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A Radical Procedure for the Anti-Markovnikov Hydroazidation of Alkenes

Ajoy Kapat, Andreas König, Florian Montermini, and Philippe Renaud*

Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, CH-3012 Bern, Switzerland

Supporting Information

ABSTRACT: A one-pot procedure for the efficient hydroazidation of alkenes involving hydroboration with catecholborane followed by reaction with benzenesulfonyl azide in the presence of a radical initiator is described. The regioselectivity is controlled by the hydroboration step and corresponds in most cases to an anti-Markovnikov regioselectivity. This procedure is applicable to a wide range of alkenes and gives excellent results with 1,2-disubstituted and trisubstituted alkenes.

Amines and their derivatives are privileged structures for drug candidates and are ubiquitous in natural products. The hydroamination of olefins represents a very attractive approach for their preparation.[1] However, this apparently simple procedure remains a challenging transformation despite a tremendous amount of recent research activity in this field. Most reported intermolecular hydroamination processes use transition-metal catalysts.[2] Carreira described a Markovnikov hydrohydrazination and hydroazidation of alkenes involving a hydrocobaltation step.[3] Anti-Markovnikov hydroamination of alkenes is particularly puzzling,[4] and recently, Studer reported a radical-mediated anti-Markovnikov hydroamination of alkenes.[5] The hydroazidation reaction[6] is particularly attractive because of the rich chemistry of organic azides.[7]

Organoboranes are very useful reagents that are easily prepared by hydroboration of alkenes and very efficiently converted into alcohols by oxidative treatment.[8] Extension of this chemistry to the formation of C−N bonds is usually achieved by reacting the organoboranes with alkyl azides.[9] Intra-[10] and intermolecular amination reactions have been reported, but the latter work well only with highly electrophilic *B*-alkyldichloro- and -difluoroboranes (Scheme 1).[9d,11] Other reagents such as chloramine-T and analogues[9e,12] have also been used.[13] In this communication, we report that under carefully conceived conditions, the reaction of alkylboranes with sulfonyl azides follows a radical pathway leading to efficient anti-Markovnikov hydroazidation of alkenes.

We recently reported that *B*-alkylcatecholboranes are extremely useful radical precursors[14] that participate in efficient chain reactions with arenesulfonyl radicals.[15] We have also reported that arenesulfonyl azides are excellent reagents for the azidation of alkyl radicals generated from halides, dithiocarbonates, and Barton esters.[16] In 1982, Ortiz and Larson investigated the reaction of trialkylboranes with arenesulfonyl azides.[17] At that time, they anticipated the formation of sulfonamides according to the mechanism observed with alkyl azides. They were surprised to observe the formation of aryl sulfides and noticed the formation of an intermediate with an IR absorption band at 2100 cm^{-1}. However, no alkyl azide was isolated, and no mechanism was proposed to rationalize this unexpected result.[17]

Our previous results with organoboron compounds and sulfonyl azides encouraged us to investigate the reaction of *B*-alkylcatecholboranes with benzenesulfonyl azide in presence of a radical initiator. The formation of alkyl azides was anticipated. α-Pinene (**1**) was selected as a model substrate for optimization of the reaction conditions. It was hydroborated with 2 equiv of catecholborane (CatBH) in dichloromethane using *N*,*N*-dimethylacetamide (DMA)[18] as a catalyst. After completion of the hydroboration, the excess CatBH was treated with *t*-BuOH, and the solvent was removed. The in situ-generated organoborane was treated at 80 °C with 3 equiv of benzenesulfonyl azide and 0.1 equiv of di-*tert*-butylhyponitrite[19] as a radical initiator (Scheme 2). Three different solvents were tested, and the results are summarized in Table 1. In benzene and 1,2-dichloroethane (DCE), the organoborane was consumed within 30 min, and the desired azide **2** was obtained in moderate yield (entries 1 and 2). In these two solvents, **2** was contaminated with sulfide **3**, and these could not be separated by column chromatography. Since *N*,*N*-dimethylformamide (DMF) proved to be an excellent solvent in the radical allylation of *B*-alkylcatecholboranes,[15d] the next reaction was run in DMF. We were pleased to observe a much cleaner reaction and a higher yield (78% isolated yield; entry 3). Interestingly, the formation of the sulfide **3** was completely suppressed.

The rationale for this dramatic solvent effect is not clear to date. We believe that a sulfurizing reagent is generated by dismutation and decomposition of the chain-reaction side product (benzenesulfinyloxy)catecholborane ($PhSO_2BCat$) (see Scheme 5). DMF may slow the formation of this sulfurizing agent by stabilizing the $PhSO_2BCat$ as a result of its Lewis basic character.[21]

The scope and limitations of the optimized procedure were tested with several alkenes, and the results are summarized in Scheme 3. Cyclohexene afforded cyclohexyl azide (**4**) in 57% isolated yield. The true yield of this transformation was significantly higher (≥75%; see below), but isolation was inefficient because of the volatility of the product. Reactions involving other secondary alkylcatecholboranes generated in situ from the corresponding trisubstituted alkenes were examined. Azide **5** was obtained from 1-phenylcyclohexene in excellent yield (95%)

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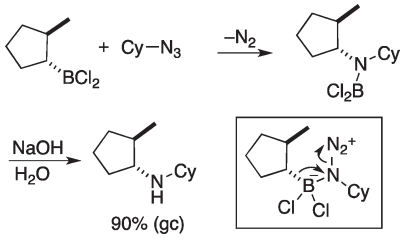
Scheme 1. Reaction of *B*-Alkyldichloroboranes with Alkyl Azides (Cy = Cyclohexyl)[11a]



Scheme 2. Hydroazidation of α-Pinene (1)

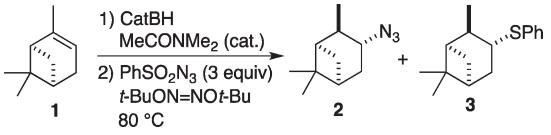


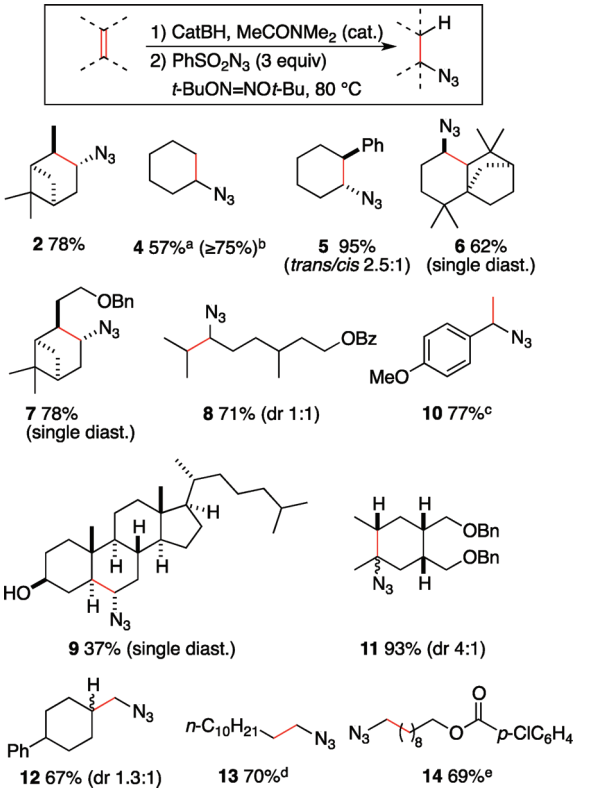
Table 1. Solvent Optimization for the Conversion of 1 to 2 According to Scheme 2

entry	solvent	% yield of **2**	**2**/**3**[b]
1	benzene	54[a]	14:1
2	DCE	61[a]	3:1
3	DMF	78	>50:1[c]

[a] An inseparable mixture of **2** and **3** was isolated; the yield was corrected according to the measured **2**/**3** ratio. [b] Determined by ^{1}H NMR analysis. [c] Compound **2** was isolated as a single diastereomer.

as a 2.5:1 trans/cis mixture of diastereomers. Traces of 1-azido-1-phenylcyclohexane (5%) were also observed, indicating that the hydroboration is not completely regioselective. Isolongifolene, *O*-benzylnopol, and *O*-benzoylcitronellol afforded the expected azides **6**–**8** in 62, 78, and 71% yield, respectively. The reaction worked with unprotected cholesterol, affording azide **9** in moderate yield (37%). Single diastereomers were detected for compound **6**, **7**, and **9**. In these three systems, the reaction took place from the less hindered face of the polycyclic radical intermediate. As anticipated, **8** was obtained as a 1:1 mixture of diastereomers (no 1,4-induction in such an acyclic system would be expected).[22] The reaction with the benzylic alkylcatecholborane obtained by hydroboration of *p*-methoxystyrene using $(Ph_3P)_3RhCl$ as a catalyst[23] led to the remarkable formation of azide **10** in 77% yield with high regioselectivity (21:1). In this case, the Markovnikov addition was achieved with satisfactory selectivity. Interestingly, the Markovnikov cocatalyzed hydroazidation developed by Carreira did not proceed with styrene derivatives.[3b] All attempts to invert the stereoselectivity by using different catalysts or performing an uncatalyzed reaction did not allow inversion of the regioselectivity. Tertiary alkylcatecholboranes obtained by hydroboration of tetrasubstituted alkenes were also investigated. *cis*-4,5-Di(benzyloxymethyl)-1,2-dimethylcyclohex-1-ene affordsed azide **11** in 93% yield as a 16:4:0.8:0.2 mixture of diastereomers. Hydroboration occurred predominantly from the less hindered face anti to the two benzyloxymethyl groups (20:1 anti/syn), and the relative configuration of the azidated carbon atom was determined by a rotating-frame

Scheme 3. Hydroazidation of Olefins[20]



[a] The isolated yield was low because of the volatility of the azide. [b] The actual yield was ≥75% (see Scheme 6). [c] Hydroboration performed with $(Ph_3P)_3RhCl$ as a catalyst. [d] 6:1 mixture of regioisomers, only major shown. [e] Contains unreacted $PhSO_2N_3$, yield corrected according to NMR.

Overhauser effect spectroscopy (ROESY) experiment (see the Supporting Information). A 4:1 diastereoselectivity was observed for the azidation step. On the basis of our results with radicals generated from iodides,[16a] the hydroazidation of terminal olefins (primary alkylcatecholboranes) was expected to be much less efficient. Nevertheless, satisfactory yields were obtained with 4-phenyl-1-methylenecyclohexane (**12**, 67%, dr 1.3:1). Similar results were obtained with 1-dodecene (**13**, 70%) and *O*-*p*-chlorobenzoyldec-9-en-1-ol (**14**, 69%). For these two monosubstituted terminal alkenes, the regioselectivity of the hydroboration was not complete, and small amounts of the corresponding secondary alkyl azides were formed.

The radical nature of the process was demonstrated by the reaction with (−)-carene (**15**) which afforded ring-opened azide **16** in 79% yield (Scheme 4). The azidation of primary alkyl radicals was expected to be a slow process that should allow slow radical rearrangements to take place before the azidation step. This point was demonstrated by the efficient 6-exo-trig cyclization of β-citronellene (**17**), which exclusively afforded cyclic azide **18** at a high (3 M) concentration of benzenesulfonyl azide (Scheme 4).

On the basis of the radical probe experiments, we propose the following reaction mechanism for hydroazidation (Scheme 5). Under heating at 80 °C, *t*-BuON═NO*t*-Bu decomposes to give *tert*-butoxyl radicals that initiate the chain reaction. Reaction of the *B*-alkylcatecholborane with a *tert*-butoxyl radical gives the

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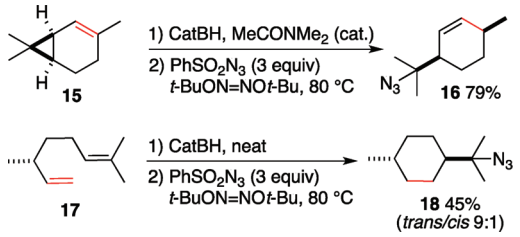
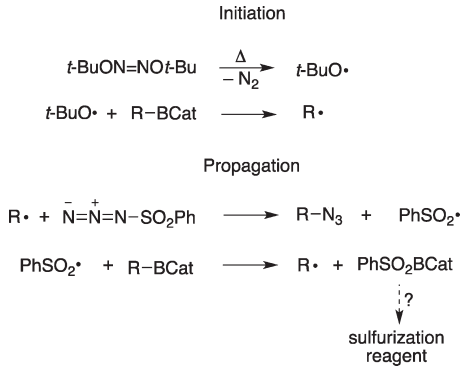
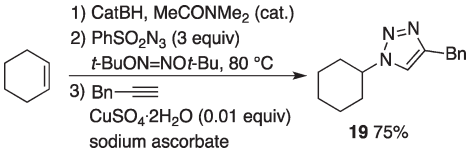
Scheme 4. Azidation Reactions Involving Rearrangement of the Radical Intermediates



Scheme 5. Proposed Mechanism



Scheme 6. Sequential Hydroboration−Azidation−1,3-Dipolar Cycloaddition Reaction



starting alkyl radical and a boronic ester. The radical reacts with benzenesulfonyl azide to give the alkyl azide and a benzenesulfonyl radical, which propagates the chain by homolytic substitution of the starting *B*-alkylcatecholborane. This last step produces 1 equiv of $PhSO_2BCat$. Decomposition of $PhSO_2BCat$ may be the origin of the thioethers observed when the reaction was run in benzene and DCE (see above). The exact nature of the sulfurizing agent is unknown.

A sequential reaction involving the hydroboration−azidation and a Cu(I)-mediated 1,3-dipolar cycloaddition[24] with 3-phenylprop-1-yne was investigated next (Scheme 6). The reaction with cyclohexene afforded 4-benzyl-1-cyclohexyl-1*H*-1,2,3-triazole (**19**) in 75% overall yield, confirming that the moderate yield of 57% observed in the azidation reaction leading to **4** (Scheme 3) resulted from the volatility of this product.

In conclusion, we have developed an unprecedented reaction between *B*-alkylcatecholborane and benzenesulfonyl azide that can be applied to the efficient hydroazidation of alkenes. The regioselectivity is controlled by the hydroboration and corresponds in most cases to a formal anti-Markovnikov regioselectivity. This procedure is applicable to a wide range of alkenes and gives excellent results with mono-, di-, and trisubstituted alkenes. The versatility of the azides, which can be easily prepared, makes this reaction particularly suitable for applications in natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
philippe.renaud@ioc.unibe.ch

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(20) General azidation procedure: CatBH (0.64 mL, 6.0 mmol) was added dropwise at 0 °C under nitrogen to a solution of the olefin (2.0 mmol) and DMA (0.020 mL, 0.2 mmol) in CH_2Cl_2 (2.0 mL). The reaction mixture was heated under reflux for 5 h, after which *t*-BuOH (0.37 mL, 4.0 mmol) was added at 0 °C to solvolyze the excess CatBH and the solution was stirred for 15 min at rt. After evaporation of the solvent under vacuum, DMF (2 mL), $PhSO_2N_3$ (1.1 g, 6.0 mmol), and DTBHN (36 mg, 0.2 mmol) were added, and the solution was stirred at 80 °C. After 2−3 h, the solution turned black, and the reaction mixture was filtered through a pad of aluminum oxide to eliminate polar boron-containing residues using Et_2O as eluent. The filtrate was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography.

(21) The formation of benzenesulfonyl radicals from $PhSO_2BCat$ presumably takes place under di-*tert*-butylhyponitrite initiation. This process becomes increasingly important as the reaction progresses and the concentration of the more reactive RBCat diminishes. The disproportionation of arenesulfonyl radicals affords arenesulfonic anhydride ($ArSO_2OSO_2Ar$) and arenesulfonothioate ($ArSO_2SAr$). See: (a) da Silva Correa, C. M. M.; Lindsay, A. S.; Waters, W. A. *J. Chem. Soc. C* **1968**, 1872. (b) Kobayashi, M.; Tanaka, K.; Minato, H. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2906. We recently showed that sulfonothioates ($ArSO_2SR$) are excellent reagents for radical-mediated sulfurization of organoboranes. See: (c) Schaffner, A.-P.; Montermini, F.; Pozzi, D.; Darmency, V.; Scanlan, E. M.; Renaud, P. *Adv. Synth. Catal.* **2008**, *350*, 1163.

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