A coupling approach for the generation of α,α-bis(enolate) equivalents: Regioselective synthesis of *gem*-difunctionalized ketones

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Supporting Information Placeholder

ABSTRACT: Regioselective α,α-difunctionalization adjacent to a ketone is a significant synthetic challenge. Here we present a solution to this problem through the transition-metal-free coupling of esters with geminal bis(boron) compounds. This forms an α,α-bis(enolate) equivalent which can be trapped with electrophiles including alkyl halides and fluorinating agents. This presents an efficient, convergent synthetic strategy for the synthesis of unsymmetrical blocked ketones.

The enolate has proven over many years to be one of the key building blocks in synthetic chemistry. A versatile class of nucleophile, enolate formation permits selective monofunctionalization adjacent to a carbonyl group with a broad range of electrophiles.[1]

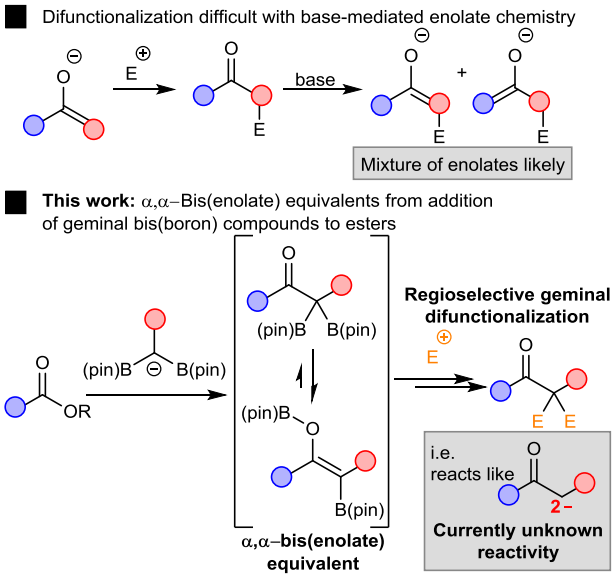
There are however, many cases where we may wish to introduce two groups adjacent to a carbonyl group in selective difunctionalization reactions, for example to form blocked carbonyl systems where further enolization is not possible. Such processes can be very difficult to perform selectively and the geminal α,α-difunctionalization of ketones through standard enolate chemistry presents a significant challenge. To achieve this will require two sequential deprotonation events, and despite much work in understanding the regioselectivity of enolate formation of a range of systems, achieving good levels of regiocontrol is not always possible.

Whilst difunctionalization through enolate chemistry is difficult, perhaps the best current method for selective geminal difunctionalization α-to a carbonyl group is through α,α-difunctionalization reactions of α-diazo carbonyl compounds.[2] Diazo compounds display donor-acceptor reactivity and during difunctionalization undergo trapping with an electrophile and nucleophile. However, this approach presents safety concerns and the harsh conditions needed for diazo carbonyl formation can limit functional group compatibility. Burtoloso has recently reported a geminal difunctionalization of donor-acceptor α-carbonyl sulfur ylids with alkyl halides which incorporates both alkyl group and halogen atom.[3]

An alternative conceptual approach for difunctionalization would involve the double-electrophilic trapping of species which display dianion-like reactivity (Scheme 1). This strategy has yet to be developed in enolate chemistry. We therefore sought to establish a route to reactive enolate-like intermediates which would react as if they were a dianion. Potentially this could be achieved through the nucleophilic substitution of an ester with a geminally dimetallated nucleophile.[4]

To achieve this we became attracted to nucleophilic species containing boron. Organoboron compounds are generally stable and non-toxic nucleophiles. In particular, an organoboron species is able to stabilize an α-carbanion through hyperconjugation with its empty p-orbital. Whilst mono-boron species are generally difficult to deprotonate, geminal bis(boron)[5] species are easily deprotonated α- to boron using strong bases such as LiTMP. Addition of a lithiated geminal bis(boron) compound to an ester should yield an α-diboryl ketone (i.e. a boron enolate).[6] This boron enolate should then be able to be trapped by an electrophile. In theory, both boron atoms should be amenable to electrophilic trapping to yield α,α-difunctionalized ketone systems and excellent regioselectivity is likely to be observed as difunctionalization should occur where the boron atoms were introduced.

Lithiated geminal bis(boron) species undergo addition to aldehydes and ketones to yield alkenyl boronates in boron-Wittig type processes,[7] and this approach was recently extended by our laboratory in developing the first homologative coupling of aldehydes and ketones through a boron-Wittig / oxidation sequence.[8] Whilst Matteson developed the addition of geminal (bis)boron species to esters and acid chlorides to give ketones in the 1970s,[9] no examples of the electrophilic double-trapping of such species beyond simple protonation have been explored to date, meaning the regioselectivity of trapping has not been explored. Mukaiyama has reported the addition of lithiated mono-boron species to esters to yield a boron-enolate which underwent aldol reaction with aldehydes,[10] whilst Srebnik has developed a related acylation/bromination sequence of zirconium-substituted organoboranes.[11]

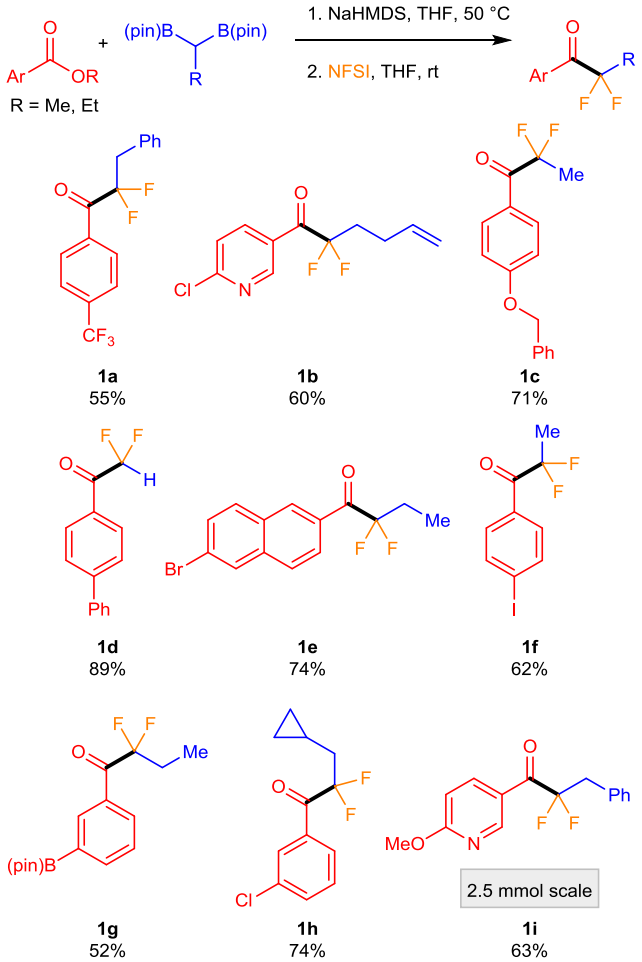


Scheme 1: Background and Strategy

This new strategy would present an attractive approach for functionalized ketone synthesis as in theory, carbonyl derivative, geminal bis(boron) compound and electrophile for enolate trapping could all be varied to quickly produce diverse libraries of compounds. Transition metal-free coupling processes such as this are of particular interest as there are strict requirements to remove potentially toxic transition metal residues from end-products, particularly pharmaceuticals.[12]

Our initial interest in terms of choice of electrophile for trapping was drawn to fluorination. Approaches to the synthesis of difluorinated ketones are rare and are generally based on the addition of pre-difluorinated building blocks, including cross-coupling of CF_2H and CF_2X groups,[13,14] radical additions of CF_2X groups,[15] additions of difluorinated organometallics,[16] fragmentations of difluorinated 1,3-dicarbonyl compounds,[17] additions of difluorocarbene[18] and reactions of difluorinated silyl enol ethers.[19] Attempts to difluorinate ketones through enolate formation generally stop at monofluorination, although geminal difluorination of enamines and imines is known.[20] Introduction of a fluorine atom α-to a carbonyl group makes formation of a second enolate at that site difficult as the first-introduced fluorine atom destabilizes a sp^2-carbanion.[21] However, difluorinated ketones are useful building blocks[22] for the synthesis of fluorinated drug-like compounds[23] whose mechanism of action is often formation of a stable ketal at an enzyme active site.[24]

We were therefore pleased to discover that reaction of a benzyl-substituted geminal bis(boron) compound with ethyl 4-(trifluoromethyl)benzoate in the presence of NaHMDS as base, followed by addition of 3 equivalents of *N*-fluorobenzenesulfonimide NFSI), a common and mild source of electrophilic fluorine yielded difluorinated coupled product **1a** with no observable mono-fluorination. Trapping of the α,α-bis(enolate) equivalent resulting from addition of geminal bis(boron) species to ester with NFSI was rapid and complete within 15 minutes; extended trapping periods on occasion led to decomposition. NFSI proved the most successful source of electrophilic fluorine most likely due to its improved solubility in THF compared to reagents such as Selectfluor. After brief optimization conditions were established which gave very good conversion to this difluorinated product.

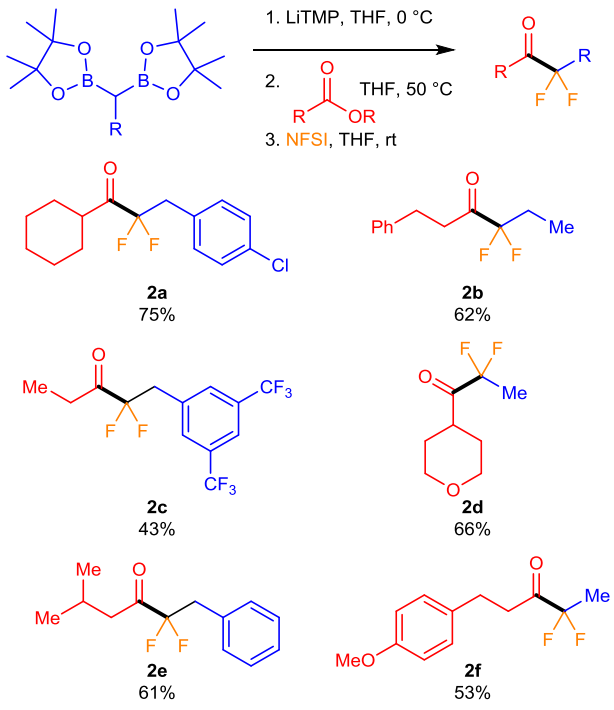


Scheme 2: Difluorinative coupling of aromatic esters

The scope of this transformation was then established (Scheme 2). A range of aromatic esters were reacted with geminal bis(boron) compounds in the presence of NaHMDS at 50 °C, followed by cooling to room temperature and addition of an NFSI solution. This showed that a range of functional groups were tolerated in this difluorinative coupling reaction, including halogenated aromatic rings (**1b, 1e, 1f, 1h**) and a pinacol-boronate (**1g)** for further coupling processes, a trifluoromethyl group (**1a)**, a terminal alkene (**1b),** and a cyclopropane ring **(1h)**. Pyridine-type heterocycles **1b** were also tolerated, including derivative **1i** which was reacted on a 2.5 mmol scale. Unsubstituted geminal bis(boron) compound was used in the synthesis of CF_2H-ketone **1d** without any appreciable under- or over-fluorination.

Whilst these conditions were operationally convenient, they were not compatible with the use of enolizable esters. To achieve this the base was changed to LiTMP, which was used to initially deprotonate the geminal bis(boron) compound. Sequential addition of ester then NFSI yielded the coupled difluorinated product (Scheme 3). Impressively, not only was this reaction entirely selective for difluorination, fluorination was exclusively observed on the side of the ketone where boron had been introduced. This confirms that enolate formation by substitution of esters with borylated nucleophiles proceeds with complete control of regioselectivity. Again, halogen atoms (**2a**) and oxygen-containing functionality (**2d, 2f**), as well as trifluoromethyl groups (**2c**) were compatible with this difluorinative coupling process.

This transition-metal-free coupling approach for the synthesis of α,α-bis(enolates) is a viable strategy for other regioselective

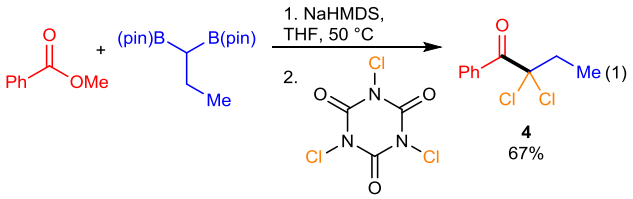


Scheme 3: Difluorinative coupling of enolizable esters

difunctionalization processes. Of particular interest would be a geminal dimethylation process. This would form a quaternary center and be a viable strategy for forming ketones blocked from enolization on one side. In addition, a 'magic methyl' effect has been proposed in medicinal chemistry, where methylation of active compounds can lead to an increase in potency through increased binding affinity through hydrophobic interactions,[25] making reactions for selective methylation of particular interest. It should be noted that on occasion high-yielding and regioselective geminal dimethylation of ketones has been possible to achieve through thermodynamic control of enolate formation, particularly in cyclic systems,[26] although the coupling method reported here offers extra flexibility over enolate formation by deprotonation.

Again, a similar strategy proved viable for the development of a dimethylative coupling using as base either NaHMDS for non-enolizable esters or LiTMP for enolizable esters (Scheme 4). For most reliable dimethylation of the resultant α,α-bis(enolate) equivalent, 5 equivalents of iodomethane were added for trapping. Geminal dimethylation was selectively observed at the side of the ketone that boron was introduced. A similar range of functionality could be tolerated including an indole (**3c**), halogen atoms (**3b, 3e, 3h**), an amine (**3f**) and ethers (**3d, 3e**), as well as a cyclopropane ring (**3g**). It is difficult to imagine the synthesis of a compound such as **3e** with its almost symmetrical structure, by standard enolate chemistry. Also, methylation occurred selectively at carbon, with no competing *O*-methylation which can plague base-mediated enolate methylation processes.

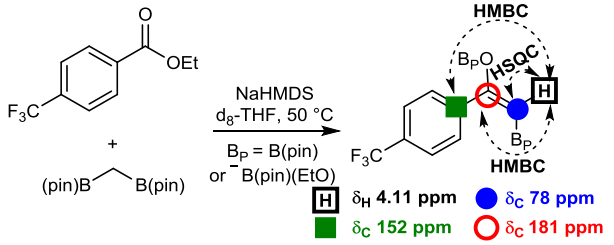
This strategy also proved appropriate for the development of a dichlorinative coupling process using trichloroisocyanuric acid. The standard conditions using NaHMDS as base afforded α,α-dichloro-ketone **4** in good yield (eq. 1). One equivalent of trichloroisocyanuric acid was sufficient to achieve dichlorination.



The bases required for these processes should be noted. In the case of non-enolizable (aromatic) esters, the ester, geminal bis(boron) compound and NaHMDS could be mixed together and heated for 15 minutes to achieve successful ketone formation. However, in the case of enolizable esters this led to poor conversion, likely due to competing ester deprotonation. Even pre-addition of NaHMDS to geminal bis(boron) compound followed by ester addition proved ineffective. To achieve successful addition to enolizable esters, first geminal bis(boron) compound had to be deprotonated by the more basic hindered base LiTMP, followed by addition of ester. We believe that the use of NaHMDS leads to an incomplete equilibrium deprotonation of geminal bis(boron) species and so is only compatible when the ester is also not enolizable, whereas LiTMP gives complete deprotonation.

To probe the nature of the intermediate enolate species further we attempted to observe it by NMR. Ethyl 4-(trifluoromethyl)benzoate and $(B(pin))_2CH_2$ were heated to 50 °C in the presence of NaHMDS in d^8-THF (Scheme 5A).[27] A species with a broad ^1H resonance at 4.11 ppm was observed, which would correspond to an enol-type C-H resonance, but too deshielded to represent an α-boryl carbonyl compound. This ^1H peak displayed a HSQC correlation to a ^{13}C NMR peak at 78 ppm, indicative of an electron-rich position of an enol, and HMBC correlations to ^{13}C NMR peaks at 152 ppm (quaternary carbon of aromatic) and 181 ppm (electron-poor position of enol-type C=C double bond). These values are similar to boron enolate species previously reported in the literature.[28]

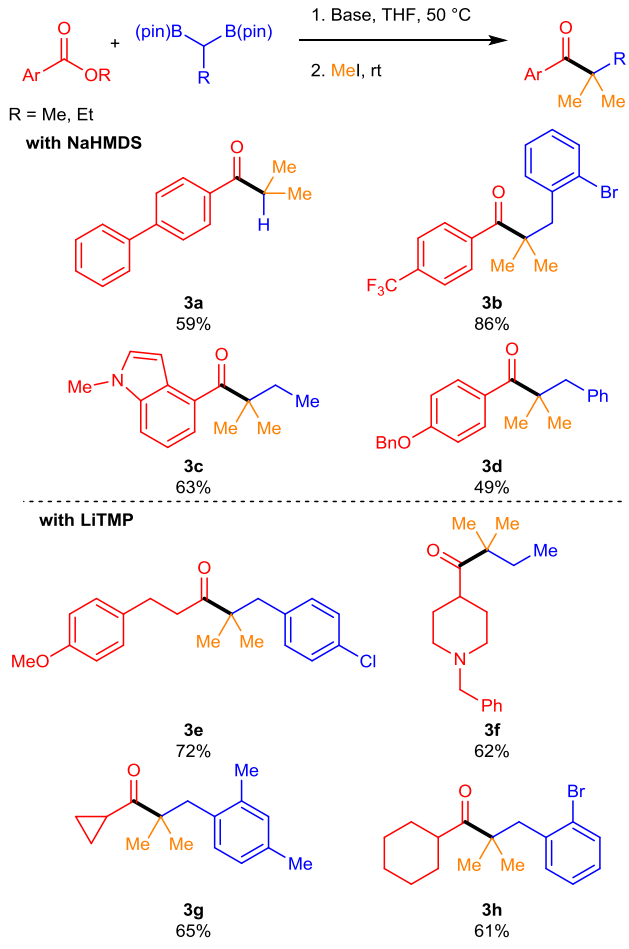
Boron enolates are typically unreactive towards alkylating agents such as iodomethane, unless boron is activated by quaternization.[29] ^{11}B NMR spectroscopy of this boron enolate shows a peak at approximately 5 ppm, which is very indicative of a $B(OR)_4^-$ species activated by coordination to boron of a nucleophilic species in the reaction mixture such as ethoxide ion released by ester substitution.[27] This coordination could explain the high reactivity observed in alkylation with iodomethane in this system.



Scheme 5: Mechanism study

Addition of NFSI or MeI to the solution containing this boron enolate resulted in selective difluorination / dimethylation. All this information supports our proposed mechanism of the double electrophilic trapping of an alpha-boryl-boron enolate, proceeding selectively with no migration of boron.[30]

In summary, we have developed a transition-metal-free coupling of esters with deprotonated geminal bis(boron) compounds, providing α-diboryl ketone intermediates which react as α,α-



Scheme 4: Dimethylative coupling

bis(enolate) equivalents. This presents a convenient strategy for difluorinative and dimethylative coupling for the synthesis of regioselectively geminally difunctionalized ketones. Future work will focus on the development of further transition-metal-free coupling approaches using this strategy.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental details, characterization data (PDF)

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Notes

The authors declare no competing financial interests.

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(30) Control experiments to establish whether protodeboronation of the bis(boron) enolate to a ketone followed by base-mediated alkylation or fluorination was a possibility did not give selective difluorination or dimethylation. See Supporting Information for details

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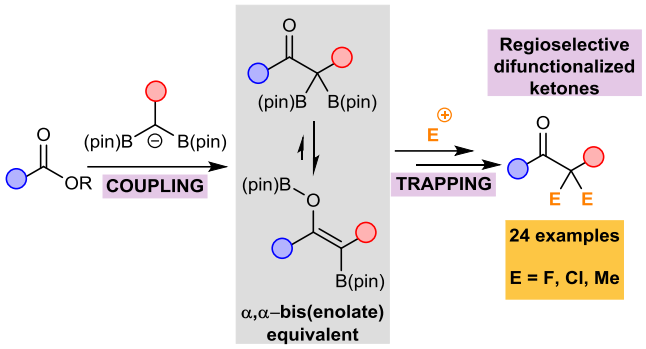
O
OR
(pin)B
B(pin)
COUPLING
(pin)B
B(pin)
α,α–bis(enolate) equivalent
E
TRAPPING
E E
Regioselective difunctionalized ketones
24 examples
E = F, Cl, Me