Alkyne 1,1-Diboration

Regio- and Stereoselective Synthesis of 1,1-Diborylalkenes via Brønsted Base-Catalyzed Mixed Diboration of Alkynyl Esters and Amides with BpinBdan

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Abstract: The NaO\textsubscript{t}Bu-catalyzed mixed 1,1-diboration of terminal alkynes using the unsymmetrical diboron reagent BpinBdan (pin = pinacolato; dan = 1,8-diaminonaphthalene) proceeds in a regio- and stereoselective fashion affording moderate to high yields of 1,1-diborylalkenes bearing orthogonal boron protecting groups. It is applicable to gram-scale synthesis without loss of yield or selectivity. The mixed 1,1-diborylalkene products can be utilized in Suzuki–Miyaura cross-coupling reactions which take place selectively at the C–B site. DFT calculations suggest the NaO\textsubscript{t}Bu-catalyzed mixed 1,1-diboration of alkynes occurs through deprotonation of the terminal alkyne, stepwise addition of BpinBdan to the terminal carbon followed by protonation with \textit{t}BuOH. Experimentally observed selective formation of (Z)-diborylalkenes is supported by our theoretical studies.

Introduction

Organoboronic acids and their derivatives have become increasingly of interest due to their widespread application in organic synthesis, materials science, and pharmaceuticals.\[1\] Alkenylboron compounds have been employed in the stereodefined construction of valuable multisubstituted alkenes including natural products, biologically active molecules, and functional materials.\[1\textsuperscript{h,2} 1,2-Diborylalkenes are well-established and are typically synthesized by catalytic diboration of alkynes using Pt,\[3\] Pd,\[4\] Cu,\[5\] Co,\[6\] Fe,\[7\] Zn\[8\] and metal-free reactions.\[9\] Recently, 1,1-diborylalkenes have emerged as versatile building blocks for the synthesis of multisubstituted alkenes, e.g. the anticancer agent tamoxifen, via selective and stepwise Suzuki–Miyaura couplings.\[10\]

Several approaches have been developed for the synthesis of 1,1-diborylalkenes. As early as 1974, Matteson et al. described a reaction of carbonyl compounds with triborylmethyllithium, which was prepared by treatment of tetraborylmethane with methyllithium (Scheme 1a).\[11\] Shimizu and Hiyama reported that B\textsubscript{2}pin\textsubscript{2} reacted with alkenylidene-type lithium carbeneoids to afford 1,1-diborylalkenes via a boron-based 1,2-migration. Alkenylidine-type lithium carbenoids were formed from 1,1-dibromoalkenes through Li–Br exchange (Scheme 1b).\[12\] Later, several transition metal-catalyzed methods were reported for the synthesis of 1,1-diborylalkenes using alkenes as starting materials (Scheme 1c). In 2003, during our study of the Rh-catalyzed dehydrogenative borylation of alkenes, we found that a 1,1-diborylalkene was formed via a double dehydrogenative borylation of 4-vinyl anisole with 2 equivalents of...
B₂pin₂.[13] Subsequently, the Iwasawa and Huang groups reported the use of palladium or cobalt catalysts for the geminal dehydrogenative diboration of terminal alkynes.[14] In a complementary approach, 1,1-diborylalkenes can be synthesized from terminal alkynes (Scheme 1d). In 2015, Sawamura developed a Brønsted base (LiOBrBu)-catalyzed 1,1-diboration of terminal alkynes bearing electron-withdrawing substituents.[2b] Very recently, more general routes to 1,1-diborylalkenes from terminal alkynes were developed by the groups of Chirik and Ingleson using cobalt or zinc catalysts.[6a,8]

Diboration of alkynes to generate the Bdan moiety was incorporated at the internal position with excellent selectivities. Bdan and Bpin were exclusively synthesized 1,1-diborylalkenes using 5 mol-% of (CyAPDI)CoCH₃ as the catalyst in the presence of MeOH. Unlike Suginome’s protocol, the diboration of alkyl alkynes with BpinBdan using LiOH as the base catalyst was performed by Chirik and co-workers, who synthesized 1,1-diborylalkenes containing two different boryl groups in a regio- and stereoselective fashion (Scheme 2e).

We initially studied the reaction using ethyl propiolate 1a and BpinBdan under a range of conditions (Table 1). Encouragingly, 1,1-diborylalkene 2a was obtained in 62 % yield when the reaction was performed in CH₂CN at 40 °C using LiOBrBu as the base catalyst (Entry 1). Analysis of the reaction mixture by GC-MS showed the presence of a trace amount of by-product, which might be the E-isomer or 1,1-isomer, with the same mass and similar fragmentation pattern as 2a. A screen of Brønsted base catalysts revealed that NaOBrBu was superior when compared to LiOBrBu, KOBrBu, and Cs₂CO₃ (Entries 1–4). Weaker organic bases, such as DABCO or Hünig’s base (iPr₂EtN), as catalysts were inefficient (Entries 5 and 6). A control reaction (Entry 7) revealed that NaOBrBu was essential for this diboration. Further screening of the amount of NaOBrBu, (2 mol-%, 5 mol-% and 20 mol-%), afforded lower yields of 2a (Entries 8–10). Only a trace of product was obtained when 1 equivalent of NaOBrBu was used (Entry 11). A survey of solvents revealed that CH₂CN was optimal (Entries 12–15). GC-MS analysis of the crude reaction mixtures showed that 2a was the main product, indicating excellent regio- and stereoselectivities (Figures S1 and S2).

Table 1. Optimization of reaction conditions.[a]

| Entry | Base (mol-%) | Solvent | Yield of 2a (%)[b] |
|-------|-------------|---------|-------------------|
| 1     | LiOBrBu (10) | CH₂CN   | 62 (56)           |
| 2     | NaOBrBu (10) | CH₂CN   | 88 (76)           |
| 3     | KOBrBu (10)  | CH₂CN   | 60 (35)           |
| 4     | Cs₂CO₃ (10)  | CH₂CN   | 42                |
| 5     | DABCO (10)   | CH₂CN   | < 5               |
| 6     | DIPA (10)    | CH₂CN   | < 5               |
| 7     | –            | CH₂CN   | 0                 |
| 8     | NaOBrBu (2)  | CH₂CN   | 54                |
| 9     | NaOBrBu (5)  | CH₂CN   | 72 (45)           |
| 10    | NaOBrBu (20) | CH₂CN   | 64 (51)           |
| 11    | NaOBrBu (100)| CH₂CN   | < 5               |
| 12    | NaOBrBu (10) | 1,4-dioxane | 72 (61)         |
| 13    | NaOBrBu (10) | Et₂O    | 65 (52)           |
| 14    | NaOBrBu (10) | MTBE    | 52 (40)           |
| 15    | NaOBrBu (10) | toluene | 60 (51)           |

[a] Reaction conditions: In an argon-filled glove box, 1a (0.24 mmol, 1.2 equiv) was treated with base (10 mol-%), BpinBdan (0.2 mmol) and solvent (2 mL) for 5 h. [b] The yields were determined by GC-MS using n-dodecane as the internal calibration standard; isolated yields are given in parentheses. DABCO: 1,4-diazabicyclo[2.2.2]octane. DIPA: di-isopropyl ethyl amine. MTBE: methyl tert-butyl ether.

With the optimized reaction conditions in hand, the mixed 1,1-diboration of a variety of alkynoates 1 was tested (Table 2). The model reaction with 1a afforded 2a in 76 % isolated yield. Alkoxo substituents ranging from a small methoxy group (2b) to much larger tert-butoxy group (2c) provided the desired products in high yields. Substrates with cyclohexyloxy (2d), benzyloxy (2e), furan-2-ylmethoxy (2f), and naphthalen-2-ylmethoxy (2g) carbonyl groups, afforded the corresponding...
products in moderate to high yields (43 %-78 %). The 1,1-diboration of phenyl propiolate (1h) and naphthalene-2-yl propiolate (1i) gave products in good yields of 65 % and 75 %, respectively. Notably, in the presence of competing internal alkyne (2j) or alkene (2k and 2l) moieties, 1,1-diboration proceeded at the terminal C≡C bond selectively. Propiolamides 1m and 1n were also compatible with this diboration protocol. Increasing the reaction time to 10 h resulted in increased conversion, and the corresponding products were isolated in 87 % and 50 % yields, respectively. Finally, this method enables a convenient gram-scale synthesis (5 mmol) without loss of yield, as demonstrated for 1a (2a: 1.47 g, 75 %). The structure and stereochemistry of the 1,1-diborylalkene products was unambiguously confirmed by single-crystal X-ray diffraction studies of 2a, 2e, 2j, and 2m (Figure 1). In contrast to the compounds containing an ester group, the formation of five-membered rings via O-B coordination of the amide group with the Bpin moiety was observed in 2m. Indeed, 11B NMR spectroscopy supports the presence of a tricoordinate and a tetracoordinate boron atom in 2m (29.2, 17.3 ppm) and 2n (29.9, 15.4 ppm).

Table 2. Scope of the mixed 1,1-diboration of terminal alkynes.[a]

| R      | Bpin-Bdan | R      | Bpin-Bdan | R      | Bpin-Bdan | R      | Bpin-Bdan |
|--------|-----------|--------|-----------|--------|-----------|--------|-----------|
| EtO    | Bpin     | MeO    | Bpin     | BuO    | Bpin     | PhO    | Bpin     |
| 2a 78%, 5 h | 2b 75%, 5 h | 2c 78%, 5 h | 2d 74%, 5 h | 2e 78%, 10 h | 2f 43%, 5 h | 2g 63%, 5 h | 2h 65%, 10 h |
| 5 mmol scale, 1.47 g, 75% | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h |
| 2i 82%, 5 h | 2j 72%, 5 h | 2k 75%, 5 h | 2l 89%, 5 h | 2m 83%, 5 h | 2n 29%, 5 h | 2o 29%, 5 h | 2p 29%, 5 h |
| 5 mmol scale, 1.47 g, 75% | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h | 50%, 10 h |

[a] Standard conditions: 1 (0.24 mmol), Bpin-Bdan (0.2 mmol), and NaOEtBu (10 mol-%) in CH3CN (2 mL) at 40 °C. Isolated yields.

To understand the mechanism and the stereoselectivity of the mixed 1,1-diboration reaction, we performed a detailed DFT investigation, the results of which are shown in Figure 2. Beginning with the acetylide anion 3 generated via deprotonation of ethyl propiolate (1a) by NaOEtBu, the more Lewis-acidic Bpin boron complexes with the alkyne terminal carbon to form anionic adduct 5 via transition state 4-ts with a barrier (ΔG°) of 12.8 kcal/mol. With cleavage of the B–B bond, Bdan then irreversibly migrates to the alkyne terminal carbon to generate the allenylidene intermediate 7 via transition state 6-ts, a process which is exergonic by 22.0 kcal/mol. The energy barrier for this step is 18.0 kcal/mol.

Another pathway (blue line) in which the Bdan boron complex with the acetylide anion 3 followed by 1,2-migration of Bpin moiety to form 7 is calculated to be unfavorable compared to the above pathway. The relative free energy of 10-ts for Bpin migration is higher than that of 6-ts by 2.9 kcal/mol. Thus, the preferred pathway for these two steps is nucleophilic attack at the Bpin moiety by 3 followed by 1,2-migration of Bdan. The contributions of the two boron atoms to the LUMO of Bpin-Bdan were also calculated and they are very similar (0.254 and 0.235). The higher Lewis-acidity of Bpin due to its more positive NBO charge than Bdan may be responsible for the preference for the formation of anionic adduct 5 which is thermodynamically more stable than 9. The proton of tBuOH, produced by the deprotonation of ethyl propiolate (1a) in the initial step, transfers to the internal carbon of allenolate 7 and generates the 1,1-diborylalkene intermediate 12 or 14 stereoselectively, followed by substrate-assisted dissociation of tBuO− to obtain either product 2a or 2a′, respectively. There is a strong driving force of more than 20 kcal/mol for the formation of 2a/2a′ (2a: 25.7 kJ/mol; 2a′: 21.3 kJ/mol) starting from 7. Of both isomers, the experimentally observed product 2a is clearly the thermodynamically favored one, and lies 4.4 kcal/mol below 2a′. In addition, the energy barrier leading to 2a via the transition state 11-ts, in which the tBuOH attacks from the same side as the Bdan group, is 7.5 kcal/mol lower in energy than that of 13-ts, leading to 2a′, with tBuOH attacking from the same side as Bpin. Therefore, 2a is the main product for both kinetic and thermodynamic reasons, and the acetylide anion 3 generated in this step closes the catalytic cycle. This last step is the stereoselectivity determining step, whereas the rate-determining step is the Bdan transfer to the alkyne terminal carbon, with the overall activation free energy being 18.9 kcal/mol.

The other two possible pathways to form 2a, both having higher energy barriers, are shown in Figure 3. The acidic protons on the Bdan group may irreversibly migrate to the carbon of
Figure 2. DFT calculations on the mechanism of the mixed 1,1-diboration of ethyl propiolate (1a) at the M11/(6-311+G(d,p), SMD)//B3LYP-D3/(6-31+G(d), SMD) level of theory. Relative free energies ($\Delta G$) are given in kcal/mol, and bond lengths are given in Å.

Figure 3. Two alternative pathways for the generation of 2a calculated at the M11/(6-311+G(d,p), SMD)//B3LYP-D3/(6-31+G(d), SMD) level of theory. Relative free energies ($\Delta G$) are given in kcal/mol, and bond lengths are given in Å.
allenyl intermediate 7 via transition state 15-ts firstly, followed by fast generation of 1,1-diborylalkene intermediate 12 by transfer of the tert-butanol proton to nitrogen via 17-ts. The relative free energy of 15-ts is higher than that of 11-ts by 10.7 kcal/mol. Another possible concerted pathway via transition state 18-ts, has a barrier of 20.4 kcal/mol, and thus is ruled out. So, the favored pathway leading to 2a is the one through 11-ts.

On the basis of our DFT calculations and experimental results (for details see SI, Part V), a possible catalytic cycle for the NaO\textsubscript{t}Bu-catalyzed mixed 1,1-diboration of alkynes is shown in Scheme 3. Deprotonation of the alkyne by the Brønsted base NaO\textsubscript{t}Bu generates acetylide A\textsuperscript{[20]} which was evidenced by the stoichiometric reaction with nBuLi. Species A reacts with BpinBdan, in which the carbanion attacks the Bpin moiety selectively vs. the less electrophilic Bdan group, to form an sp\textsuperscript{2}-sp\textsuperscript{3} alkynyl borate intermediate B\textsuperscript{[1g,15k,15l,21]}. Then, 1,2-migration of the Bdan moiety in B to the terminal carbon atom of the alkyne occurs to generate allenolate intermediate C. Proton transfer to the internal carbon of alkyne produces, stereoselectively, 1,1-diborylalkene intermediate D and, finally, product 2 is obtained with the release of tert-butanol and regeneration of acetylide anion A.

Scheme 3. The proposed catalytic cycle for the mixed 1,1-diboration of terminal 1.

The synthesis of 1,1-diborylalkenes bearing two different boryl groups (Bpin and Bdan) is particularly attractive because their differing reactivities allow selective and stepwise Suzuki–Miyaura cross-couplings\textsuperscript{[6a,16–17,19,22]}. Thus, Suzuki–Miyaura coupling of 2a with aryl iodides 27a–e, gave the corresponding (Z)-alkenylboronates 28 as single isomers in moderate yields (Scheme 4). A 2D NOESY study of compound 28a supports our assignment of the (Z)-configuration (Figure S8).

Conclusion

In conclusion, we have developed a simple and highly selective mixed diboration of terminal alkynes with BpinBdan catalyzed by inexpensive and readily available NaO\textsubscript{t}Bu. Diverse 1,1-diboryl alkylates and 1,1-diborylacrylamides with two different boron protecting groups, which were difficult to prepare previously, were obtained in moderate to high yields with excellent atom-economy. Our DFT calculations suggest a catalytic cycle of acetylene deprotonation, BpinBdan stepwise addition followed by protonation. Finally, Suzuki–Miyaura cross-coupling reactions of the products occurred exclusively at the Bpin position affording trisubstituted alkenes.

Acknowledgments

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Keywords: Boronate esters · Borylation · Cross-coupling · Synthesis design · Structure elucidation

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