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Beyond Benzyl Grignards: Facile Generation of Benzyl Carbanions from Styrenes

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Abstract

The facile generation of benzyl anion equivalents from styrenes has been achieved. A Cu-catalyzed hydroboration is used in conjunction with sterically-induced cleavage of the C-B bond with *t*BuOK. Quenching this reactive intermediate with heterocumulene electrophiles, including CO₂, CS₂, isocyanates and isothiocyanates, yields benzylic C-C bond formation. The utility of this methodology was demonstrated in a synthesis of the non-steroidal anti-inflammatory drug (+)-flurbiprofen.

Keywords

carboxylation; cleavage reaction; benzyl anion; Cu catalysis; cascade reactions

Introduction

The reaction of a carbanion with an electrophile is one of the most general approaches employed for the formation of new C-C bonds.^[1] However, certain types of carbanionic species are difficult or inconvenient to prepare; hence, many synthetic chemists opt for more indirect approaches to construct the desired bonds. An excellent example is the benzyl anion, which could undergo reaction with heterocumulene electrophiles to yield a number of valuable bioactive molecules (Figure 1). However, the generation of these reactive species is far from trivial and suffers from more than just the expected functional group incompatibility. Direct deprotonation at a benzylic position often leads to competing metallation of the aromatic ring, while the oxidative additions of metals, including Mg, Zn, Cd and Mn, to benzyl halides are problematic due to the competitive formation of bibenzyl

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products.^{[2],[3]} Thus, the formation of benzyl carbanions has traditionally relied either on the use of toxic main-group precursors, including benzylselenides, benzylstannanes, benzyltellurides and benzylmercury compounds, or on the cleavage of benzyl oxygen and benzyl-sulfur bonds with lithium.^{[2g],[4],[5]}

Results and Discussion

A more convenient and environmentally friendly approach would involve generating a benzyl anion from an olefin precursor, perhaps *via* the intermediacy of a benzyl boronic ester. This could minimize single-electron pathways and the subsequent formation of homocoupling by-products that plague current methods. Benzyl carbons have been previously functionalized by the treatment of benzyl boronic esters with strong bases to give borates, which undergo subsequent reaction with a variety of electrophiles.^[6] These elegant methods developed by Matteson, Aggarwal, Crudden and others rely on the use of pyrophoric and, in some cases, very specific, organolithium bases. The desired products cannot be accessed directly from the styrene; however, the transfer of the chirality from an enantioenriched boronic ester to the product with excellent fidelity is a nice feature of these systems.^[6] In our case, the products of interest contain highly acidic protons at the benzylic position, which obviates the need for an asymmetric approach. In fact, on an industrial scale, flurbiprofen and ibuprofen are prepared and utilized as the racemates. If resolution is necessary, flurbiprofen can be treated with (*R,R*)-thiomine and the undesired enantiomer recycled.^[7] Currently, this approach is much more economical than utilizing existing asymmetric syntheses of the molecule.

We hypothesized that C-C bond formation at a benzyl carbon might be facilitated under mild conditions using the combination of a bulky boronic ester and a bulky alkoxide base. Attack of the base on the boron of the boronic ester would generate the boronate, which could then undergo heterolytic C-B bond cleavage to generate a highly reactive benzyl carbanion.^[8] Initial proof-of-principle was provided by treatment of a primary benzylic boronic ester with potassium *tert*-butoxide in the presence of CO₂ (eq 1). Continued experimentation demonstrated that the Cu species was not necessary to promote the carboxylation reaction. In addition, this transformation proved to be chemoselective, as a non-benzylic boronic ester did not yield the desired carboxylic acid product (eq 2). In this paper, we report the generation and C-C bond-forming reactions of highly reactive benzyl anion equivalents from styrenes using a one-pot Cu-catalyzed hydroboration followed by simple treatment with KO^tBu and a heterocumulene electrophile.

(1)

(2)

A secondary pinacol-based boronic ester **1a**, accessed from a Cu-catalyzed Markovnikov hydroboration of 1-vinylnaphthalene, was chosen for initial studies to determine if sterically induced C-B bond cleavage to yield a benzyl anion could be accomplished (Table 1).^[9] Yun and co-workers have described an enantioselective version of this highly regioselective hydroboration reaction, but we were able to employ CuCl in conjunction with a bis(diphenylphosphino)benzene (dppbz) ligand to accomplish the racemic reaction (see the Experimental and Supporting Information for further details). CO₂ was employed as the electrophile, as this readily available and inexpensive C1 source would lead to the formation of phenylacetic acids such as **2a**.^[10] The identity of both the anion and the cation proved important. NaOtBu (entry 1) gave incomplete conversion, while LiOtBu was completely ineffective (data not shown). KOtBu was the superior base (entries 5-10), with KHMDS (entry 2) giving none of the desired **2a**. The addition of the appropriate crown ethers to the reaction mixture did not improve the results. A variety of fluoride sources known to form boronate complexes from boronic esters (KF, TBAF, TASF and CsF, entry 3) were also unsuccessful, perhaps due to their lack of steric bulk. The optimal solvents were ethereal in nature, with diethyl ether at -40 °C resulting in an 86% yield of **2a** (entry 5) and THF a 75% yield (entry 6). Dioxane and DME gave **2a** in moderate yields, but were not as effective as THF or diethyl ether. Noticeable temperature effects were also apparent, particularly in relation to the amount of protodeboronated **3a** that was produced in the reaction.^[11]

Although conversion to **2a** was observed at temperatures as low as -78 °C (entry 7), complete conversion of the starting material did not occur until the temperature reached -15 °C (entry 8). The increase in conversion at higher temperatures (entries 8-9) came at the expense of increased amounts of by-product **3a**, which resulted from the deprotonation of the acidic proton of the product **2a** by unreacted anionic species present in the mixture. With this protodeboronation pathway in mind, the optimal reaction conditions utilized base-substrate mixing at room temperature followed by cooling the solution to -78 °C before addition of CO₂. This minimized the undesired protodeboronation and provided higher and more consistent yields in subsequent studies.

With an optimized method in hand for the carboxylation of the benzylic boronic esters, the scope of the reaction was explored. Both 1- and 2-naphthylene-derived boronic esters **1a** and **1b** (Table 2, entries 1 and 2) were converted to the corresponding carboxylic acids in 82% and 75% yields, respectively. A tertiary boronic ester **1c** (entry 3) was converted smoothly to the tertiary carboxylic acid **2c** in good yield. It was not necessary to utilize a terminal olefin, as additional substitution at the β-position of the olefin was tolerated (entry 4). Other aromatic systems, including those based on biphenyl systems (entries 7 and 8), successfully gave the carboxylic acids. The success of the carboxylation was greatly improved using electron-withdrawing groups on the styrenyl and phenanthryl systems (entries 5-10). Ketone

and ester groups survived the reaction conditions, provided the temperature of base-substrate mixing was lowered (entries 5 and 9).

The simplicity of the carboxylation conditions allowed it to be telescoped with a Cu-catalyzed hydroboration to achieve a convenient hydrocarboxylation process (Table 3).^{[9a],[12]} The hydroboration was conducted using either toluene or THF as the solvent, then the reaction mixture was transferred *via* cannula to a solution of KO^tBu in THF at the appropriate temperature. Alternatively, the KO^tBu could be added to the hydroboration mixture to achieve a one-pot process. Gratifyingly, the carboxylation was compatible with the hydroboration process and the overall yields for the two-step, one-pot reaction approached those observed for the one-step conversion of the isolated boronic ester to the carboxylic acid product.

Other heterocumulenes, including isocyanates, isothiocyanates, and CS₂, were suitable electrophiles for the reaction (Table 4). Conditions for the CO₂ carboxylation could be extended to CS₂ for the preparation of dithiocarboxylic acids in good isolated yields (entry 1). Reactions with isothiocyanates (entries 2-4) and isocyanates (entries 5-8) generally proceeded in high yields and did not require cooling the reaction to -78 °C prior to electrophile addition. Although isothiocyanates reacted smoothly with the 4-CO₂Me substrate at -78 °C (entries 2-4, compounds **5c**, **5f** and **5i**), isocyanates tended to competitively form oligomers, resulting in diminished yields (entries 5-8, compounds **6c**, **6f**, **6i** and **6l**). These functionalizations could also be accomplished in a single pot from the styrene precursors, as illustrated for the syntheses for **4b** (entry 1), **5a** (entry 2) and **6a** (entry 5).

Finally, alkyl and benzyl halides were suitable electrophiles for benzylic functionalization (Table 5). MeI, *i*PrBr and BnBr, were all successfully coupled to **1a** in yields of 60%, 59% and 67%, respectively. In the case of *i*PrBr (entry 2), this represented a convenient approach to the coupling of two secondary carbons at a benzylic position using an inexpensive Cu catalyst.

Other electrophiles, including aldehydes, ketones, ketenes and Bestmann's ylide (Ph₃P=C=C=O), exhibited varying degrees of success in reactions with the anionic benzyl species generated from **1a**.^[13] The reaction of the benzyl anion with ketones and aldehydes did not result in exclusive addition to the carbonyl, but rather in significant competing formation of the enolate. Oligomerization was observed in all attempts to utilize ketenes or Bestmann's ylide as the electrophile.

The utility of our methodology was demonstrated in a short synthesis of flurbiprofen (Scheme 1). This molecule is a non-steroidal anti-inflammatory drug (NSAID) for the treatment of the inflammation and pain caused by osteoarthritis and rheumatoid arthritis.^[14] (*R*)-Flurbiprofen has been considered as a treatment for metastatic prostate cancer and analogues of this molecule have been explored for the treatment of Alzheimer's disease.^{[15],[16]} The commercially available 4-bromo-2-fluorobiphenyl was cross-coupled with a vinyl boronic ester to yield the olefin precursor for the key reaction in 91% yield. Our

one-pot Cu-catalyzed hydroboration/carboxylation proceeded in 83% yield to provide flurbiprofen in a three-step, two-pot process from a commercially available starting material.

The apparent generation of a highly reactive benzylic carbanion using KO^tBu as a relatively weak base was quite surprising. The presence of the boronic ester might lower the pK_a of the benzylic proton sufficiently to allow direct deprotonation by KO^tBu. However, the conversion of a tertiary boronic ester **1c** to the corresponding carboxylic acid **2c** (Table 1, entry 3) occurred in good yield. Additionally, when an enantioenriched tertiary boronic ester **11** was subjected to the reaction conditions, racemic **12** was obtained (eq 3), indicating significant cleavage of the C-B bond prior to electrophile attack. Additional evidence that the reaction proceeded through a benzyl carbanionic species were the improved yields obtained with substrates bearing electron-withdrawing groups on the aromatic ring. This suggested that stabilization of a benzyl anion was important to the success of the reaction.

(3)

A proposed polar mechanism is illustrated in Scheme 2.^[17] Reaction of the base with the boron of **13** yields the expected boronate complex **14**. A sterically-induced cleavage of the C-B bond would give the presumed benzyl anion **15**, which then reacts rapidly with the electrophile. The necessity of employing 2 equivalents of base is not clear; however, the formation of **17** may help to facilitate the reaction by driving the equilibrium in the desired direction.

Conclusion

In conclusion, a convenient method for generating benzyl anions from styrenes has been demonstrated. This approach avoids the tedious and often capricious preparation of secondary and tertiary benzylic Grignards/organolithiums and exhibits greater functional group tolerance. The mild nature of the method allows for a one-pot transformation of styrene derivatives to a number of valuable motifs, including phenylacetic acids and amides. A three-step, two-pot synthesis of flurbiprofen from commercially available starting materials was accomplished in 76% overall yield, demonstrating the utility of the method. The chemoselective nature of the sterically-induced bond cleavage could also prove a powerful method for sequential transformations of molecules containing multiple C-B bonds obtained through well-precedented diborylations of olefins and allenes.^[18] Future work is focused on the employing this method in diastereoselective tandem one-pot diborylation/functionalization reactions of olefins, dienes and allenes.

Experimental Section

General Procedure for the transition metal-free carboxylation of benzyl boronic esters

KOtBu (2.20 mmol, 2.2 equiv) and THF (8 mL) were loaded into a 100 mL Schlenk flask under an inert atmosphere. The flask was cooled to the desired temperature (rt, -45 °C, or -78 °C) before the boronic ester (1.0 mmol, 1.0 equiv) was added *via* cannula or syringe as a solution in THF (2 mL). The reaction mixture was stirred for 10 min, then cooled to -78 °C. The flask was evacuated and backfilled with CO₂ three times (CO₂ was supplied using a Schlenk line). The flask was allowed to warm to room temperature under one atmosphere of CO₂ and stirred for 3 h. The reaction was then quenched with 1 M HCl and extracted with several portions of dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and the volatiles removed under reduced pressure. The crude residue could be purified by column chromatography on silica gel (hexanes/ethyl acetate gradient).

In some cases, the insolubility of the carboxylic acid in the organic phase necessitated the addition of several equivalents of methyl iodide prior to the aqueous quench. The corresponding methyl ester was then isolated by extraction and purified by column chromatography on silica gel.

Procedure for the one-pot hydrocarboxylation of styrenes via a Cu-catalyzed hydroboration/carboxylation

In the glovebox, a mixture of CuCl (0.03 equiv), bisdiphenylphosphinobenzene (0.033 equiv), and NaOtBu (0.03 equiv) was suspended in scrupulously dry toluene (0.33 M). The flask was tightly sealed and the mixture was removed from the glovebox and stirred for 10 min at rt. 4,4,5,5-Tetramethyl-[1,3,2]dioxaborolane (1.1 equiv) was added and the reaction mixture stirred for an additional 10 min. The desired styrene substrate (1 equiv) was introduced into the reaction as a solution in toluene *via* syringe. The reaction flask was placed in a pre-heated oil bath at 65 °C and left to stir overnight. The mixture was then diluted with THF to yield an overall solvent composition of 3:2 toluene: THF. A solution of KOtBu (2.2 equiv) in THF (0.22 M) was added and the reaction mixture stirred for 15 min. The flask was cooled to -78 °C, evacuated and backfilled with CO₂ three times (CO₂ was supplied through a Schlenk line). The mixture was warmed back to room temperature, stirred for 1 h, quenched with 1 M HCl and then extracted with several portions of dichloromethane. The combined organic layers were dried over Na₂SO₄ and the volatiles removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/ethyl acetate gradient).

General procedure for the preparation of dithiocarboxylic acids from benzyl boronic esters

KOtBu (2.20 mmol, 2.2 equiv) and THF (8 mL) were placed in a 100 mL Schlenk flask under an inert atmosphere. The flask was cooled to the appropriate temperature (rt, -45 °C, or -78 °C) before the boronic ester (1.0 mmol, 1.0 equiv) was added *via* cannula or syringe in THF (2 mL). The solution was allowed to stir for 10 min. The flask was then cooled to -78 °C and the reaction mixture treated with CS₂ (5.00 mmol, 5 equiv). The flask was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with 5% NH₄OH solution and extracted with one portion of diethyl ether. The aqueous phase was

acidified with concentrated HCl and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na₂SO₄ and the volatiles removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/ethyl acetate gradient).

General procedure for the reaction of isothiocyanates or isocyanates with benzyl boronic esters

KOtBu (2.20 mmol, 2.2 equiv) and THF (8 mL) were loaded into a 100 mL Schlenk flask under an inert atmosphere. The flask was cooled to the appropriate temperature (rt, -45 °C, or -78 °C) and the boronic ester (1.0 mmol, 1.0 equiv) was added *via* cannula or syringe in THF (2 mL). The solution was allowed to stir for 10 min, then held at the temperature necessary to generate the reactive anionic intermediate. The isothiocyanate or isocyanate (1.10 mmol, 1.10 equiv) was then rapidly injected into the reaction mixture either neat or as a THF solution. The solution was stirred for 1 min prior to the addition of saturated NH₄Cl (10 mL). The aqueous mixture was extracted with several portions of dichloromethane, the combined organic layers washed with brine, dried over Na₂SO₄ and the volatiles removed under reduced pressure. The crude residue was then purified by column chromatography on silica gel or was recrystallized from hexanes/ethyl acetate.

General Procedure for the reaction of alkyl halides with benzyl boronic esters

The boronic ester (0.4 mmol, 1.0 equiv) was dissolved in dry THF (4 mL) and treated with KOtBu (0.880 mmol, 2.2 equiv). The solution was stirred at room temperature for 10 min prior to injection of the alkyl halide (2.0 mmol, 5 equiv). The solution was stirred for 1 min before an aliquot of saturated aqueous NH₄Cl was added to quench the reaction. The reaction mixture was extracted with portions of dichloromethane, the combined organic layers washed with brine, dried over MgSO₄ and filtered. The volatiles were removed under reduced pressure and the residue was purified by column chromatography (hexanes/ethyl acetate gradient). The characterization data of the isolated products were consistent with reported characterization data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Bioactive molecules containing benzylic functionalization.

[a] 1.2 equiv HBpin, 3.0 mol % CuCl, 3.0 mol % 1,2-diphenylphosphinobenzene, 6.0 mol % NaOtBu, > 95:5 regioselectivity.

Scheme 1. A short synthesis of (+)-flurbiprofen.

Scheme 2. Potential polar mechanism for the sterically-induced bond cleavage.

Table 1Initial optimization of the benzylic anion formation and quenching with CO₂.

Entry	Base	Solvent	Temperature	1a:2a:3a ^[a]
1	NaOtBu	THF	rt	65:17:trace
2	KHMDS	THF	rt	70:0:30
3	CsF	THF	rt	100:0:0
4	KOtBu	hexane	0 °C	65:16:18
5	KOtBu	Et ₂ O	-40 °C	trace:86:10
6	KOtBu	THF	-40 °C	9:75:16
7	KOtBu	THF	-78 °C	25:62:12
8	KOtBu	THF	-15 °C	trace:60:23
9	KOtBu	THF	-0 °C	trace:56:26
10	KOtBu	THF	rt, -78 °C	0:82:trace

^[a] ¹H NMR yields based on bibenzyl as the internal standard.

Table 2Substrate scope for the sterically induced C-B bond cleavage using CO₂ as the electrophile. ^[a]The entire reaction was performed at -78 °C.^[b]The acid was esterified prior to isolation.^[c]The entire reaction was performed at -45 °C.

Table 3

One-pot hydroboration/carboxylation of styrenes.

^[a] 1.2 equiv HBpin, 3.0 mol % CuCl, 3.0 mol % 1,2-diphenylphosphinobenzene, 6.0 mol % NaOtBu, THF.

Table 4

Other heterocumulene electrophiles.

$\text{Ar}-\text{CH}(\text{Me})-\text{BPin} \xrightarrow[\text{rt, THF}]{\text{2.2 equiv KO}^t\text{Bu, then CS}_2, \text{R-NCO, or R-NCS}} \text{Ar}-\text{CH}(\text{Me})-\text{C}(\text{X})(\text{YR})$				
Entry	Electrophile	Product	Ar	Yield
1	CS ₂		4a 1-naphthyl	81%
			4b 4-PhC ₆ H ₄	66%
			4b 4-PhC ₆ H ₄	62% ^[a]
			4c 4-CO ₂ MeC ₆ H ₄	81%
2	Ph-NCS		5a 1-naphthyl	92%
			5a 1-naphthyl	81% ^[a]
			5b 4-PhC ₆ H ₄	90%
			5c ^[b] 4-CO ₂ MeC ₆ H ₄	89%
3	<i>p</i> -MeOC ₆ H ₄ -NCS		5d 1-naphthyl	91%
			5e 4-PhC ₆ H ₄	91%
			5f ^[b] 4-CO ₂ MeC ₆ H ₄	81%
4	<i>p</i> -FC ₆ H ₄ -NCS		5g 1-naphthyl	88%
			5h 4-PhC ₆ H ₄	85%
			5i ^[b] 4-CO ₂ MeC ₆ H ₄	80%
5	Ph-NCO		6a 1-naphthyl	81%
			6a 1-naphthyl	70% ^[a]
			6b 4-PhC ₆ H ₄	74%
			6c ^[b] 4-CO ₂ MeC ₆ H ₄	44%
6	<i>p</i> -MeOC ₆ H ₄ -NCS		6d 1-naphthyl	87%
			6e 4-PhC ₆ H ₄	83%
			6f ^[b] 4-CO ₂ MeC ₆ H ₄	46%
7	<i>p</i> -FC ₆ H ₄ -NCS		6g 1-naphthyl	91%
			6h 4-PhC ₆ H ₄	87%
			6i ^[b] 4-CO ₂ MeC ₆ H ₄	47%
8	Cy-NCO		6j 1-naphthyl	92%
			6k 4-PhC ₆ H ₄	83%
			6l ^[b] 4-CO ₂ MeC ₆ H ₄	26%

^[a]Yield for the one-pot reaction using styrene as the substrate.^[b]Reaction conducted at -78 °C.

Table 5

Alkyl halide electrophiles.^[a] ^[a] NMR yield using 1,1,2,2-tetrachloroethane as an internal standard.