While mechanistic aspects of this process remain under study, preliminary experiments shed light on the rudiments of the underlying features. By subjecting isotopically-labelled boron "ate" complex (**25**)¹⁸ to the reaction conditions (eq. 1, Scheme 3), it was found that the Ni-catalyzed coupling reaction occurs stereospecifically and with *anti* addition of the migrating group and the electrophile to the alkene, giving **26**. This observation is

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consistent with a mechanism involving nickel-induced metallate shift as opposed to alternate one-electron processes that might involve acyl radical addition to the alkene.¹⁹ To probe whether a Ni⁰-Ni^{II} redox cycle might represent the operative mechanism, the oxidative addition adduct **27** was independently synthesized using the method reported by Gong⁷, and treated with allylbenzene-derived borate complex **1**. As depicted in equations (2) and (3), the stoichiometric experiment furnished the conjunctive coupling product in 43% yield, suggesting that the Ni^{II} oxidative addition adduct is a competent intermediate in the conjunctive cross-coupling reaction. Lastly, as depicted in equation (4), with a chiral, enantiomerically-enriched bis(oxazoline) ligand (**L6**), a modest dependence of reaction enantioselectivity on the identities of electrophile was observed. This observation is suggestive of a scenario in which the



Scheme 3. Experimental observations about conjuctive coupling with acyl electrophiles and proposed mechanism.

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electrophile is associated with the metal center before a stereochemistry-determining, and likely irreversible, 1,2-metallate-shift. Thus, observations about the described cross coupling support a mechanism involving oxidative addition of the carbonyl electrophile to a Ni(0) complex²⁰ ($A \rightarrow B$, Scheme 3, box), followed by binding of the ate complex, metallate shift, and reductive elimination to deliver the product.

Although β -(pinacolato)boryl ketones have received ample study in the chemical synthesis community, β-trialkyl(boryl) ketones are novel species and a study of their structure and chemistry was of interest. The ¹¹B NMR resonance of β-boryl ketone 28 (δ 22.0 ppm) exhibits a significant upfield shift relative to a non-functionalized trialkylborane (δ 70-80 ppm).²¹ This feature is consistent with tight coordination between the boron and carbonyl oxygen atom. Reasoning that this chelation would enhance the acidity of the carbonyl α -protons and allow for the formation of a rigid cyclic enolate structure, we examined deprotonation/alkylation reactions of 28 (Scheme 4). Initial attempts with LDA or (i-Pr)2NEt (see SI) provided no evidence of productive deprotonation; however, when 28 was treated with methyllithium followed by iodomethane, alkylation product 29 was obtained with a high level of anti diastereomeric purity. 22 Remarkably, products derived from nucleophilic addition of CH₃Li to the internally-activated ketone were not detected. То understand the origin of reactivity and stereoselectivity in the deprotonation/alkylation reaction, we attempted to obtain a crystal structure of 28. While these attempts were unsuccessful, x-ray quality crystals of the methylamine-derived Schiff base were obtained (31) and these reveal internal chelation between boron and the heteroatom. Of note, due to the steric demands of the bicyclo[3.3.1]nonane framework, the substituent (Cy) at the stereogenic carbon atom is directed in an axial orientation and



Scheme 4. Structure and reactivity of a β -trialkylboryl carbonyl.

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appears to block access to one face of the prochiral α -carbon atom. It appears plausible that an enolate derived from **28** would have a similar conformation and this would allow an electrophile to approach only from the less hindered face, thereby accounting for the excellent *anti* diastereoselectivity.²³

In conclusion, we have described a catalytic cross-coupling between four-coordinate boron "ate" complexes and carbonyl electrophiles. This process provides a simple route to β -trialkylboryl carbonyls which exhibit uncommon and synthetically useful reactivity.

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Conjunctive Coupling: A new route to synthetically useful β -boryl carbonyls is enabled by the Ni-catalyzed addition of alkenyl boron "ate" complexes to activated carboxylic acids.

Chunyin Law, Yan Meng, Seung Moh Koo, and James P. Morken*

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