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Domino Reactions

# Enantioselective Copper(I)-Catalyzed Borylative Aldol Cyclizations of Enone Diones**

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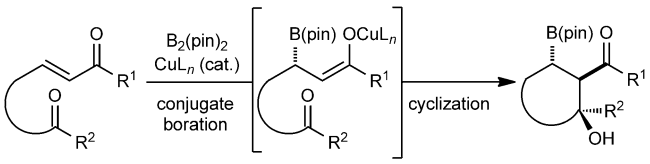
The in situ trapping of metal enolates generated by the catalytic hydrometalation of α,β-unsaturated carbonyl compounds has proven to be a mild and versatile method for carbon–carbon bond construction.[1] Not only does this strategy allow precise control of the site of enolization of substrates containing several acidic sites, the use of chiral metal/ligand complexes can also enable products to be formed with high levels of diastereo- and enantiocontrol. In this context, we and others have developed various copper(I)-catalyzed or copper(I)-mediated reductive aldol,[2–5] Mannich,[6] and Michael[7] reactions to furnish products with high diastereo- and enantioselectivities.

While these processes are effective, the development of related transformations in which metal enolate generation is initiated not by the formation of a carbon–hydrogen bond, but by a carbon–heteroatom bond which can then be exploited in subsequent functionalizations, should also be of high value. Given the recent developments in enantioselective copper(I)-catalyzed conjugate boration reactions,[8,9] we envisaged a domino conjugate boration/aldol cyclization sequence in which a copper enolate generated from the initial conjugate boration is trapped by a pendant ketone to deliver cyclic products containing multiple stereocenters (Scheme 1).

Relevant precedent for such a process is relatively limited.[10] Hoveyda and co-workers have described racemic N-heterocyclic-carbene-catalyzed conjugate boration of a cyclic enone with subsequent in situ trapping of the resulting boron enolate with benzaldehyde,[10a] whereas Kanai, Shibasaki, and co-workers reported a similar enantioselective process catalyzed by a chiral copper/bisphosphine complex.[10b] Recently, Riant and co-workers developed a racemic copper-catalyzed conjugate boration/intermolecular aldol sequence of acyclic or cyclic α,β-unsaturated carbonyl compounds.[10c] However, analogous processes in which the aldol reaction occurs in an intramolecular fashion have not, to our knowledge, been reported, despite the potential for the generation of useful functionalized cyclic building blocks.




***Scheme 1.*** Proposed conjugate boration/aldol cyclization.

In view of the precedent set by Krische and co-workers, who described highly diastereo- and enantioselective rhodium-catalyzed conjugate arylation/aldol cyclizations of enone diones,[11] we wondered whether a related process involving copper-catalyzed conjugate boration could be developed. Herein, we report the enantioselective copper-catalyzed domino conjugate boration/aldol cyclization of enone diones to give a range of highly functionalized bicyclic products.[12–17] This desymmetrization process results in the formation of one boron–carbon bond, one carbon–carbon bond, and four contiguous stereocenters, two of which are quaternary, with high levels of diastereo- and enantioselection.

Our studies commenced with evaluation of various common chiral bisphosphine ligands (**L1**–**L4**; 5.5 mol%) in the domino conjugate boration/aldol cyclization of the enone dione **1a** with $B_2(pin)_2$ (1.1 equiv) in the presence of CuCl (5 mol%) and NaO*t*Bu (7.5 mol%) in THF (0.1M) at room temperature (Table 1, entries 1–4). Although the desired bicyclic product **3a** was formed in greater than 95:5 d.r. [(major isomer):(Σ other isomers)] in several cases, appreciable quantities of the product **2a** resulting from conjugate boration without cyclization were often observed (Table 1, entries 1, 2, and 4). With the Taniaphos ligand **L3**, **2a** was the sole product (Table 1, entry 3). Regarding enantioinduction, the Josiphos ligand **L4**[8c,d] provided the best results, furnishing **3a** as the major product (**3a**/**2a** = 93:7) in 85% *ee* (Table 1, entry 4).[18] Additional optimization revealed that the inclusion of MeOH[8c,d] (2.0 equiv; Table 1, entry 5) and halving the concentration of the reaction (Table 1, entry 6) led to further increases in enantioselectivity, albeit with a lower ratio of **3a**/**2a** (Table 1, entry 6). Fortunately, the use of more-hindered alcohol additives improved this ratio without sacrificing enantioselectivity (Table 1, entries 7 and 8), with *i*PrOH providing the best results (entry 7). It should be noted that there is the potential for enantioenrichment of **3a** through a ligand-controlled double asymmetric process, in which the copper enolate containing the minor stereogenicity formed in

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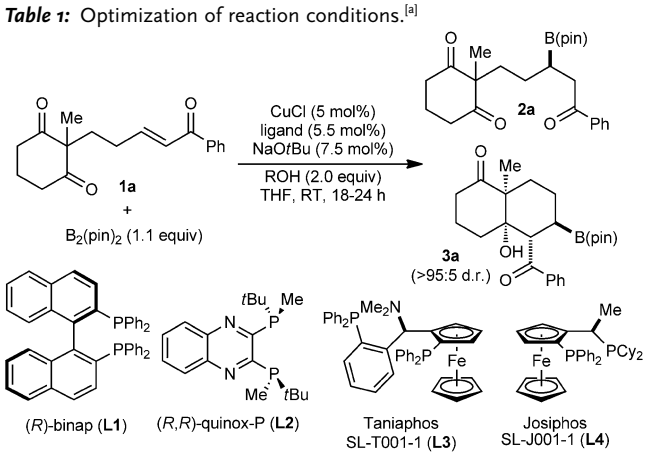
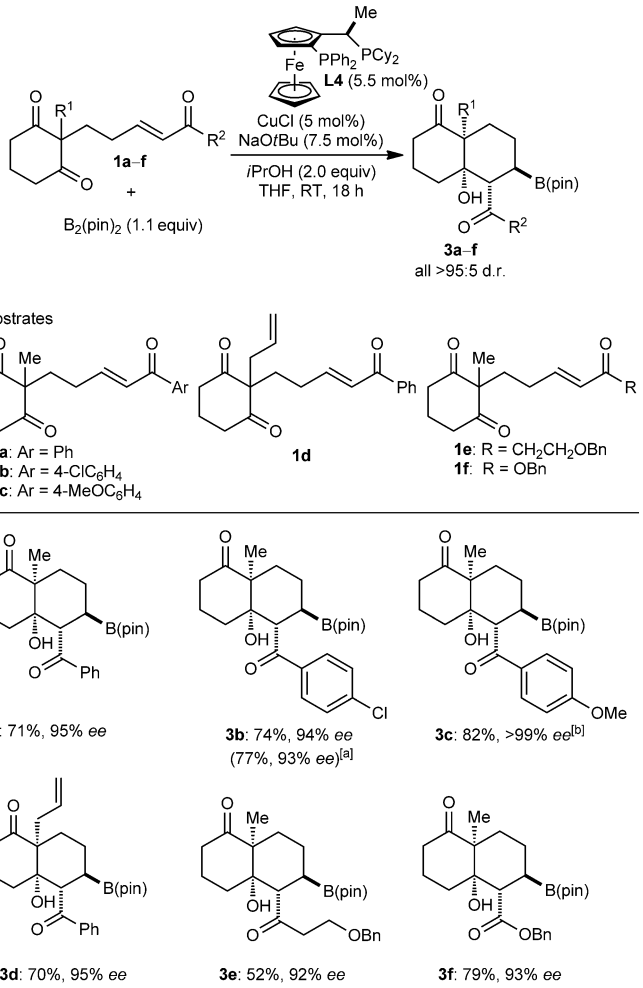
***Table 1:*** Optimization of reaction conditions.[a]

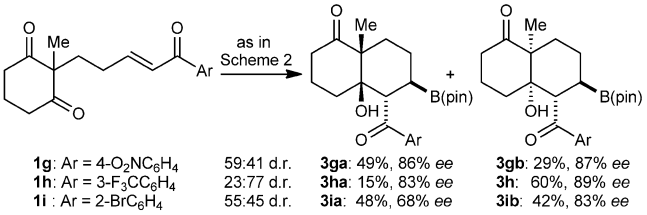



| Entry | Ligand | Conc [M] | ROH | Conv [%][b] | **3a**/**2a**[b] | **3a** *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | **L1** | 0.1 | – | >95 | 86:14 | 70 |
| 2 | **L2** | 0.1 | – | >95 | 31:69 | 16[d] |
| 3 | **L3** | 0.1 | – | 56 | <5:95 | –[e] |
| 4 | **L4** | 0.1 | – | >95 | 93:7 | 85 |
| 5 | **L4** | 0.1 | MeOH | >95 | 87:13 | 90 |
| 6 | **L4** | 0.05 | MeOH | >95 | 72:28 | 95 |
| 7 | **L4** | 0.05 | *i*PrOH | >95 | 87:13 | 94[f] |
| 8 | **L4** | 0.05 | *t*BuOH | >95 | 84:16 | 94 |

[a] Reactions were conducted using **1a** (0.20 mmol). [b] Determined by $^1$H NMR spectroscopy of the unpurified reaction mixture. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Opposite enantiomer of **3a** obtained. [e] Enantiomeric excess of **2a** was 6%. [f] Uncyclized product **2a** was isolated in 12% yield with 93% *ee*. pin = pinacolato, Cy = cyclohexyl.




***Scheme 2.*** Borylative aldol cyclizations of enone diones to form decalins. The reactions were performed with **1a–f** (0.30 mmol) in THF (6 mL). Yields are of pure isolated major diastereomers. Diastereomeric ratios [(major isomer):(Σ other isomers)] were determined by $^1$H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase, and refer to the major diastereomer. [a] Values in parentheses refer to a reaction conducted using 3.15 mmol of **1b**. [b] Reaction conducted with *t*BuOH (2.0 equiv) in place of *i*PrOH.




***Scheme 3.*** Borylative aldol cyclizations of substrates **1g–i**.

the initial conjugate boration either does not cyclize, or cyclizes to form an epimeric product. However, **2a** and **3a** were formed with similar *ee* values (93% *ee* for **2a** and 94% *ee* for **3a**) from the experiment of Table 1, entry 7, which suggests that a double asymmetric process does not occur to any significant extent in this case.

As shown in Scheme 2, a range of enone diones underwent borylative aldol cyclization under the optimized reaction conditions to furnish [6,6]-bicyclic products with high levels of diastereoselection (> 95:5 d.r.) and enantioselection (≥ 92% *ee*).[18] In addition to the original substrate **1a**, which gave **3a** in 71% yield and 95% *ee*, substrates containing a 4-chlorophenyl ketone or a 4-methoxyphenyl ketone performed well (products **3b** and **3c**). Substrate **1d**, containing an allyl group rather than a methyl group at the 2-position of the cyclic 1,3-diketone, was also a competent substrate (product **3d**). The process is not limited to α,β-unsaturated aromatic ketones; the reactions of substrates **1e** and **1f**, which contain an aliphatic ketone and an α,β-unsaturated ester, respectively, were also highly stereoselective (products **3e** and **3f**). The reaction may also be performed on a larger scale. The reaction of **1b** on a 3.15 mmol scale provided 1.06 g (77% yield) of **3b** in 93% *ee*.

The reaction of substrate **1g**, which contains a 4-nitrophenyl ketone, was poorly diastereoselective and gave two separable products (Scheme 3). The major product **3ga** was isolated in 49% yield and 86% *ee*, but interestingly, the relative stereochemistry of this compound differed from those products depicted in Scheme 2.[18] The originally expected product **3gb** was the minor component in this reaction (29% yield, 87% *ee*). Two diastereomeric products were also isolated from the reactions of substrates **1h** and **1i**, which

contain a 3-(trifluoromethyl)phenyl and a 2-bromophenyl ketone, respectively.

Plausible reactive conformations that rationalize the diastereochemical outcomes of these reactions are illustrated in Figure 1. The formation of the products **3a–f**, **3gb**, **3hb**, and

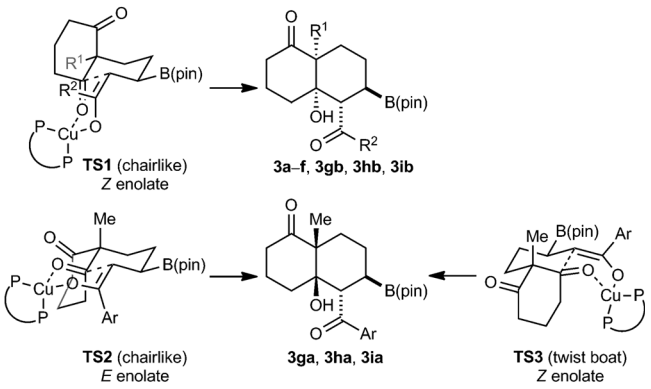
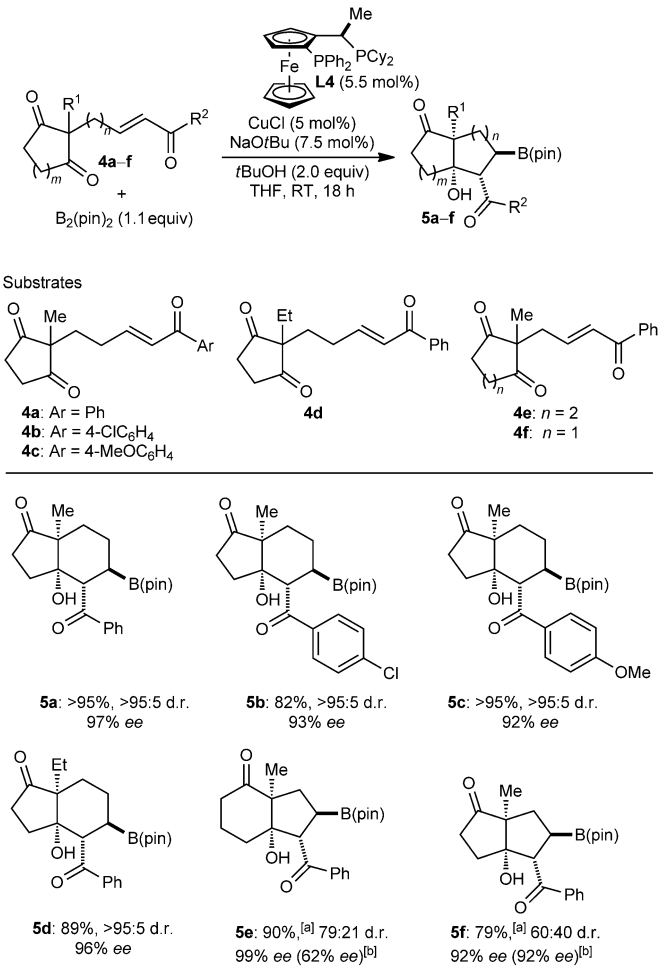



***Figure 1.*** Models to explain diastereoselectivity of the reactions.

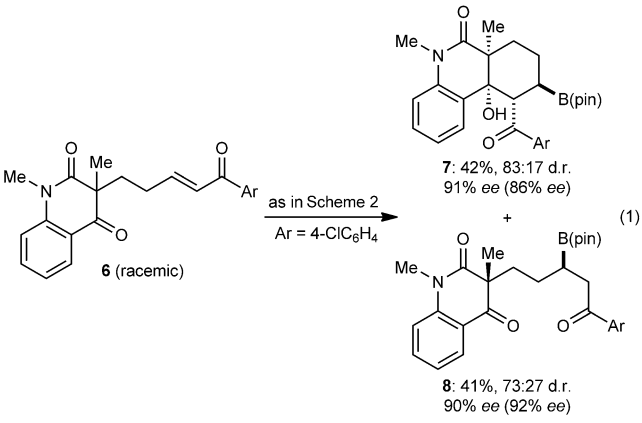
**3ib** may be explained by aldol cyclization through a *Z* enolate in the chairlike Zimmerman–Traxler-type transition-state[19] **TS1**, in which the B(pin) substituent occupies a pseudoequatorial position in the tether connecting the dione and enolate components. The formation of **3ga**, **3ha**, and **3ia** may be accounted for on the basis of cyclization through an *E* enolate in the chairlike transition-state **TS2**, or through a *Z* enolate in the twist-boat transition-state **TS3**.[20] However, the reasons that determine the propensity of a particular substrate to react through one or more of the possible pathways are not clear at the present time.

The scope of the enantioselective borylative cyclization was additionally extended to the preparation of products containing different ring sizes (Scheme 4). In these cases, the use of *t*BuOH in place of *i*PrOH proved to be marginally superior. Pleasingly, [5,6]-, [6,5]-, and [5,5]-bicyclic ring systems were formed with good yields and high levels of enantioinduction (92–99% *ee* for the major diastereomer).[18] As with the decalin systems (Scheme 2), the major diastereomers for the [5,6]-hydrindanes, **5a–d**, have the *syn-syn-anti* configuration shown, as confirmed by X-ray crystallographic analysis of **5d**.[18] Lower levels of diastereoselection were observed with products **5e** and **5f**, which were isolated as inseparable mixtures of diastereomers.

Next, the parallel kinetic resolution[21] of a racemic chiral enone-1,3-dicarbonyl substrate was examined.[11] Under standard conditions using *i*PrOH as the alcohol additive, the substrate **6**, containing a cyclic β-ketoamide, provided the tricycle **7** in 42% yield, 83:17 d.r., and 91% *ee* (for the major diastereomer), along with the uncyclized product **8** in 41% yield, 73:27 d.r., and 90% *ee* (for the major diastereomer) [Eq. (1)].[22] The formation of each of the products **7** and **8** as an inseparable diastereomeric mixture indicates that the parallel kinetic resolution was only moderately effective for this substrate. When the reaction was performed with the achiral ligand $P(OEt)_3$, **7** and **8** were obtained in diastereomeric ratios similar to those indicated in Equation (1), thus suggesting that the diastereoselectivity of the cyclization




***Scheme 4.*** Borylative aldol cyclizations of enone diones to form hydrindanes and diquinanes. The reactions were performed with **4a–f** (0.30 mmol) in THF (6 mL). Yields are of isolated material. Diastereomeric ratios [(major isomer):(Σ other isomers)] were determined by $^1$H NMR analysis of the unpurified reaction mixtures. Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. [a] Isolated as an inseparable mixture of diastereomers. [b] Enantiomeric excess values in parentheses refer to the minor diastereomer, the stereochemistry of which was not assigned unambiguously.

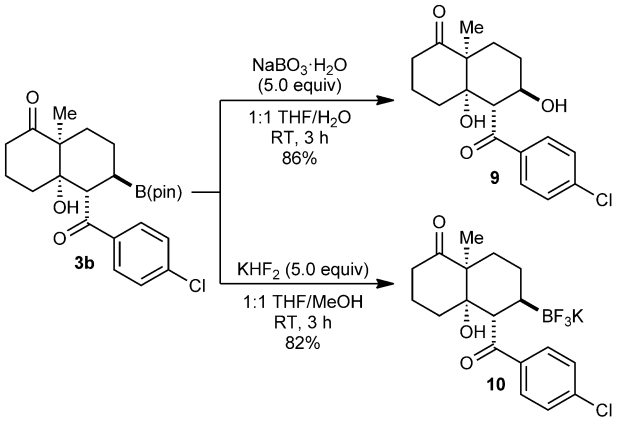



(1)

event is governed predominantly by the substrate. However, the high levels of enantioselectivity obtained for products **7** and **8** in Equation (1) suggests this process is still potentially useful.

To demonstrate the utility of the cyclization products, further transformations of the decalin **3b** were conducted (Scheme 5). Treatment of **3b** with $NaBO_3 \cdot H_2O$[23] provided




***Scheme 5.*** Further transformations of product **3b**.

the secondary alcohol **9** in 86% yield. Furthermore, formation of the potassium trifluoroborate salt **10** was readily achieved by reaction of **3b** with $KHF_2$.[24]

In summary, we have described highly enantioselective copper(I)-catalyzed borylative aldol cyclizations of enone diones that result in densely functionalized decalin-, hydrindane-, and diquinane-based products containing four contiguous stereocenters, two of which are quaternary. Work to develop additional enantioselective metal-catalyzed domino processes is underway in our laboratories.

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[18] The relative and absolute stereochemistries of the products herein were assigned by analogy to those of **3b**, **3ia**, and **5d**, which were determined by X-ray crystallography. See the Supporting Information for full details. CCDC 891571 (**3b**), 891572 (**3ia**), and 891573 (**5d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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