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Stereoselective Synthesis of Trisubstituted Alkenylboron Reagents by Boron-Wittig Reaction of Ketones

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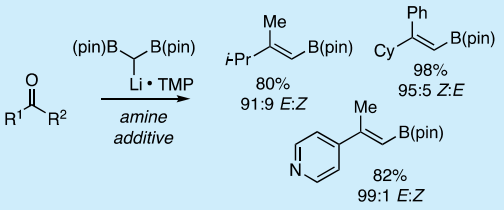
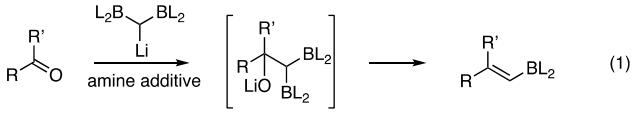
Supporting Information

ABSTRACT: Application of the boron-Wittig reaction to ketone electrophiles provides a straightforward route to trisubstituted alkenylboronic esters. With either a pentamethyldiethylenetriamine or trimethyl-1,4,7-triazacyclononane additive, the olefination can occur with very high levels of stereocontrol and in good chemical yield.



In the 1970s, Pelter[1] and Matteson[2] developed a boron-Wittig reaction that accomplishes homologation of aldehydes via the intermediacy of alkenylboron intermediates. Whereas Pelter employed geminal bis(trialkylboranes), Matteson employed geminal bis(ethylene glycolboronates). In both cases, the reactivity of the alkenylboron intermediate was sufficiently high as to render isolation of the organoboron impractical. Recently, we have investigated the boron-Wittig reaction between aldehydes and geminal bis(pinacolboronates) as a route to easily isolable disubstituted alkenylboronate products.[3] In the context of an ongoing natural products synthesis project, we required access to a stereodefined trisubstituted alkenylboronate and considered that the boron-Wittig reaction of ketone electrophiles might provide an efficient inroad (Scheme 1). Of note, recent experiments by

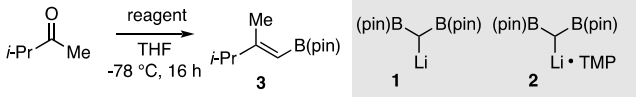
Scheme 1. Site-Selective Functionalization of 1,2-Bis(boronates)



Pattison[4] as well as Shibata and Endo[5] probed the boron-Wittig reaction of ketones, but in the former case the intermediate alkenylboronates were not isolated, and in the latter case the authors focused on the construction of tetrasubstituted alkenylboroantes.[6] In this paper, we demonstrate that, for a number of ketones, an efficient and highly stereoselective boron-Wittig reaction to construct trisubtituted alkenylboronates can be accomplished and we show that the stereoselectivity can be significantly affected by the use of amine additives, with triamine derivatives being particularly effective.

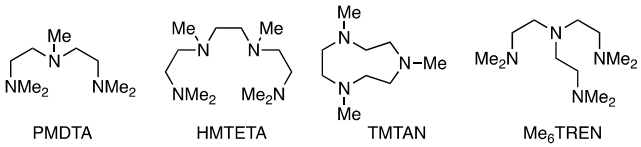
Our preliminary studies probed the reactivity of methyl isopropyl ketone in the boron-Wittig reaction. As depicted in Table 1, when pure lithiated geminal bis(boronate) **1**, conveniently prepared as described by Cho,[7] was employed

Table 1. Effect of Amine Additives on Stereoselection in Boron-Wittig Reaction of Methyl Isopropyl Ketone



entry	reagent	additive (equiv)	3 (%)[a]	E/Z[b]
1	**1**	none	50	60:40
2	**2**	none	54	75:25
3	**1**	TMEDA (1.5)	54	78:22
4	**1**	PMDTA (1.2)	62	90:10
5	**1**	PMDTA (1.5)	63	94:6
6	**1**	HMTETA (1.5)	50	78:22
7	**1**	TMTAN (1.5)	63	93:7
8	**1**	Me_6TREN (1.5)	60	79:21

[a]Isolated yield of purified product. [b]*E*/*Z* ratios determined by ^{1}H NMR of unpurified reaction mixture.



as an olefination reagent, the *E* isomer of product was formed in a 60:40 *E*/*Z* ratio and in 50% yield. Notably, when the lithiated geminal bis(boronate) was prepared by *in situ* deprotonation of $CH_2(Bpin)_2$ with LiTMP (giving complex **2**), the olefination occurred with improved stereoselectivity (75:25 *E*/*Z*) and in comparable yield. This result suggested that the presence of amine additives should have an impact on reaction stereoselectivity of the boron-Wittig reaction, and this feature was probed more thoroughly. Of relevance to this hypothesis, studies by Matteson showed that addition of amine additives could enhance reaction efficiency in boron-Wittig

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reactions.[2a] In this case, while use of amine-free reagent **1** in conjunction with TMEDA resulted in a slight increase in stereocontrol during the boron-Wittig reaction (entry 3), use of the 1.2 equiv of triamine compound PMDTA resulted in a marked improvement in stereoselection (entry 4), which could be improved even more by use of 1.5 equiv of reagent (94:6 *E*/*Z*, entry 5). Of note, use of another triamine ligand (TMTAN, entry 5) also afforded enhanced selectivity while two tetraamine additives provided only moderate results (entries 6, 8).

To learn about the substrate scope and practical implementation of the amine-modified boron-Wittig reaction, we investigated the reaction of isopropyl methyl ketone further. Rather than employing pure lithiated geminal diboron reagent **1**, we investigated whether use of *in situ* deprotonation with LiTMP, followed by addition of the amine additive PMDTA, could still furnish the alkenylboronate in high selectivity and yield. After some optimization, it was found that isomerically enriched product (91:9 *E*/*Z*) could be obtained and that, with 2 equiv of reagent, consistently high isolated yields were also observed. As depicted in Figure 1, alkenyl

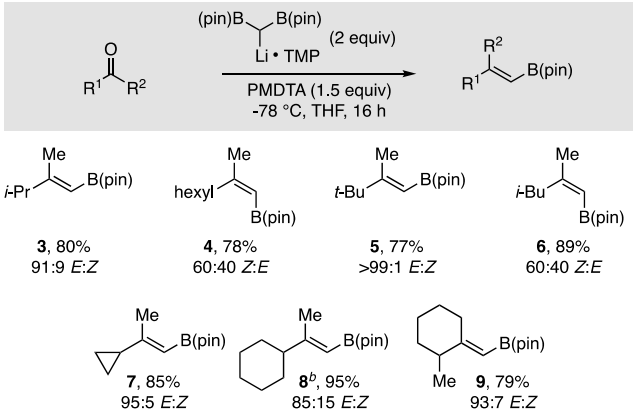


Figure 1. Conversion of aliphatic ketones to alkenylboronates by the boron-Wittig reaction. Isolated yields are of purified material and represent an average of two experiments. Stereoisomer ratio determined by ^{1}H NMR analysis.

boronate **3** was obtained in 80% yield under these conditions. Examination of other substrates revealed that ketones bearing an α-substituent generally reacted in high levels of stereocontrol (products **5**, **7**–**9**) whereas ketones lacking such a steric bias between the two carbonyl substituents provided only moderate levels of stereoselection and, remarkably, favored the *Z* isomer of alkenylboronate (**4**, **6**).

Examination of aryl alkyl ketone substrates with PMDTA as the amine additive showed that selectivity could remain high so long as the alkyl group retains an α branch (Figure 2, method a). For instance, phenyl *tert*-butyl ketone furnished the alkenylboronate **12** in excellent yield and stereoselectivity. Similar observations were made for compounds **13**–**15**. Notably, acetophenone furnished the *E* isomer in lower stereoselection. Given the expected utility of alkenylboronates that derive from boron-Wittig reaction of aryl methyl ketone substrates, we reinvestigated acetopheone but with TMTAN as the amine additive. In these experiments, it was found that optimal results were obtained with 0.5 equiv of TMTAN additive. As shown in Figure 2 (method b), with the addition of TMTAN, the stereoselectivity for olefination of acetophe-

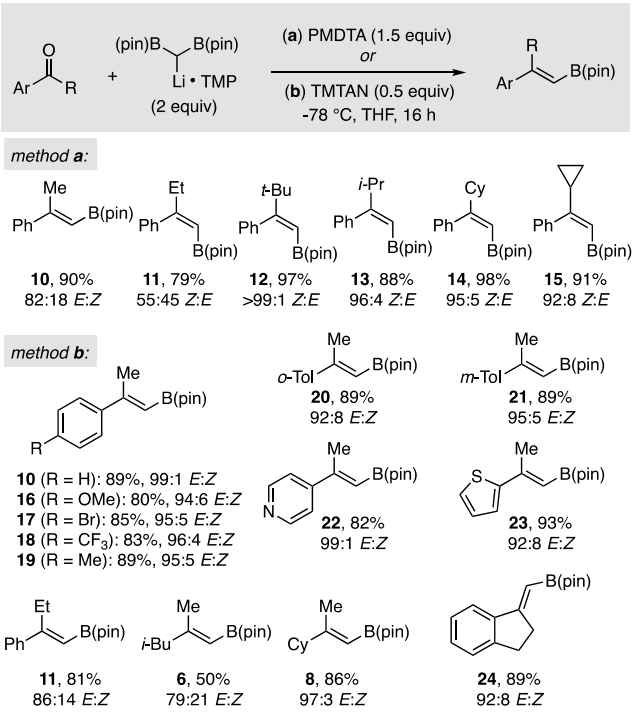
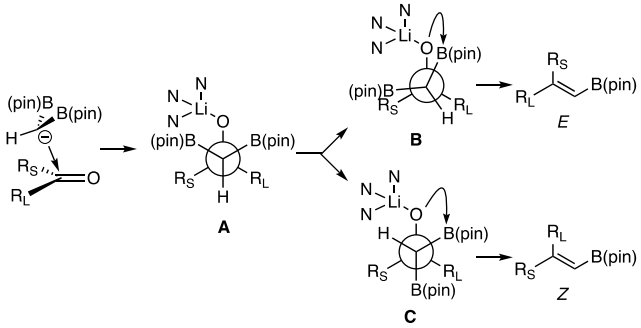


Figure 2. Boron-Wittig reaction of aryl ketones in the presence of PMDTA and TMTAN additives. Isolated yields are of purified material and represent an average of two experiments. Stereoisomer ratio determined by ^{1}H NMR analysis.

none increased from 82:18 to 99:1 *E*/*Z*. Comparably high levels of *E* stereoselection were observed with other aryl and heteroaryl methyl ketones, and even a less encumbered dialkyl ketone could now furnish the *E* isomer (**6**) *albeit* with only moderate stereoselectivity.

The level and sense of stereoselectivity in the boron-Wittig reaction may be rationalized by the mechanism proposal put forward in Scheme 2. We consider that addition of the geminal

Scheme 2. Proposed Origin of Stereoselectivity in the Boron-Wittig Reaction of Ketones



bis(boronate) carbanion to the ketone may proceed as shown in Scheme 2 where, in line with a model put forward by Bassindale and Taylor,[8] the smallest group on the nucleophile (H) would lie between the carbonyl substituents. This addition mode would furnish **A** as the immediate addition product. We consider that if O–B elimination is rapid (faster than bond rotation), then reaction through **B** giving the *E* alkene should be favored, as it minimizes steric interactions with the nonreacting B(pin) group. In contrast, if elimination is slow, bond rotation may allow conversion of **A** to **C** where the small

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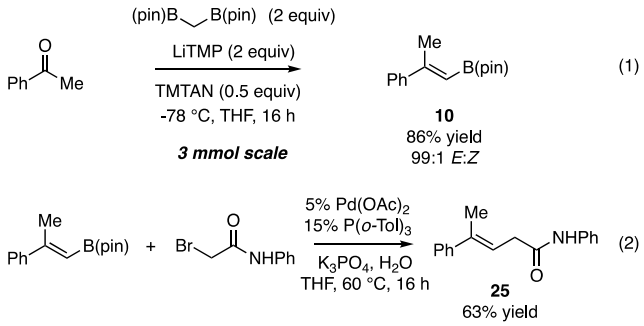
H atom is sited proximal to the large Li(triamine) group; elimination would then give the *Z* alkene. In connection to this, studies by Reich show that PMDTA and TMTAN convert dimeric Li enolates into monomeric complexes, with TMTAN being much more effective.[9] During the boron-Wittig reaction, we suspect that the intermediacy of dimeric alkoxides may serve to stabilize the addition product and thereby allow path **C** to operate, whereas with TMTAN rapid elimination through **B** occurs thus furnishing a greater proportion of the *E* product. Further computational experiments to study the details of this working model are in progress and will be described separately.

Practical aspects of the boron-Wittig reaction of ketones were examined as depicted in Scheme 3. First, it was

Scheme 3. Practical Aspects of the Boron-Wittig Reaction of Ketones



determined that the reaction can be conducted on a preparatively useful scale: a reaction employing 3 mmol of acetophenone as substrate provided the alkenyl boronate product **8** in comparable yield and stereoselectivity as reactions conducted on a smaller scale. With respect to the synthesis target mentioned in the introduction, we require access to stereodefined β,γ-unsaturated amides. It was found that employing the pinacol alkenyl boronates produced by the boron-Wittig reaction in Suzuki–Miyaura cross-coupling with an α-bromoamide provides a simple route to these compounds with preservation of the alkene geometry.

In conclusion, we have developed a modified boron-Wittig reaction that applies to ketone substrates and furnishes trisubstituted alkenyl boronic esters as the reaction product. This process provides direct access to many of these important motifs in an efficient and stereoselective fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01663.

Procedures, characterization, and spectral and chromatographic data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. Hindered Organoboron Groups in Organic Chemistry. 23. The Interactions of Dimesitylboron Stabilised Carbanions with Aromatic Ketones and Aldehydes to Give Alkenes. *Tetrahedron* **1993**, *49*, 7077.

(2) (a) Matteson, D. S.; Moody, R. J. Deprotonation of 1, 1-Diboronic Esters and Reactions of the Carbanions with Alkyl Halides and Carbonyl Compounds. *Organometallics* **1982**, *1*, 20. (b) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. Reaction of Aldehydes and Ketones with a Boron-Substituted Carbanion, Bis(ethylenedioxyboryl) Methide. Simple Aldehyde Homologation. *J. Am. Chem. Soc.* **1975**, *97*, 5608. (c) Matteson, D. S.; Jesthi, P. K. Lithium Bis-(ethylenedioxyboryl) Methide and its Reactions with Carbonyl Compounds and with the Chlorotriphenyl Derivatives of Germanium, Tin and Lead. *J. Organomet. Chem.* **1976**, *110*, 25. (d) Matteson, D. S.; Moody, R. J. Carbanions from Deprotonation of Gem-Diboronic Esters. *J. Am. Chem. Soc.* **1977**, *99*, 3196.

(3) Coombs, J. R.; Zhang, L.; Morken, J. P. Synthesis of Vinyl Boronates from Aldehydes by a Practical Boron–Wittig Reaction. *Org. Lett.* **2015**, *17*, 1708.

(4) Stephens, T. C.; Pattison, G. Transition-Metal-Free Homologative Cross-Coupling of Aldehydes and Ketones with Geminal Bis (boron) Compounds. *Org. Lett.* **2017**, *19*, 3498.

(5) (a) Endo, K.; Hirokami, M.; Shibata, T. Stereoselective Synthesis of Tetrasubstituted Alkenylboronates via 1, 1-Organodiboronates. *J. Org. Chem.* **2010**, *75*, 3469. (b) Endo, K.; Sakamoto, A.; Ohkubo, T.; Shibata, T. Stereoselective Synthesis of Allylsilanes Bearing Tetrasubstituted Olefin via 2,2-Diborylethylsilane. *Chem. Lett.* **2011**, *40*, 1440.

(6) For application of the boron-Wittig reaction to the construction of alkenylsilylboronates, see: La Cascia, E.; Cuenca, A. B.; Fernández, E. Opportune gem-Silylborylation of Carbonyl Compounds: A Modular and Stereocontrolled Entry to Tetrasubstituted Olefins. *Chem. - Eur. J.* **2016**, *22*, 18737.

(7) Lee, Y.; Park, J.; Cho, S. H. Generation and Application of (Diborylmethyl)zinc(II) Species: Access to Enantioenriched gem-Diborylalkanes by an Asymmetric Allylic Substitution. *Angew. Chem., Int. Ed.* **2018**, *57*, 12930.

(8) Bassindale, A. R.; Ellis, R. J.; Lau, J. C.-Y.; Taylor, P. G. The Prediction of the Stereochemical Outcome of Reactions Between Prochiral Carbanions and Prochiral Carbonyl Compounds in the Absence of Chelation Control. *J. Chem. Soc., Chem. Commun.* **1986**, 98.

(9) (a) Kolonko, K. J.; Biddle, M. M.; Guzei, I. A.; Reich, H. J. Solution Structures of Lithium Enolates of Cyclopentanone, Cyclohexanone, Acetophenones, and Benzyl Ketones. Triple Ions and Higher Lithiate Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 11525. (b) Kolonko, K. J.; Guzei, I. A.; Reich, H. J. Structure and Dynamics of α-Aryl Amide and Ketone Enolates: THF, PMDTA, TMTAN, HMPA, and Crypt-Solvated Lithium Enolates, and Comparison with Phosphazenium Analogues. *J. Org. Chem.* **2010**, *75*, 6163.

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