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Formation of (*Z*) Dialkylboron Enolates from Enolsilanes: Stereoconvergent Transmetallation and Diastereoselective Aldol Reactions

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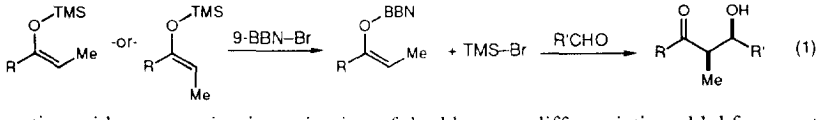
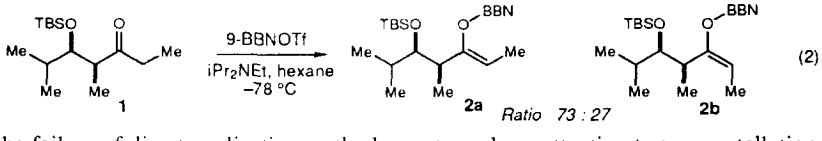
Abstract: Transmetallation of (*E*) and (*Z*) enolsilanes using halodialkylborane (R_2BX) reagents provides predominantly the (*Z*) dialkylboron enolate under mild conditions. These enolates afford high levels of *syn* selectivity in subsequent aldol reactions.

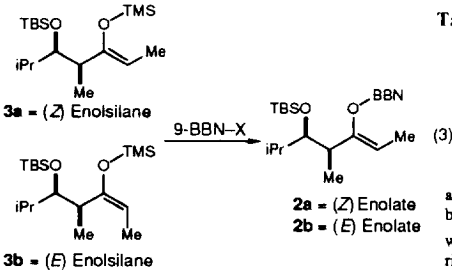
The stereoselective generation of (*Z*) and (*E*) dialkylboron enolates continues to be of central interest owing to the exceptional stereochemical fidelity of these species in the aldol reactions.[1] While reliable methods exist for the direct enolization of ethyl ketones to afford the corresponding (*Z*) enolates (R_2BOTf, R_3N), these procedures break down for sterically hindered ketones. For example, the kinetic enolization of *tert*-butyl ethylketone affords predominantly the (*E*) boron enolate (3:1) by direct enolization methods.[1a] In this Letter we report a complementary route to (*Z*) dialkylboron enolates *via* transmetallation of the corresponding (*Z*) or (*E*) enolsilanes with bromodialkylboranes (eq 1). This method affords higher (*Z*) enolate selectivity for more sterically hindered ethylketones. Furthermore, the subsequent aldol reactions exhibit the anticipated stereochemical fidelity undiminished by the presence of the TMSBr byproduct which is not an aldol catalyst.



In connection with our ongoing investigation of double stereodifferentiating aldol fragment coupling reactions, we required a geometrically defined (*Z*) boron enolate of ethyl ketone **1** (eq 2).[2] However, extensive optimization of enolization conditions, including variations in the base, solvent, boron ligands and counter ion, and order of reagent addition,[1,3] failed to afford a stereoselective (*Z*) boron enolate as measured by the aldol *syn* : *anti* stereoselectivity. This is likely due to the aforementioned steric bulk of the ketone which precludes kinetic formation of the (*Z*) stereochemistry (eq 2).[4]



With the failure of direct enolization methods, we turned our attention to transmetallation of the corresponding enolsilanes. Transmetallation of these substrates with dialkylboron triflates[5] has been shown to afford the derived (*Z*) boron enolate stereoselectively; however, the resulting aldol reaction with aldehydes is compromised by the trimethylsilyl triflate byproduct which catalyzes a competing non-stereoselective aldol process. Wada has demonstrated that transmetallation may also be achieved with dialkylboron halides, although no aldol reactions were reported using these reagents.[6] In an extension of this study, we found that the (*Z*) dialkylboron enolate **2a** could be generated stereoselectively *via* transmetallation with a variety halodialkylboranes derived from 9-borabicyclo[3.3.1]nonane (9-BBN-X, X = Cl, Br, I) (Table I). The reactions were directly monitored by variable temperature ^1H NMR spectroscopy.[7] The rate of the reaction was found to strongly depend on the halide component of the haloborane reagent, with the rate decreasing in the order I >



(3)

Table I. Transmetallation of **3a** and **3b** with Halodialkylboranes (eq 3)

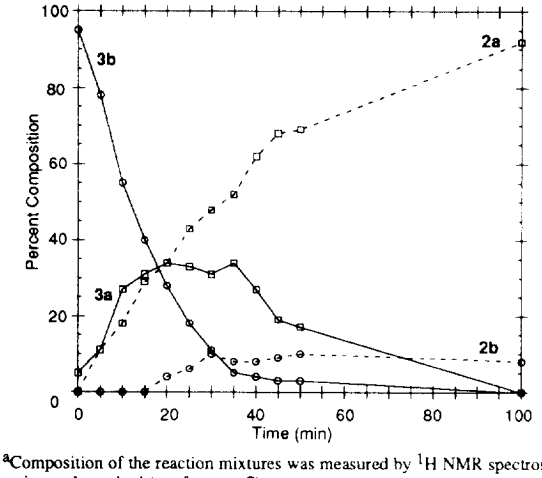
Entry	3a : 3b	9-BBN–X	Temp (min)[a]	2a : 2b[b]
A	08 : 92	9-BBN–I	-50 °C (<20)	95 : 5
B	08 : 92	9-BBN–Br	0 °C (20)	92 : 8
C	>97 : 03	9-BBN–Br	0 °C (20)	91 : 9
D	08 : 92	9-BBN–Br[c]	35 °C (15)	no rxn
E	08 : 92	9-BBN–Cl	r. t. (24 hr)	no rxn

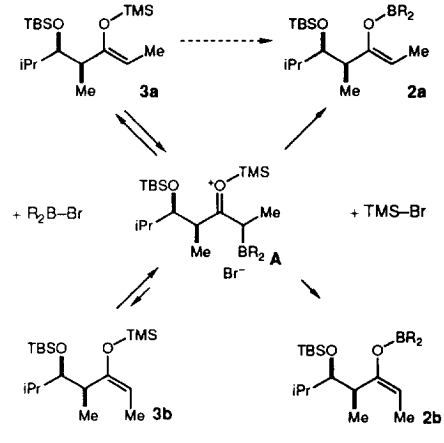
[a]All reactions were carried out in CD_2Cl_2 except where otherwise noted. [b]Enolate ratio was measured by ^1H NMR spectroscopy. Enolate geometry was unambiguously assigned by ^1H nOe experiments. [c]This reaction was carried out in d_8-toluene.

Br >> Cl. Reaction rates were found to be solvent dependent, proceeding smoothly in methylene chloride but not in toluene (entry D). Surprisingly, the (*Z*) enolate was generated stereoselectively from either the (*E*) or the (*Z*) enolsilane (entries B and C).[8,9]

The course of the transmetallation of (*E*) enolsilane **3b** (entry B) was monitored by ^1H NMR spectroscopy (Fig 1). Di-*tert*-butylpyridine (0.2 equiv) was added to prevent Bronsted acid catalyzed decomposition of the silyl-protected ketone. This additive was found to slightly retard the rate of the transmetallation reaction. Over the course of the reaction, significant isomerization of (*E*) enolsilane **3b** to the corresponding (*Z*) enolsilane **3a** was observed under these conditions, and after 20 minutes, the residual enolsilane was predominantly **3a**. In a similar NMR experiment, transmetallation of the (*Z*) enolsilane **3a** (entry C) afforded an intermediate amount of the (*E*) enolsilane **3b**, although the total amount of (*E*) enolsilane never exceeded 7% over the course of the reaction. Control experiments indicated that geometric isomerization is occurring within the enolsilane manifold, either by 9-BBNBr (*vide infra*) or by the adventitious formation of a Bronsted acid contaminant.[10]

Figure I. Transmetallation and Proposed Mechanism for the Formation of (*Z*) Boron Enolates from (*E*) Enolsilanes.



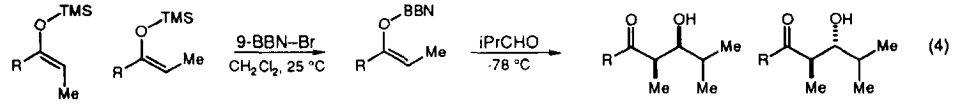


[a]Composition of the reaction mixtures was measured by ^1H NMR spectroscopy at ambient temperature with 0.2 equiv di-*tert*-butylpyridine as an internal standard (see footnote 7).

It is possible that enolsilane isomerization may be coupled to the transmetallation process, (Figure I). For example, it is plausible that the enolsilane undergoes initial carbometallation by 9-BBNBr to afford an intermediate such as **A**. This species could either partition back to the (*Z*) enolsilane (reversibly) or on to the (*Z*) boron enolate (irreversibly). The presence of intermediate **A** is consistent with the following observations: (a), the enolsilanes equilibrate under the aprotic reaction conditions by some mechanism involving 9-BBNBr;[11] (b), the reaction does not proceed in nonpolar solvents such as toluene, implicating the presence of a polar intermediate; (c), the reaction is stereoconvergent, implicating a possible common intermediate from both the

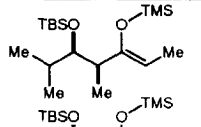
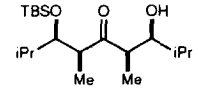
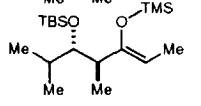
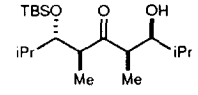
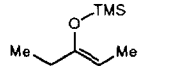
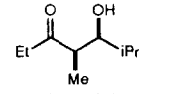
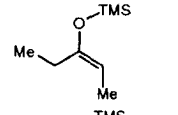
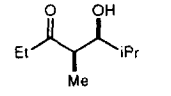
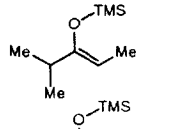
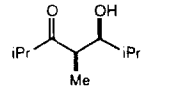
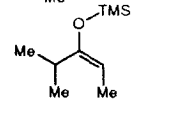
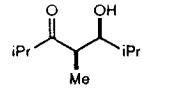
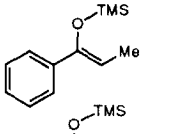
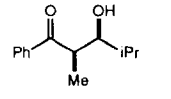
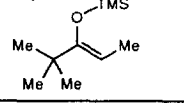
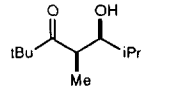
(*E*) and (*Z*) enolsilanes. With regard to this final observation, we cannot rule out the alternative isomerization from **3b→3a**, followed by direct transmetallation from the (*Z*) enolsilane to the (*Z*) enolate. This would require that the stereospecific transmetallation of the (*E*) enolsilane proceed at a much slower relative rate, which has been observed in transmetallations employing $TiCl_4$.[12]

This transmetallation procedure was found to be general for the selective formation of (*Z*) dialkylboron enolates from a variety of ethyl ketones (Table II). The stereoconvergency of the transmetallation process appears to be common as well, with higher selectivity for (*Z*) enolate formation from more sterically encumbered ethyl ketones (compare entries C, E, and H). Furthermore, the resulting aldol reactions employing isobutyraldehyde exhibited near perfect stereochemical fidelity between enolate (*Z*) / (*E*) geometry and product *syn* / *anti* stereochemistry.[14] The illustrated indirect route to (*Z*) dialkylboron enolates is therefore complementary to existing direct enolization methods for diastereoselective aldol addition reactions.



Enolsilane (E) or (Z) *(Z) Boron Enolate* *Syn : Anti* (4)

Table II. Aldol Reactions from (*Z*) Boron Enolates Derived From 9-BBNBr Transmetallation of Enolsilanes

Entry	Enolsilane Substrate	(*Z*) : (*E*) ratio[a]	Enolate (*Z*) : (*E*)	Major Product	*Syn* : *Anti*[d]	Yield[e]
A		(>95 : 5)	92 : 8[b]		92 : 8	66%
B		(>95 : 5)	92 : 8[c]		92 : 8[f]	68%
C		(>95 : 5)	83 : 17[b]		84 : 16	66 %
D		(6 : 94)	82 : 18[b]		82 : 18	71%
E		(91 : 9)	89 : 11[b]		91 : 9	89 %
F		(15 : 85)	89 : 11[b]		89 : 11	70 %
G		(88 : 12)	>95 : 5[c]		97 : 3	89 %
H		(>95 : 5)	>95 : 5[c]		>99 : 1	76 %

[a]Enolsilane and enolate ratios were measured by ^1H NMR spectroscopy (see footnote 7). [b]The geometry of the major enolate isomer was assigned based on ^1H NMR spectroscopy nOe experiments. [c]The geometry of the major enolate isomer was assigned based on the resulting aldol diastereoselectivity. [d]Aldol diastereoselectivity was determined by GLC analysis of the silylated reaction mixtures. Stereochemical assignments were made by comparison of ^1H NMR spectra with data previously published for each product.[13] [e]Combined yield of the purified diastereomers. [f]The *syn* product was formed as a 97 : 3 mixture of the two *syn* diastereomers.

The transmetallation process reported here affords a mild method for the selective formation of (*Z*) dialkylboron enolates from either (*E*) or (*Z*) enolsilanes. The low reactivity of the trialkylsilane byproduct allows for highly diastereoselective aldol reactions from these boron enolates.

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References and Footnotes

1. (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111. (b) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 7346-7352 and references cited therein.
2. (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073-9074. For aldol reaction study involving the (*E*) boron enolate of **1**, see: (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127-2142.
3. (a) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1993**, *58*, 7162-7169. (b) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, *58*, 147-153.
4. A selective (*Z*) boron enolization has been achieved with a substrate closely related to ketone **1**, see: Paterson, I.; McClure, C. K. *Tetrahedron Lett.* **1987**, *28*, 1229-1232.
5. Kuwajima, I.; Kato, M.; Mori, A. *Tetrahedron Lett.* **1980**, *21*, 4291-4294.
6. Wada, M. *Chem. Lett.* **1981**, 153-156.
7. ^{1}H NMR spectroscopy experiments were performed on Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometers. For each variable temperature experiment the probe was cooled to –50 °C and warmed at 10 °C/10 min intervals to the indicated reaction temperature. All percent composition experiments were performed by integration of the vinylic proton signals, and are accurate to ± 3%.
8. Preparation of (*E*) enolsilanes, see: (a) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571-9574. Preparation of (*Z*) enolsilanes, see: (b) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526-5528.
9. A similar stereoconvergent transmetallation has been observed using halodialkoxyboranes, see: (a) Gennari, C.; Columbo, L.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1984**, *40*, 4051-4058. However, the corresponding enol borates exhibit low stereochemical fidelity between enolate geometry and aldol diastereoselectivity, see: (b) Hoffman, R.; Ditrich, K. *Tetrahedron Lett.* **1984**, *25*, 1781-1784.
10. 2,6-Di-*tert*-butylpyridinium ion is a sufficiently strong Bronsted acid to promote enolsilane isomerization under the reaction conditions. Hindered tertiary amines such as ethyldiisopropylamine, although sufficiently basic to prevent isomerization through their conjugate acids, also inhibit the transmetallation process.
11. A similar carbometallation species has been identified in reactions of enolsilanes with $SnCl_4$, see: Nakamura, E.; Kuwajima, I. *Chemistry Lett.* **1983**, 59-62.
12. Nakamura, E.; Shimada, J-I; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341-3342.
13. Entries A, B, C, and D: Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *117*, 1047-1049. Entries E, F, and H: Heathcock, C. H.; Davidson, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027-3037. Entry G: The stereochemistry was established by ^{1}H NMR spectroscopy of the corresponding acetonide.
14. **General Experimental Procedure:** To a solution of the enolsilane (1.0 equiv) in CH_2Cl_2 (0.10 M) under nitrogen at ambient temperature was added 0.20 equiv of 2,6-di-*tert*-butylpyridine, followed by neat 9-BBNBr (1.0 equiv). After stirring for 2 h at ambient temperature, the solution was cooled to –78 °C, and 1.5 equiv of isobutyraldehyde was added. After 1-3 hr at –78 °C the reaction was quenched by the addition of an equivalent volume of 1:1 MeOH:pH 7 buffer. The resulting mixture was extracted with CH_2Cl_2 / H_2O. The organic layer was concentrated *in vacuo*, and the residue was dissolved in a solution of 2:1 MeOH:30% H_2O_2 (0.1 M) at 0 °C. After stirring for 1-3 h the aldol adduct was obtained by extractive isolation. Product purification by flash chromatography afforded the pure aldol diastereomers, with ^{1}H NMR analysis consistent with those previously reported for each compound (see reference 13).

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