# Sequential Coupling of Zincated Hydrazone, Alkenylboronate, and Electrophile That Creates Several Contiguous Stereogenic Centers

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Aldol-type 1,2-addition of a metal enamide to a carbonyl group can diastereoselectively create two stereogenic centers if mutual face selectivity for the enamide and the carbonyl enantiofaces is controlled well. Likewise but more interestingly, syn stereoselective[1] 1,2-addition of a metal enamide to a 1,2-disubstituted olefin can create three contiguous stereogenic carbon centers at positions $\alpha$, $\beta$, and $\gamma$ to the imine carbon atom (cf. hydrazone **E** in Scheme 1). In addition, the fourth stereogenic center may be created on the electrophilic carbon atom in the electrophile $E^+$ upon coupling with **D** (cf. Table 1, entry 8). Such a reaction, however, has been difficult to achieve either because of the low reactivity of 1,2-substituted olefins toward the enamide or because of the difficulty to trap an intermediate such as **D** with an electrophile in a selective manner.[2,3a,5] We report here that *E*- (and *Z*-) alkenylboronates (**C**) behave as good acceptors[4] of zincated hydrazones[5] (**B**) and that the overall coupling reaction take place with up to >99% diastereostereoselectivity (*ds*). The boron group in the product can be converted stereospecifically to a hydroxy group.

**Scheme 1.** Stereocontrolled Construction of Multistereogenic Centers by Addition/Trapping Sequence
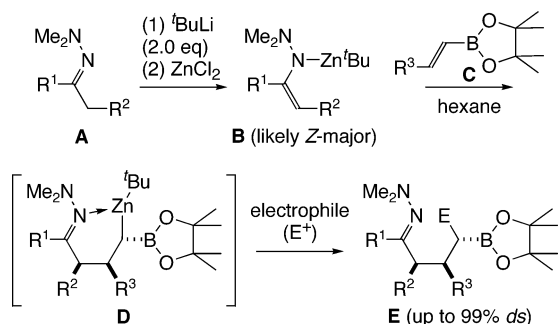


Scheme 1 outlines the procedure: A zincated hydrazone **B** is prepared from the corresponding hydrazone **A** by treatment with 2 equiv of *tert*-butyllithium (1 equiv for deprotonation and another as a ligand on the zinc atom) followed by addition of 1 equiv of zinc chloride. The zincated hydrazone **B** undergoes syn addition at 0 °C to the *E*- (or *Z*-) alkenylboronate **C** in hexane to give the B/Zn bimetallic species **D**, which upon electrophilic trapping gives a $\gamma$-borylhydrazone **E** in good to high overall yield.

We first examined the reaction between *E*-hexenylboronate **3** and the *N,N*-dimethylhydrazone of 3-pentanone to investigate the effect of a nontransferable "dummy" ligand (R) on the zinc atom (**2a**−**2c**). The nature of the dummy ligand has a significant impact on both the stereoselectivity and the reaction rate. The zincated hydrazone **2a** bearing a *tert*-butyl ligand gave, reacting at 0 °C for 24 h, the highest proportion of what we call here a "syn" adduct **4** in excess (95.2:4.8) to the alternative "anti" adduct in 88% yield. The relative stereochemistry of **4** was determined by the method described in Supporting Information, which also reports on the

stereochemical assignment of other products in Table 1. The intermediate **2a**−**2c** may be predominantly in *Z*-geometry in light of the data in Table 1 (vide infra). The use of the dummy ligand was mandatory to achieve the high yield. The *N*-alkyl- and *N*-aryl imines that were used in our previous studies[3] have been found to be low-yielding in the present reaction (eq 1).
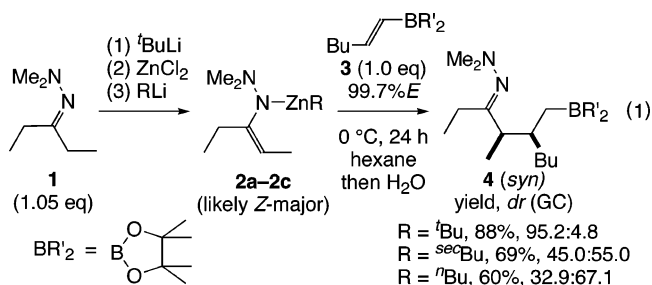


Table 1 summarizes the results of the addition/trapping sequence with various zincated hydrazones, alkenylboronates, and electrophiles. A zincated hydrazone **5** of likely *Z*-double bond geometry (vide infra) prepared from a 1-cyclohexylpropan-1-one hydrazone reacted with *E*-propenylboronate **6** (99.3% *E*) to give a syn adduct **9**$_{syn}$ that possesses two stereogenic centers in 93% yield with 99.2% diastereoselectivity (entry 1). The reactions of **5** with *E*-octenyl-boronate **7** and *E*-styrylboronate **8** also proceeded with 99.5 and 99.6% *ds*, respectively (entries 2 and 3). The reaction with *Z*-propenylboronate **12** (99.1% *Z*) gave an alternative anti diastereomer **9**$_{anti}$ as a major product (82% *ds*, entry 4).

The reaction of a cycloheptanone hydrazone **13** with the *E*-boronate **6** gave an anti adduct **14**$_{anti}$ with 81% *ds* at room temperature (entry 5). On the other hand, the reaction with the *Z*-borate **12** took place more rapidly (at 0 °C) to give the syn diastereomer **14**$_{syn}$ with 98.5% *ds* (entry 6).[6] The inversion of the diastereoselectivity between the acylic (**5**) and the cyclic (**13**) hydrazones suggests to us that the acyclic enamide **5** (and **2a**−**2c**) is in *Z*-geometry. In addition, the observed diastereoselectivity suggests a six-centered boat transition state of the syn carbometalation reaction.[3b]

We can create one additional (entries 7, 9, and 10) and two additional stereogenic centers (entry 8) by trapping the B/Zn intermediate **D** with a carbon electrophile. The reaction between **5** and **6** followed by treatment with allyl bromide (2.4 equiv) in the presence of CuCl (1 equiv) in Et$_2$O gave a $\gamma$-borylhydrazone **15** in 86% yield with overall 99.2% *ds*. When THF or HMPA was used as a solvent, the stereoselectivity eroded to 67% owing to the epimerization of the carbon center to which the Zn and the B atoms are bonded (vide infra). The stereochemistry of this third stereogenic center combined with the syn addition of the first addition reaction indicates that the electrophilic trapping occurred with overall retention of the stereochemistry of the B/Zn intermediate (vide infra). This addition/trapping sequence can be applied for aryl ketone hydrazone to give adduct **19** with 97.6% *ds* (entry 10).

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**Table 1.** Stereoselective Addition to Alkenylboronate and Trapping

| entry[a] | zincated hydrazone[b,c] | alkenyl -boronate[d] | electro -phile[e] | major diastereomer yield[f], dr[g] |
|---|---|---|---|---|
| 1 | **5** (likely Z-major) | **6**: R = Me 99.3% E | H₂O | **9**: 93%, 99.2:0.8 (syn) |
| 2 | **5** | **7**: R = ⁿHex 99.5% E | | **10**: 87%, 99.5:0.5 |
| 3 | **5** | **8**: R = Ph 99.6% E | | **11**: 80%, 99.6:0.4 |
| 4 | **5** | **12** 99.1% Z | H₂O | **9** (anti) 86%, 18.0:82.0 |
| 5[h] | **13** | **6** 99.3% E | H₂O | **14** (anti) 48%, 19.0:81.0 |
| 6 | **13** | **12** 99.1% Z | H₂O | **14** (syn) 75%, 98.5:1.5 |
| 7 | **5** | **6** | allyl Br | **15** 86%, >99.2:0.5:0.2:<0.1 |
| 8 | **5** | **6** | 2-cyclohexenone | **16** 69%, >95%ds[i] |
| 9 | **13** | **12** | methallyl Br | **17** 70%, >94.7:3.5:1.7:<0.1 |
| 10 | **18** | **3** | allyl Br | **19** 80%, 97.6:1.0:1.0:0.4 |

[a] Addition reactions were carried out in hexane at 0 °C for 12–48 h. [b] Zincated hydrazones were prepared as those in Scheme 1. [c] 1.05 equiv of **5** or 1.25 equiv of **13** and **18**. [d] BR′₂ = 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl. [e] Electrophilic trappings were carried out in Et₂O with 1–2 equiv of CuCl and 2–4 equiv of electrophile. [f] Isolated yield. [g] Diastereomeric ratios (dr) were determined by GC analyses of a crude product unless otherwise noted. [h] Addition reaction was carried out for 48 h at room temperature. [i] Percentage of the major isomer over all others determined by ¹H NMR spectra.

The chemistry can be extended to the creation of four stereogenic centers (entry 8). Thus, starting with **5**, a 1,4-addition of the B/Zn intermediate to 2-cyclohexen-1-one in the presence of Me₃SiCl[7] and CuCl afforded the three-component coupling product **16** in 69% overall yield with >95% overall ds. While we defer detailed discussion, we can understand the stereochemistry of the 1,4-addition in terms of the reported transition state of the conjugate addition of an organocopper compound to cyclohexenone[8] (see Supporting Information).

The B/Zn intermediate **D** undergoes slow epimerization as to the C–Zn stereochemistry under the reaction conditions. This is shown by the production of the compounds possessing the same β- and γ-stereochemistry (cf. **15** and **17**) starting with E- and Z-alkenylboronate (entries 7 and 9). We noted that the stereoselectivity of the product starting with the Z-boronate (entry 9) is rather condition-dependent, while that with the E-boronate (entries 7, 8, and 10) is constantly high, considering that the relative configuration of the chelate **D** starting with the E-alkenylboronate is thermodynamically more stable than the one starting with the Z-boronate.

The γ-borylhydrazones such as **17** are amenable to further transformations (eq 2). For instance, hydrolysis of the hydrazone moiety can be achieved readily (albeit slight stereochemistry erosion), the ketone group can be reduced stereoselectively with BH₃·THF, and the boron group was converted stereospecifically to an alcohol (the terminal double bond was hydrogenated before the reduction to avoid complication). The diol **21** was obtained with 85% diastereoselectivity among other minor diastereomers accounting for the rest. Esterification of the diol and recrystallization gave diester **22** with 99% ds, and the stereochemisty was determined by X-ray crystallography.
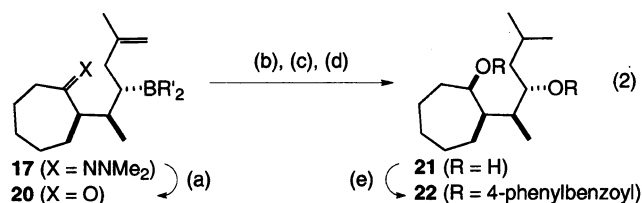
(a) propionic acid/H₂O; 70% yield, 95% ds, (b) Pd/C (0.5 eq) under 2 MPa of H₂ in MeOH, (c) BH₃•THF (3.0 eq) in THF, then in vacuo, (d) MeOH/H₂O₂; 81% yield, 94% net ds for 3 steps, (e) pyridine (6.0 eq)/ 4-phenylbenzoyl chloride (6.0 eq) in THF; 94% yield, after single recrystalization; 56% yield, 99% diastereomeric purity.

**Supporting Information Available:** Details of the experimental procedure and characterization and physical data of products (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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