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Nucleophilic addition of benzylboronates to activated ketones

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ABSTRACT

A method has been developed for the addition of benzylboronic acid pinacol ester to activated ketones including trifluoromethyl ketones in good yields. The use of DABCO as an additive was found to enhance the rate and efficiency of this reaction. In reactions of ketones with a second carbonyl group present such as an ester or amide, good chemoselectivity for the ketone was observed. Competition experiments suggest an electrophile relative reactivity order of CF_2H ketone > CF_3 ketone > aldehyde under these reaction conditions.

Introduction

Organofluorine molecules have been developed for many applications including their use in medicinal chemistry, agrochemistry and polymer chemistry [1,2]. Fluorine substituents have been found to alter the lipophilicity and metabolic stability of compounds, resulting in drug candidates with favorable therapeutic profiles [1,3]. Trifluoromethyl groups are increasingly present in molecules with biological activity [4]. Our research group has been developing alkylboronates as nucleophiles with carbonyl electrophiles [5] and sought to evaluate trifluoromethyl ketones to expand this methodology.

The trifluoromethyl alcohol motif is found in numerous pharmaceutically relevant molecules [4]. Compounds with a trifluoromethyl alcohol have found relevance as sleep inducers [6], as anti-inflammatory drugs [7,8], and as cholesteryl ester transfer protein inhibitors (Fig. 1) [3,9]. Trifluoromethyl alcohols such as those synthesized in this report have previously been evaluated as anti-fertility drugs [10]. Common syntheses of trifluoromethyl alcohols have been performed through addition of an anionic CF_3 group to a ketone or aldehyde [11–18]. Alternatively, nucleophilic addition to a trifluoromethyl ketone has been reported using dialkylzinc reagents with additives required to prevent competitive reduction of the trifluoromethyl ketones [19,20]. Previous work in our laboratory revealed that activation of an alkylboronic ester with a Lewis base formed a nucleophilic boronate intermediate [5,21–24]. These nucleophiles were found to react with aldehydes and imines [5,25]. This report will highlight trifluoromethyl ketones as electrophiles in 1,2-nucleophilic addition reactions with benzylboronate nucleophiles and examine competition experiments between trifluoromethyl ketones and other carbonyl electrophiles to determine their relative reactivity in this reaction.

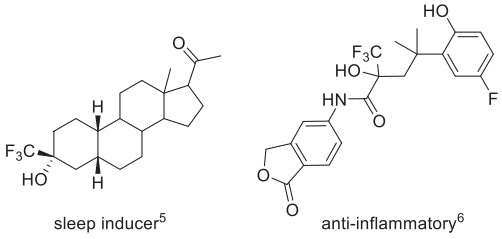

Fig. 1. Medicinally relevant trifluoromethyl alcohols.

Results and discussion

We began our studies with ketone electrophiles by activating the benzylboronic ester with *sec*-butyl lithium [5,25,26]. While examining polar aprotic additives for the reaction with ketones [5,27], the use of 1,4-diazabicyclo[2.2.2]octane (DABCO) as an additive increased the rate of the 1,2-addition and subsequent yield of alcohol product (Table 1). It is assumed DABCO coordinates the lithium counterion, making the boronate nucleophile more reactive. All substrates exhibited an increase in yield when using DABCO as an additive. Reactions employing trifluoromethyl ketones with electron-donating groups provided the most dra-

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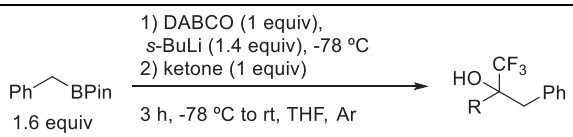
Table 1
DABCO as an additive.



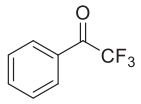
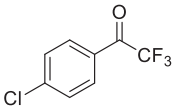
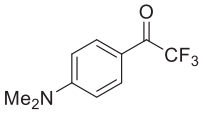
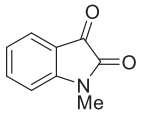
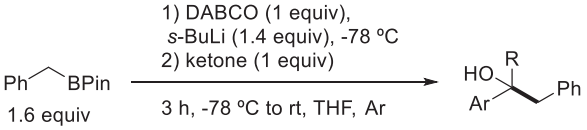
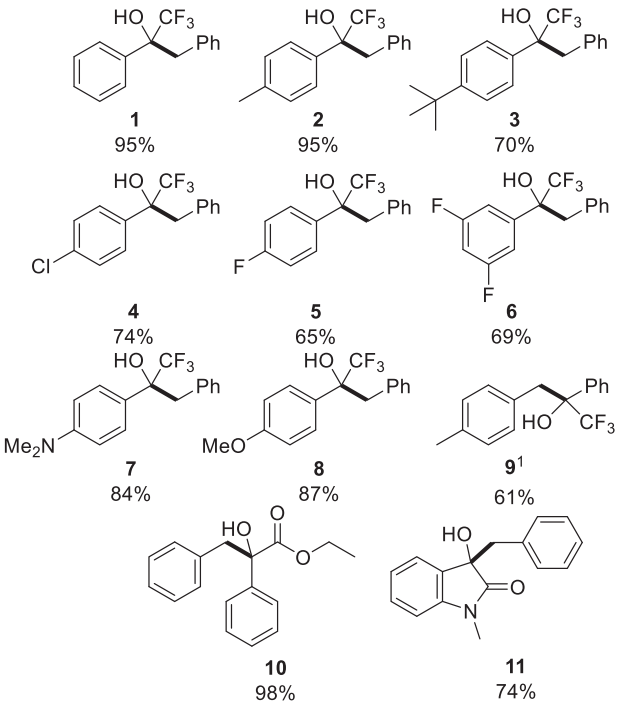
Substrates	Yield (%) with DABCO	Yield (%) no DABCO
	95	70
	74	61
	84	54
	74	51

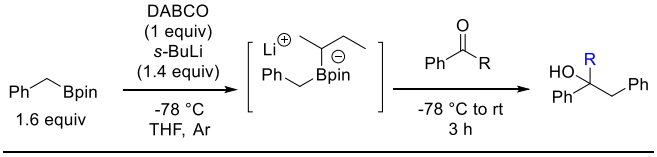
Table 2
Substrate scope.

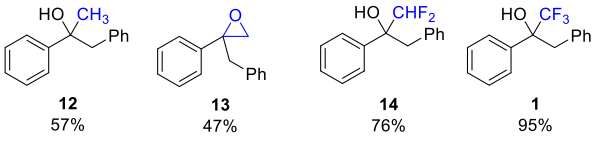




[1]4-methylbenzylboronic acid pinacol ester was used.

Table 3
Reactions varying the number of α-fluorine substituents on acetophenone.





matic increase in yield. DABCO has previously been shown to coordinate to the lithium in $LiCH_2SiMe_3$, forming a higher aggregate octamer of the base that was more reactive than the parent hexamer [28]. While DABCO has also been reported to activate pinacolborane for the reduction of imines via borenium ion catalysis, a control reaction with DABCO and no *sec*-butyl lithium provided no desired product, so borenium ion catalysis does not appear to be operative in our reaction [29,30].

Next, a substrate scope of trifluoromethyl and other activated ketones was examined (Table 2). Yields were generally good for aryl trifluoromethyl ketones with substituents of varying electronics. Halogen substituents were the most electron withdrawing groups examined with trifluoromethylacetophenone derivatives due to the formation of hydrates when more electron withdrawing substituents such as NO_2 or CF_3 were present [31]. Some of the highest yields were using trifluoromethyl ketones with electron donating groups as seen with products **7** and **8**. The 4-methylbenzylboronic ester was a capable nucleophile, providing product **9** in 61% yield. The reaction exhibited good chemoselectivity for a ketone in the presence of ester and amide functional groups, providing good yields of the alcohol products **10** and **11**.

We also examined the reactivity of the benzylboronate with a series of differentially fluorinated acetophenone derivatives (Table 3). The reaction with acetophenone provided 57% yield of product under the reaction conditions with starting ketone (41%) also recovered. Additional reaction time was not effective at improving the conversion in this reaction, showing the limits of the substrate scope using the benzylboronate nucleophile. 2-Fluoroacetophenone reacted and upon unanticipated intramolecular substitution provided epoxide **13** in a 47% yield.[32] 2,2-Difluoroacetophenone was an excellent substrate providing a 76% yield of the desired alcohol. This series of reactions demonstrate the compatibility of the reaction conditions when using ketones with enolizable protons and reveals a general trend that increased fluorine substitution alpha to the carbonyl provides an activating effect toward nucleophilic addition in this reaction.

To gain a better understanding of the relative electrophilicity of carbonyl groups with α-fluorine substituents [33], two competition experiments were performed. A reaction using 2,2,2-trifluoroacetophenone and benzaldehyde was conducted with one equivalent of nucleophile (Scheme 1). The trifluoromethyl ketone is more sterically hindered, but also more electrophilic given the known equilibrium between electron-deficient trifluoromethyl ketones and their respective hydrates [31]. From the outset, it was not clear which would be more reactive under the reaction conditions. In this reaction, a 68:32 ratio of tertiary to secondary alcohol products was observed, revealing 2,2,2-trifluoroacetophenone was more reactive than benzaldehyde. A second competition

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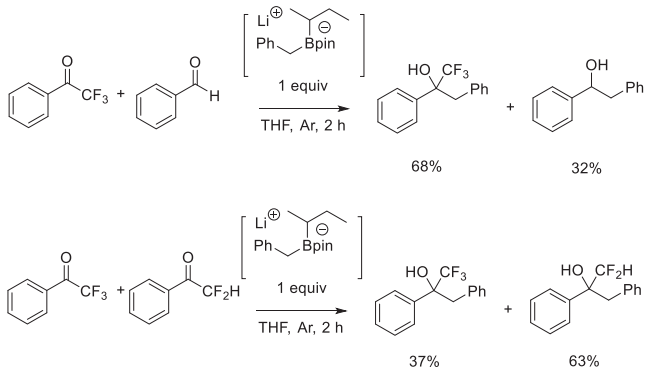

Scheme 1. Competition experiments.

between 2,2,2-trifluoromethylacetophenone and 2,2-difluoroacetophenone provided a 37:63 ratio of the alcohol products with the CHF_2 ketone reacting faster. From these two experiments, the relative reactivity order was found to be: CHF_2 ketone > CF_3 ketone > aldehyde under these reaction conditions. Electronic activation was found to be the controlling factor in the competition between the CF_3 ketone and aldehyde, while steric effects controlled the reactivity in the competition between the CF_3 and CHF_2 ketone. Previously, a series of competitions using fluorinated carbonyl compounds in a Rh-catalyzed arylation reaction revealed a relative reactivity order of aldehyde > CHF_2 ketone > CF_3 ketone [34]. Steric differences can account for the relative reactivity trend observed in this previously published work. The differences in reactivity observed between the two systems can be attributed to differences in their respective mechanisms. The Rh-catalyzed reaction is proposed to go through a closed transition state with precoordination of the carbonyl by the Rh-aryl nucleophile before nucleophilic addition [34,35]. Required precoordination to the carbonyl would explain the importance of sterics in the Rh-catalyzed 1,2-addition. In contrast, our reaction proceeds through an open transition state based on the previously observed diastereoselectivity in reactions with *N-tert*-butanesufinylimines [5,25]. These differences in mechanism help rationalize the differences in relative reactivity of carbonyls observed in competition experiments in these two different reaction systems.

Conclusions

A benzylation of activated ketones has been developed using benzylboronic acid pinacol ester. DABCO was found to be a beneficial polar aprotic additive that accelerated the rate of the reaction. Reactions with aryl trifluoromethyl ketones as electrophiles provided the alcohol products in good yields. Excellent chemoselectivity for addition to a ketone in the presence of esters and amides was observed. Competition experiments revealed an electrophile relative reactivity order of CHF_2 ketone > CF_3 ketone > aldehyde under the reaction conditions with a combination of both steric effects and electronic activation used to rationalize this observed reactivity order.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151505.

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