CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200642

Beyond Benzyl Grignards: Facile Generation of Benzyl Carbanions from Styrenes

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Abstract: Benzylic functionalization is a convenient approach towards the conversion of readily available aromatic hydrocarbon feedstocks into more useful molecules. However, the formation of carbanionic benzyl species from benzyl halides or similar precursors is far from trivial. An alternative approach is the direct reaction of a styrene with a suitable coupling partner, but these reactions often involve the use of precious-metal transition-metal catalysts. Herein, we report the facile and convenient generation of reactive benzyl anionic species from styrenes. A Cu^{I}-catalyzed Markovnikov hydroboration of the styrenic double bond by using a bulky pinacol borane source is followed by treatment with KO*t*Bu to facilitate a sterically induced cleavage of the C–B bond to produce a benzylic carbanion. Quenching this intermediate with a variety of electrophiles, including CO_2, CS_2, isocyanates, and isothiocyanates, promotes C–C bond formation at the benzylic carbon atom. The utility of this methodology was demonstrated in a three-step, two-pot synthesis of the nonsteroidal anti-inflammatory drug (±)-flurbiprofen.

Keywords: benzyl anion · carbanions · carboxylation · cleavage reactions · Cu catalysis · domino 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] Certain types of carbanionic species are difficult or inconvenient to prepare and many synthetic chemists opt for more indirect approaches to construct these bonds. An excellent example is the benzyl anion, which could undergo reactions with heteroallene 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, and the oxidative additions of metals, including Mg, Zn, Cd, and Mn, to benzyl halides are problematic due to the competitive formation of bibenzyl products.[2,3] Thus, the formation of benzyl carbanions has traditionally relied 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]

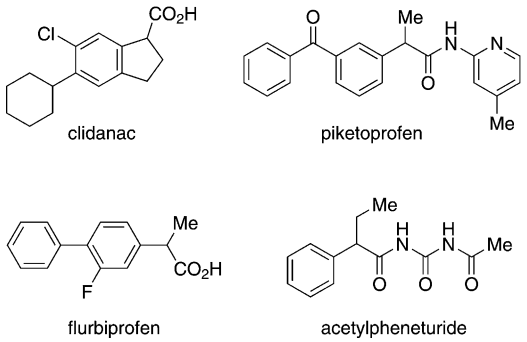

Figure 1. Bioactive molecules containing benzylic functionalization.

Results and Discussion

A more convenient and environmentally friendly approach for the synthesis of benzyl carbanions might involve generating a benzyl anion from an olefin precursor, perhaps via a benzyl boronic ester intermediate. This could minimize single-electron pathways and the subsequent formation of homocoupling byproducts that plague current methods. Benzyl carbon atoms have been previously functionalized by the treatment of benzyl boronic esters with strong bases to give borates, which undergo subsequent reactions 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 styrene; however, the transfer of chirality from an enantioenriched boronic ester to the product with excel-

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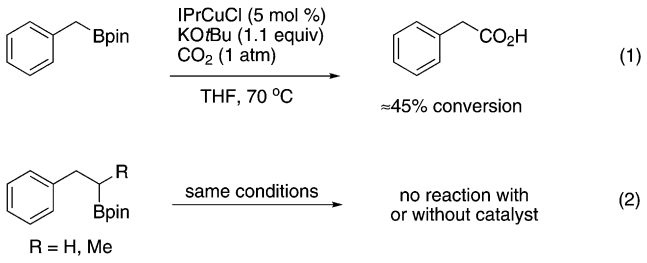
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200642.

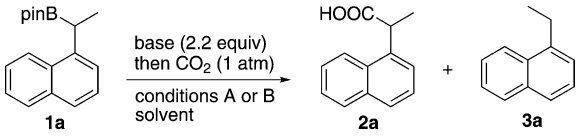
lent fidelity is a nice feature of these systems.[6] In our case, the products of interest contain highly acidic protons at the benzylic position, which avoids the need for an asymmetric approach. In fact, on an industrial scale, flurbiprofen and ibuprofen are prepared and utilized as the racemates. If resolution is necessary, flurbiprofen can be treated with (*R,R*)-thiomicamine and the undesired enantiomer is 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 by using the combination of a bulky boronic ester and a bulky alkoxide base. Attack of the base at the boronic ester boron atom would generate the boronate, which could then undergo heterolytic C–B bond cleavage to generate a highly reactive benzyl carbanion.[8] Initial confirmation was provided by the treatment of a primary benzylic boronic ester with potassium *tert*-butoxide (KO*t*Bu) in the presence of CO_2 [Eq. (1); Bpin = pinacolborane (4,4,5,5-tetramethyl-1,3,2-dioxaborolane), IPr = 2,6-di(isopropylphenyl)imidazolium]. 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)]. Herein, we report the synthesis and C–C bond-forming reactions of highly reactive benzyl anion equivalents from styrenes by using a one-pot Cu-catalyzed hydroboration followed by simple treatment with KO*t*Bu and a heteroallene electrophile.



A secondary pinacol-based boronic ester **1a**, accessed from a Cu-catalyzed Markovnikov hydroboration of 1-vinylnapthalene, was chosen for initial studies to determine whether sterically induced C–B bond cleavage to produce 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 Section and Supporting Information for further details). CO_2 was employed as the electrophile because 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. NaO*t*Bu (Table 1, entry 1) resulted in the incomplete conversion of **1a** to the product,

Table 1. Initial optimization of the benzylic anion formation and quenching with CO_2.



Entry	Base	Solvent	*T* [°C]	Yield (**1a**/**2a**/**3a**) [%][a]
1	NaO*t*Bu	THF	RT	65:17:trace
2	KHMDS	THF	RT	70:0:30
3	CsF	THF	RT	100:0:0
4	KO*t*Bu	hexane	0	65:16:18
5	KO*t*Bu	Et_2O	−40	trace:86:10
6	KO*t*Bu	THF	−40	9:75:16
7	KO*t*Bu	THF	−78	25:62:12
8	KO*t*Bu	THF	−15	trace:60:23
9	KO*t*Bu	THF	0	trace:56:26
10	KO*t*Bu	THF	RT, −78	0:82:trace

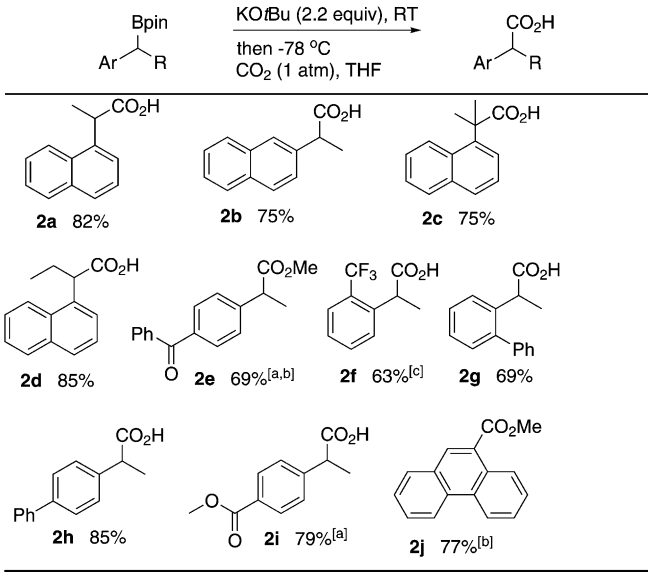
[a] Yields were derived from ^{1}H NMR spectroscopy and are based on bibenzyl as the internal standard.

whereas LiO*t*Bu was completely ineffective (data not shown). KO*t*Bu was the superior base (Table 1, entries 5–10), with the use of potassium hexamethyldisilazide (KHMDS) (Table 1, entry 2) providing none of the desired **2a** product. 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, tetra-*n*-butylammonium fluoride (TBAF), tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and CsF, Table 1, entry 3) were also unsuccessful, perhaps due to their lack of steric bulk. The optimal solvents for the reaction were ethereal in nature, with the use of diethyl ether at −40 °C providing an 86% yield of **2a** (Table 1, entry 5), and the use of THF providing a yield of 75% (Table 1, entry 6). Dioxane and 1,2-dimethoxyethane (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 (Table 1, entry 7), complete conversion of the starting material did not occur until the temperature reached −15 °C (Table 1, entry 8). The increase in conversion at higher temperatures (Table 1, entries 8 and 9) came at the expense of an increased amount of byproduct **3a**, which resulted from the removal 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 CO_2 (Table 1, entry 10). 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** were converted to the corresponding carboxylic

Table 2. Substrate scope for the sterically induced C–B bond cleavage by using CO_2 as the electrophile.



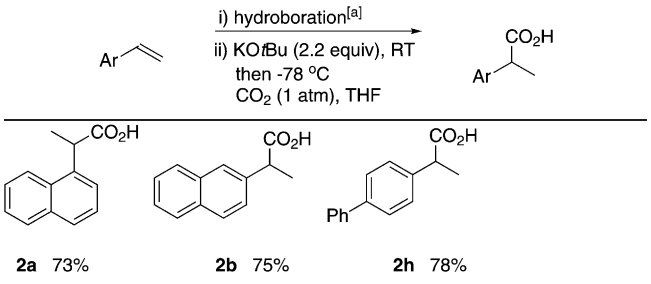
[a] The entire reaction was performed at −78 °C. [b] The acid was esterified prior to isolation. [c] The entire reaction was performed at −45 °C.

acids **2a** and **2b** in 82 and 75% yields, respectively (Table 2). A tertiary boronic ester **1c** was also converted smoothly to the tertiary carboxylic acid **2c** (Table 2) in good yield. Additional substitution at the β-position of the olefin was tolerated, as shown by the formation of **2d** (Table 2); thus it was not necessary to utilize a terminal olefin. Other aromatic systems based on biphenyl systems successfully gave the carboxylic acids **2g** and **2h** (Table 2). The success of the carboxylation was greatly improved by using electron-withdrawing groups on the styrenyl and phenanthryl systems, examples include **2e**–**2j** (Table 2). Ketone and ester groups survived the reaction conditions provided the temperature of the base–substrate mixing step was lowered (products **2e** and **2i**, Table 2).

The simplicity of the carboxylation conditions allowed the reaction to be telescoped with a Cu-catalyzed hydroboration to achieve a convenient hydrocarboxylation process (Table 3).[9a,12] The hydroboration was conducted by using either toluene or THF as the solvent, then the reaction mixture was transferred by cannula to a solution of KO*t*Bu in THF at the appropriate temperature. Alternatively, the KO*t*Bu was 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 into the carboxylic acid product.

Other heteroallenes, including isocyanates, isothiocyanates, and CS_2, were suitable electrophiles for the reaction (Table 4). Conditions for the CO_2 carboxylation could be extended to CS_2 for the preparation of dithiocarboxylic acids in good isolated yields (Table 4, entry 1). Reactions with isothiocyanates (Table 4, entries 2–4) and isocyanates (Table 4, entries 5–8) generally proceeded in high yields and did not require cooling to −78 °C prior to electrophile addition. Although isothiocyanates reacted smoothly with the 4-CO_2Me-containing substrate at −78 °C (Table 4, entries 2–4, compounds **5c**, **5f**, and **5i**), isocyanates tended to competitively form oligomers, which resulted in diminished yields (Table 4, 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 of **4b** (Table 4, entry 1), **5a** (Table 4, entry 2), and **6a** (Table 4, entry 5).

Table 3. One-pot hydroboration/carboxylation of styrenes.

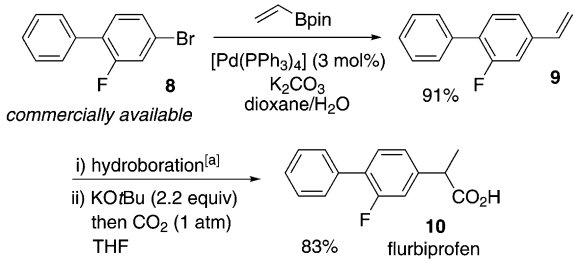


[a] HBpin (1.2 equiv), CuCl (3.0 mol%), bis(diphenylphosphino)benzene (DPPBz, 3.0 mol%), NaO*t*Bu (6.0 mol%), THF.

Finally, alkyl and benzyl halides were also suitable electrophiles for benzylic functionalization (Table 5). MeI, *i*PrBr, and BnBr (Bn = benzyl) were all successfully coupled to **1a** in yields of 60, 59, and 67%, respectively (Table 5, compounds **7a**, **7b**, and **7c**). In the case of *i*PrBr, this represented a convenient approach to the coupling of two secondary carbon atoms at a benzylic position by using an inexpensive Cu catalyst.

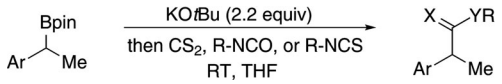
Other electrophiles, including aldehydes, ketones, ketenes, and the Bestmann ylide ($Ph_3P{=}C{=}C{=}O$), exhibited varying degrees of success in reactions with the anionic benzyl species generated from **1a**.[13] The reaction of the benzyl anion with ketones and aldehydes did not result in exclusive addition to the carbonyl, but rather in the significant competing formation of the enolate. Oligomerization was observed in all attempts to utilize ketenes or the Bestmann ylide as the electrophile.

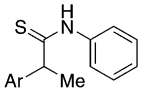
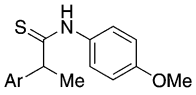
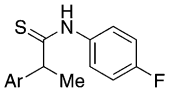
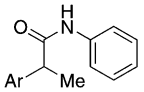
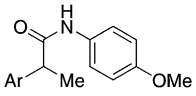
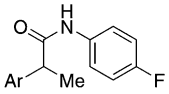
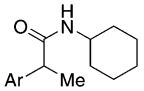
The utility of our methodology was demonstrated in a short synthesis of flurbiprofen (Scheme 1). This molecule



Scheme 1. A short synthesis of (±)-flurbiprofen. a) HBpin (1.2 equiv), CuCl (3.0 mol%), bis(diphenylphosphino)benzene (3.0 mol%), NaO*t*Bu (6.0 mol%), >95:5 regioselectivity.

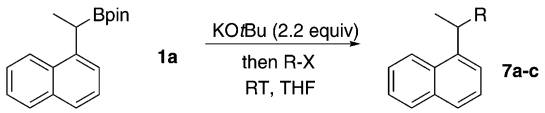
Table 4. One-pot hydroboration/carboxylation of other heteroallene electrophiles.

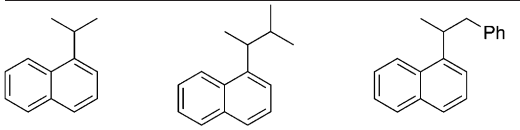


Entry	Electrophile	Product		Ar	Yield [%]
1	CS_2		**4a**	1-naphthyl	81
			4b	4-PhC_6H_4	66
			4b	4-PhC_6H_4	62[a]
			4c	4-$CO_2MeC_6H_4$	81
2	Ph-NCS		**5a**	1-naphthyl	92
			5a	1-naphthyl	81[a]
			5b	4-PhC_6H_4	90
			5c[b]	4-$CO_2MeC_6H_4$	89
3	*p*-$MeOC_6H_4$-NCS		**5d**	1-naphthyl	91
			5e	4-PhC_6H_4	91
			5f[b]	4-$CO_2MeC_6H_4$	81
4	*p*-FC_6H_4-NCS		**5g**	1-naphthyl	88
			5h	4-PhC_6H_4	85
			5i[b]	4-$CO_2MeC_6H_4$	80
5	Ph-NCO		**6a**	1-naphthyl	81
			6a	1-naphthyl	70[a]
			6b	4-PhC_6H_4	74
			6c[b]	4-$CO_2MeC_6H_4$	44
6	*p*-$MeOC_6H_4$-NCO		**6d**	1-naphthyl	87
			6e	4-PhC_6H_4	83
			6f[b]	4-$CO_2MeC_6H_4$	46
7	*p*-FC_6H_4-NCO		**6g**	1-naphthyl	91
			6h	4-PhC_6H_4	87
			6i[b]	4-$CO_2MeC_6H_4$	47
8	Cy-NCO		**6j**	1-naphthyl	92
			6k	4-PhC_6H_4	83
			6l[b]	4-$CO_2MeC_6H_4$	26

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

Table 5. One-pot hydroboration/carboxylation of alkyl halide electrophiles.[a]





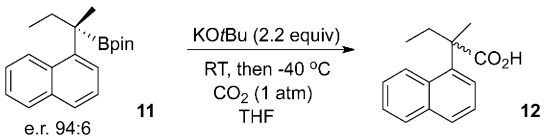
7a 60% **7b** 59% **7c** 67%

[a] Yields were derived from ^1H NMR spectroscopy and are based on 1,1,2,2-tetrachloroethane as an internal standard.

is a nonsteroidal anti-inflammatory drug (NSAID) used for the treatment of the inflammation and pain caused by osteroarthritis 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 (**8**) was cross-coupled with a vinyl boronic ester to give a 91% yield of the olefin precursor (**9**) for the key reaction step. Our one-pot Cu-catalyzed hydroboration/carboxylation proceeded in 83% yield to provide flurbiprofen (**10**) in a three-step, two-pot process from a commercially available starting material (Scheme 1).

The apparent generation of a highly reactive benzylic carbanion by using KO*t*Bu 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*t*Bu. However, the conversion of a tertiary boronic ester **1c** to the corresponding carboxylic acid **2c** (Table 1) occurred in good yield. Additionally, if 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 included the improved product yields obtained from substrates with electron-withdrawing groups on the aromatic ring. This suggested that stabilization of a benzyl anion was important to the success of the reaction.

A proposed polar mechanism for the sterically induced bond cleavage is illustrated in Scheme 2.[17] Reaction of the base with the boron atom in **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 two equivalents of base is not

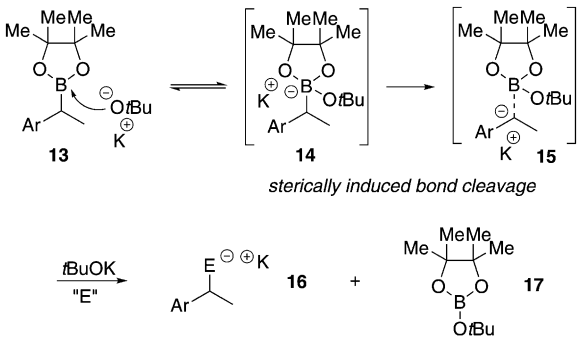


(3)

clear; however, the formation of **17** may help to facilitate the reaction by driving the equilibrium in the desired direction.

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 Grignard or organolithium reagents, and



Scheme 2. A potential polar mechanism for sterically induced bond cleavage.

exhibits greater functional-group tolerance. The mild nature of the method allows 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 commerically available starting materials was accomplished in 76% overall yield, demonstrating the utility of this method. The chemoselective nature of the sterically induced bond cleavage could also prove to be a powerful method for sequential transformations of molecules containing multiple C–B bonds obtained through previously described diborylations of olefins and allenes.[18] Future work is focused on employing this method in diasteroselective tandem one-pot diborylation/functionalization reactions of olefins, dienes, and allenes.

Experimental Section

General procedures:

Transition-metal-free carboxylation of benzyl boronic esters: KO*t*Bu (2.20 mmol, 2.2 equiv) and THF (8 mL) were placed in a Schlenk flask (100 mL) under an inert atmosphere. The flask was cooled to the desired temperature (RT, −45 or −78 °C) before a solution of the boronic ester (1.0 mmol, 1.0 equiv) in THF (2 mL) was added by cannula or syringe. The reaction mixture was stirred for 10 min, then cooled to −78 °C. The flask was evacuated and backfilled with CO_2 three times (CO_2 was supplied by using a Schlenk line). The flask was allowed to warm to room temperature under a CO_2 atmosphere (1 atm) and was stirred for 3 h. The reaction was then quenched with HCl (1 M) and extracted with several portions of dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and the volatile compounds were removed under reduced pressure. The crude residue was 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.

One-pot hydrocarboxylation of styrenes by a Cu-catalyzed hydroboration/carboxylation: In a glovebox, a mixture of CuCl (0.03 equiv), bis(diphenylphosphino)benzene (0.033 equiv), and NaO*t*Bu (0.03 equiv) was suspended in 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 was stirred for an additional 10 min. The desired styrene substrate (1 equiv) in toluene was added by syringe. The reaction flask was placed in a pre-heated oil bath at 65 °C and stirred overnight. The mixture was then diluted with THF to yield an overall solvent composition of 3:2 toluene/THF. A solution of KO*t*Bu (2.2 equiv) in THF (0.22 M) was added and the reaction mixture was stirred for 15 min. The flask was cooled to −78 °C, evacuated, and backfilled with CO_2 three times (CO_2 was supplied through a Schlenk line). The mixture was warmed to room temperature, stirred for 1 h, quenched with HCl(1 M), and then extracted with several portions of dichloromethane. The combined organic layers were dried over Na_2SO_4 and the volatile compounds were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/ethyl acetate gradient).

Preparation of dithiocarboxylic acids from benzyl boronic esters: KO*t*Bu (2.20 mmol, 2.2 equiv) and THF (8 mL) were placed in a Schlenk flask (100 mL) under an inert atmosphere. The flask was cooled to the appropriate temperature (RT, −45 or −78 °C) before a solution of the boronic ester (1.0 mmol, 1.0 equiv) in THF (2 mL) was added by cannula or syringe. The solution was allowed to stir for 10 min. The flask was then cooled to −78 °C and the reaction mixture was treated with CS_2 (5.00 mmol, 5 equiv). The flask was allowed to warm to room temperature and stirred for 1 h. The reaction was quenched with a solution of NH_4OH (5%) and then 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 Na_2SO_4, and the volatile compounds were removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/ethyl acetate gradient).

Reaction of isothiocyanates or isocyanates with benzyl boronic esters: KO*t*Bu (2.20 mmol, 2.2 equiv) and THF (8 mL) were placed in a Schlenk flask (100 mL) under an inert atmosphere. The flask was cooled to the appropriate temperature (RT, −45 or −78 °C) and a solution of the boronic ester (1.0 mmol, 1.0 equiv) in THF (2 mL) was added by cannula or syringe. The solution was allowed to stir for 10 min, then kept 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 mixture was stirred for 1 min prior to the addition of saturated NH_4Cl (10 mL). The aqueous mixture was extracted with several portions of dichloromethane, and the combined organic layers were washed with brine, dried over Na_2SO_4, and the volatile compounds were removed under reduced pressure. The crude residue was then purified by column chromatography on silica gel, or was recrystallized from hexanes/ethyl acetate.

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 KO*t*Bu (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 NH_4Cl was added to quench the reaction. The reaction mixture was extracted with portions of dichloromethane, the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The volatile compounds 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 those reported previously.

Acknowledgements

The authors thank Dr. Charles Fry of the University of Wisconsin–Madison for assistance with NMR spectroscopy. Funding was provided by start-up funds from the University of Wisconsin–Madison. The NMR facilities at UW–Madison are funded by the NSF (CHE-9208463, CHE-9629688) and the NIH (RR08389-01).

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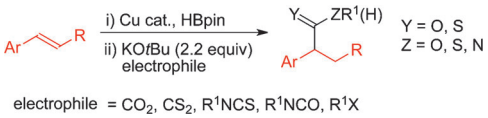
Received: February 27, 2012
Published online: ■■ ▮▮, 2012



Make or break: The facile generation of benzyl anion equivalents from styrenes has been achieved by using a Cu-catalyzed hydroboration in conjunction with sterically induced cleavage of the C–B bond with *t*BuOK. Quenching this reactive intermediate with heteroallene electrophiles yields benzylic C–C bond formation (see scheme), and the utility of this methodology has been demonstrated by a synthesis of the nonsteroidal anti-inflammatory drug (±)-flurbiprofen.

Benzyl Carbanions

*R. D. Grigg, J. W. Rigoli, R. Van Hoveln, S. Neale, J. M. Schomaker** ..... ▮▮▮▮–▮▮▮▮

Beyond Benzyl Grignards: Facile Generation of Benzyl Carbanions from Styrenes