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An Alternative Approach to Aldol Reactions: Gold-Catalyzed Formation of Boron Enolates from Alkynes

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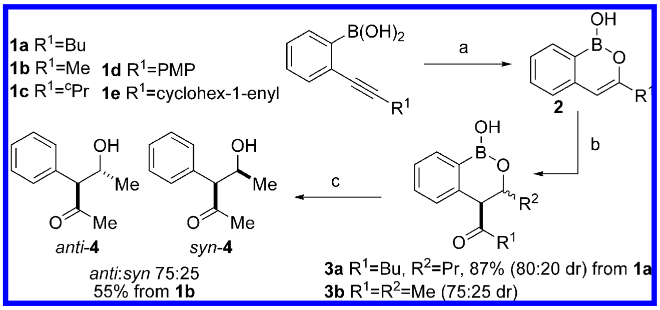
The aldol reaction is one of the most well established and widely used methods for the formation of carbon−carbon bonds.[1] However, without natural substrate bias, the chemoselective formation of an enolate from one carbonyl component in the presence of another is extremely challenging. Therefore, the most commonly employed solution is the use of a preformed enolate or enolate equivalent.[2] A method for the direct generation of an enolate from a non-carbonyl precursor would provide a more elegant approach, but such methods are rare and generally incompatible with the presence of enolizable aldehydes.[3] In this communication, we describe the first catalytic method for the generation of enolates from unactivated alkynes. The conditions are extremely mild, and the enolate can be generated even in the presence of aldehydes prone to self-condensation.

We envisaged that a boron enolate could be obtained by the gold-catalyzed[4] addition of a boronic acid to an alkyne.[5] To demonstrate this concept, we prepared *ortho*-alkynylbenzene boronic acid **1a** in two steps from bromoiodobenzene.[6] Treatment of **1a** with 1 mol % PPh$_3$AuNTf$_2$[7] led to the rapid formation of isolable boron enolate **2** (R^1 = Bu)[8] in 85% yield (Scheme 1). There was no evidence for the formation of products via 5-*exo-dig* cyclization in contrast to the Au-catalyzed cyclization of the corresponding carboxylic acids.[9] Selective formation of the six-membered ring in our case may be due to possible aromatic stabilization present in **2**.[8] Boron enolate **2** underwent aldol reaction with butyraldehyde at room temperature to give the cyclic boronate **3a** as a mixture of separable diastereoisomers. Gratifyingly, in a one-pot procedure where the boron enolate was generated *in the presence of the aldehyde*, the aldol product **3a** was obtained in 87% isolated yield (80:20 dr) over two steps.

To determine the stereochemistry of the products, we then prepared cyclic boronate **3b** (75:25 dr), which underwent protodeborylation to give the known alcohols **4** (75:25 dr).[10] The major diastereoisomer was found to be *anti*-**4**, derived from *trans*-**3b**. Careful comparison of the ^{1}H NMR spectra of the cyclic boronate **3a** with that of **3b** indicated that *trans*-**3a** was the major product in the reaction of boronic acid **1a**.[11]

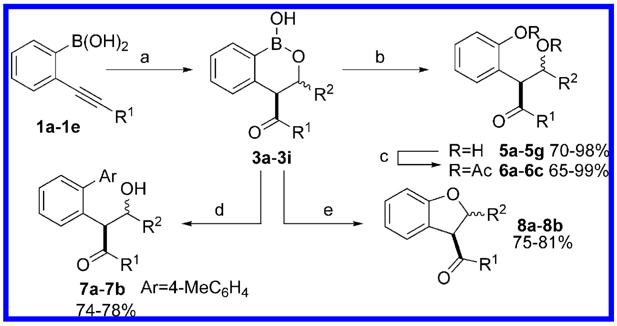
The one-pot enolate formation/aldol reaction was found to be applicable to a range of alkynes and aldehydes (Scheme 2 and Table 1). The mild enolate formation conditions were even compatible with acetaldehyde which is prone to self-condensation in the presence of acid or base.[12] In some cases, the cyclic boronates **3a**−**i** were prone to retro-aldol reaction and could not be isolated via chromatography. However, the cyclic boronate provides a useful handle for further transformations, and the crude reaction products could be used directly in subsequent steps. Multistep sequences were developed for direct conversion of the boronic acids **1a**−**e** into phenols/acetates (**5** or **6**), biaryls (**7**), or 2,3-dihydrobenzofurans[13] (**8**) via oxidation,[14] Suzuki−Miyaura coupling,[15] or Chan−Lam coupling,[16] respectively. These latter reactions are the first examples of intramolecular Chan−Lam coupling reactions[17] employing aliphatic alcohols.[18] Excellent isolated yields of the final products were obtained over two or three steps. In each case, the diastereoisomers were assigned by comparison of the ^{1}H NMR spectra of the cyclic boronates **3c**−**i** with **3a**−**b**.[11] Importantly, no change in diastereomeric ratio was observed during the post-aldol transformations.

Scheme 1. Gold-Catalyzed Boron Enolate Formation/Aldol Reaction



^{a} 1 mol % PPh$_3$AuNTf$_2$, CH$_2$Cl$_2$, rt, 1 h. ^{b} R^{2}CHO, CH$_2$Cl$_2$, rt, 2 h. ^{c} 10 mol % CuSO$_4$•5H$_2$O, H$_2$O, 60 °C, 16 h.

Scheme 2. Transformation of Aldol Products **3** via Oxidation, Suzuki Reaction, or Chan−Lam Coupling



^{a} 1−2 mol % PPh$_3$AuNTf$_2$, R^{2}CHO, CH$_2$Cl$_2$, rt, 1−12 h. ^{b} mCPBA, CH$_2$Cl$_2$, rt, 30 min. ^{c} Ac$_2$O, pyridine, rt, 2 h. ^{d} 3 mol % (PPh$_3$)$_2$PdCl$_2$, CsF, ArI, CH$_2$Cl$_2$, 37 °C, 10 h. ^{e} 5 mol % Cu(OAc)$_2$•H$_2$O, MeOH, 40 °C, 10 h.

The above reactions demonstrate that the gold-catalyzed addition of a boronic acid to an alkyne is a feasible method for accessing boron enolates for use in aldol reactions. We were also keen to explore intermolecular boron enolate formation as this would allow the use of catalytic quantities of boronic acid. Pleasingly, on stirring aldehyde **9**[19] (Scheme 3) with 2 mol % PPh$_3$AuNTf$_2$ and 30 mol % of commercially available boronic acid **10**, a slow reaction took place over the course of 3 days to give enone **11**[20] as the sole product in 50% isolated yield. In this case, as expected, complete selectivity for Markovnikov addition of the boronic acid to the alkyne is observed. Enone **11** could potentially be produced via a

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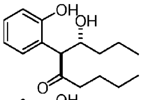
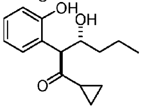
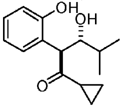
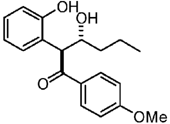
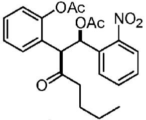
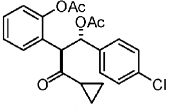
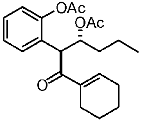
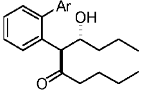
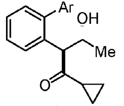
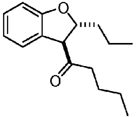
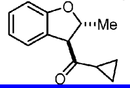
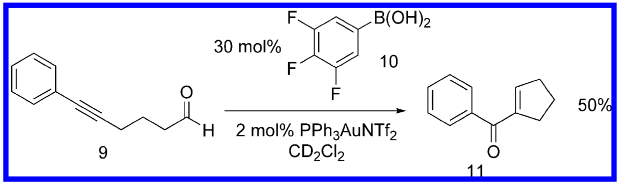
Table 1. Gold-Catalyzed Enolate Formation/Aldol Reactions Followed by Oxidation, Suzuki−Miyaura, or Chan−Lam Coupling

product[a]		isolated yield[b]	*anti:syn*
	**5a**	91%	80:20
	**5b**	97%	67:33
	**5c**	98%	67:33
	**5d**	70%	67:33
	**6a**	99%	45:55
	**6b**	77%	55:45
	**6c**	65%	75:25
	**7a**[c]	78%	79:21
	**7b**[c]	74%	62:38
	**8a**	75%	79:21
	**8b**	81%	66:34

a Major isomer.[b] Yield over 2/3 steps from boronic acid **1**.[c] Ar = 4-MeC_6H_4.

Scheme 3. Combined Au/$ArB(OH)_2$-Catalyzed Aldol Condensation



gold-catalyzed alkyne−carbonyl metathesis, analogous to reported Ag-catalyzed reactions.[21] However, in the absence of the arylboronic acid **10** no reaction occurred with the gold catalyst over a similar time period, providing evidence to support the intermediacy of a boron enolate.

In summary, we have developed an efficient catalytic method for generating boron enolates from unactivated alkynes. The enolate formation is exceptionally mild, and the enolates can be trapped by aldehydes present in the reaction mixture. Intramolecular enolate formation/aldol reactions provide access to a range of functionalized scaffolds in excellent yield, after subsequent transformation of the boronic acid. We have also demonstrated the feasibility of a combined gold/boronic acid catalyzed aldol condensation reaction. Further work is underway to explore the scope of this novel approach to enolate chemistry.

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Supporting Information Available: Detailed experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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