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A Facile, One-Pot Synthesis of β-Substituted (*Z*)-Acrylonitriles Utilizing an α-Diaminoboryl Carbanion

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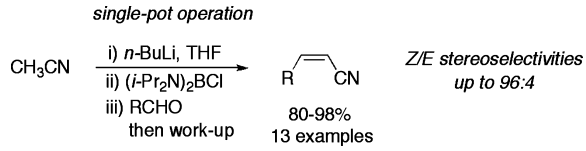
ABSTRACT



A simple three-step single-pot procedure for *Z*-stereoselective synthesis of β-monosubstituted acrylonitriles has been established. The reaction involves olefination of aldehydes with an in situ generated α-diaminoboryl carbanion species. Various aromatic and aliphatic aldehydes were smoothly converted into the corresponding (*Z*)-olefin products (up to 96:4 ratio) in good yields (80−98%).

A variety of β-substituted acrylonitriles are useful intermediates in organic synthesis, and their common functional moiety, α,β-unsaturated cyanide, is often utilized as (1) a Michael reaction acceptor,[1] (2) a Heck coupling partner,[2] and (3) an activated alkene in the Baylis−Hilman reaction,[3] etc.[4] Many of those acrylonitriles are typically prepared from an aldehyde by means of phosphorus- or silicon-based olefination in a stereoselective manner (e.g., Wittig/Horner−Emmons[5,6] and Peterson[7,8] type reactions). However, in practice, *Z*-stereoselective conditions[6,8,9] are still limited and less accomplished in terms of the overall reaction efficiency as well as operational simplicity.

As an α-phosphoryl and silyl carbanion species, α-boryl carbanion[10] exhibits an excellent olefinating ability.[11−14] However, the Lewis acidic nature of the boron often complicates the base-induced carbanion generation step, deprotonation of α-hydrogen, as a result of the use of a strong base, which preferentially leads to an undesired "ate"

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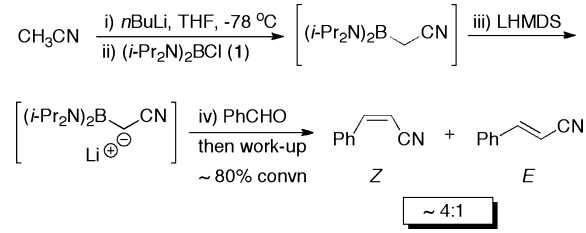
complex rather than a carbanion. To overcome this major drawback, Rathke, Pelter, and Matteson have successfully found effective solutions: (1) the use of a sterically hindered non-nucleophilic base (LiTMP),[11,15] (2) the use of a sterically hindered dimesityl borane,[12,16] and (3) the use of an electron-rich dialkoxyborane.[13,17] These primary studies clearly indicate that efficient deprotonation relies heavily on two major parameters: steric shielding and electronic factors around boron.

Interestingly, among a variety of organoborane species, a diaminoboryl group "$(R_2N)_2B$-" has an exceptionally mild Lewis acidic property due to the strong back-donation of electron density from nitrogen's lone pair electrons to boron's vacant p orbital.[18,19] Since such an electron-rich diaminoboryl group is seemingly highly base-compatible, and also the sterically tunable amino ligand can protect the boron site from a base and/or a nucleophile, those two key functions are particularly advantageous for the study of α-boryl carbanion chemistry. Although an electron-rich boryl system often decreases stabilization of an adjacent carbanion species as a result of the lowering of boron's π-accepting nature, attachment of an appropriate electron-withdrawing and/or anion-stabilizing functional group on the α-carbon should help to form a stable carbanion species as well as increase the acidity of α-hydrogens. On the basis of these assumptions, we anticipated that a diaminoboryl acetonitrile $(R_2N)_2BCH_2CN$ would be an ideal olefinating reagent for the synthesis of β-substituted acrylonitrile. To the best of our knowledge, there is no general synthetic path to access such boryl acetonitriles, though the ate complex form (KBF_3CH_2CN) was recently reported by the Molander group.[20]

To begin, a four-step single-pot procedure comprising (i) preparation of lithioacetonitrile, (ii) formation of boryl acetonitrile, (iii) generation of an α-boryl carbanion, and (iv) olefination of an aldehyde was initially designed/tested (Scheme 1). The use of a readily available bis(diisopropylamino)chloroborane reagent **1**[21] successfully gave desired olefination products based on ^{1}H NMR evidence (~80% conversion). Interestingly, the observed major stereoisomer was a thermodynamically less stable *Z*-form (*Z*:*E* = ~4:1). Attempts to examine the effects of different solvent (Et_2O), reaction temperature (−40 °C), base (KHMDS, LDA, and LiTMP), and additive (TMEDA) led to inferior stereoselectivity and/or conversion.

Scheme 1. Initially Attempted One-Pot Olefination



Although a sterically hindered non-nucleophilic base (LHMDS, etc.) was initially employed to avoid the formation of an undesired "ate" complex, further optimization revealed that even treating **1** with 2 equiv of nucleophilic $LiCH_2CN$ followed by the addition of an aldehyde still gave desired product in excellent yield (94%) with (*Z*)-stereoselectivity (*Z*:*E* = 82:18). This implies that, following the formation of borylacetonitrile, the remaining $LiCH_2CN$ (1 equiv) was effectively utilized as a base to form a corresponding carbanion **2** (Scheme 2). [Note: the use of a sterically less demanding diaminoboryl reagent, $(Me_2N)_2BBr$,[22] did not give satisfactory results but instead afforded a low yield of product (<60%) plus formation of a side adduct,[23] under the reaction conditions. In addition, the major stereoisomer was an (*E*)-olefin (*Z*:*E* = ~1:2).]

Scheme 2. Optimized One-Pot Olefination

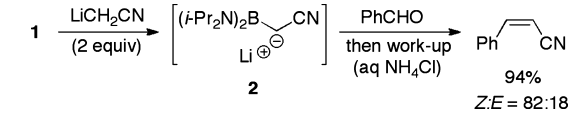


Table 1 illustrates several representative aldehydes examined. Various aromatic aldehydes including *ortho*-, *meta*-, and *para*-substituted benzaldehydes (entries 1−4) consistently led to decent (*Z*)-stereoselectivity (*Z*:*E* = ~80:20), although an *ortho*-substituted system was slightly less selective than the others. A heteroaromatic furfural was also smoothly converted into the desired (*Z*)-olefination product (entry 5). Interestingly, aliphatic aldehydes bearing an α-acidic proton (entries 6 and 7) still exclusively gave the corresponding olefinic products in excellent yield without

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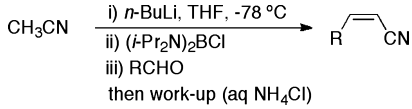
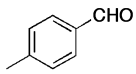
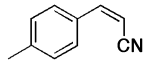
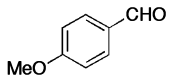
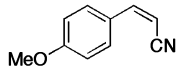
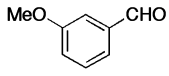
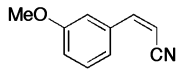
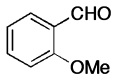
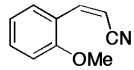
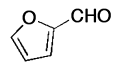
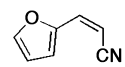
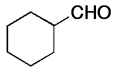
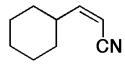
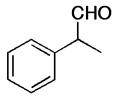
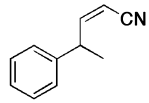
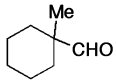
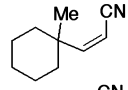
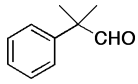
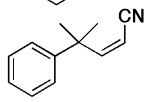
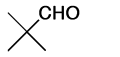
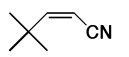
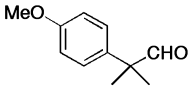
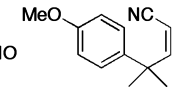
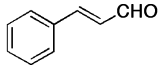
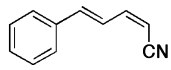
(22) Available from Sigma-Aldrich (product no. 476668).

(23) $PhCH(OH)CH_2CN$.

competitive enolization. The use of sterically congested aldehydes (entries 8−11) greatly improved the *Z*/*E* ratio to 96:4. However, a structurally much less hindered aldehyde, *trans*-cinnamaldehyde (entry 12), resulted in low (*Z*)-stereoselectivity.

Table 1. One-Pot Synthesis of β-Substituted (*Z*)-Acrylonitriles

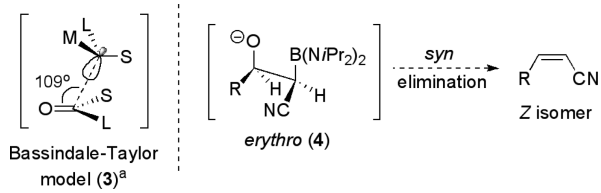


entry	aldehyde	product	*Z*:*E* [a]	yield (%)[b]
1			81:19	97
2			83:17	86
3			78:22	80
4			73:27	94
5			80:20	82
6			88:12	92
7			83:17	94
8			96:4	98
9			96:4	91
10			95:5	98[c]
11			94:6	86
12			65:35	88

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Combined isolated yield of *Z* and *E* isomers. [c] NMR yield (internal standard).

These experimental results indicate that the stereoselectivity correlates well with the steric factors of both the aldehyde and the diaminoboryl reagent. In contrast, the electronic factor of the reactant seems far less significant on the basis of comparisons of selectivities among benzaldehyde, *p*-tolualdehyde, and *p*-anisaldehyde. Although the exact mechanism is unclear at this point, the Bassindale−Taylor model of steric approach control,[24] which reasonably explains the (*Z*)-stereoselective outcome in the Peterson-type olefination, may be applicable in explaining our olefination mechanism. Thus, the use of a bulky diaminoboryl reagent as well as aldehyde would preferentially lead to an erythro oxyanion intermediate **4** (or anionic oxaboratane species) through the carbanion approach model **3** (Scheme 3). Subsequently, a possible *syn* elimination of **4** should afford the (*Z*)-olefin product as the major isomer.

Scheme 3. Plausible *Z*-Stereoselective Olefination Mechanism[a]



[a] S, M, and L represent small, medium, and large substituents, respectively.

In summary, a simple three-step single-pot procedure for the synthesis of a β-monosubstituted (*Z*)-acrylonitrile, employing a novel α-diaminoboryl carbanion mediated olefination, has been established. A variety of aromatic and aliphatic aldehydes were efficiently converted into the corresponding (*Z*)-olefin product. In addition, our approach utilizing a mildly Lewis acidic diaminoboryl group successfully overcame a common technical difficulty to access an α-boryl carbanion, which is a potentially versatile species in organic synthesis. Further application of an α-diaminoboryl carbanion system to a wide range of electrophiles is currently under investigation in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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