Enantioselective Catalysis

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Enantioselective Synthesis of Boron-Substituted Quaternary Carbon Stereogenic Centers through NHC-Catalyzed Conjugate Additions of (Pinacolato)boron Units to Enones**

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In fond memory of Harry H. Wasserman

Abstract: *The first examples of Lewis base catalyzed enantioselective boryl conjugate additions (BCAs) that generate products containing boron-substituted quaternary carbon stereogenic centers are disclosed. Reactions are performed in the presence of 1.0–5.0 mol% of a readily accessible chiral accessible N-heterocyclic carbene (NHC) and commercially available bis(pinacolato)diboron; cyclic or linear α,β-unsaturated ketones can be used and rigorous exclusion of air or moisture is not necessary. The desired products are obtained in 63–95% yield and 91:9 to >99:1 enantiomeric ratio (e.r.). The special utility of the NHC-catalyzed approach is demonstrated in the context of an enantioselective synthesis of natural product antifungal (−)-crassinervic acid.*

NHC- vs. Cu-Catalyzed enantioselective BCA:
Chemoselectivity: NHC-catalyzed reactions promote BCA selectively in the presence of functional groups such as aldehydes, alkynes, allenes, and phenols

State-of-the-art in catalytic enantioselective BCA:
With R = H (more common): Cu-, NHC-, and phosphine-catalyzed variants reported
With R ≠ H (less common): Only Cu-catalyzed variants reported; Cu-free version unknown

Scheme 1. Comparison of Cu-catalyzed and Cu-free enantioselective boron conjugate addition (BCA). B(pin) = (pinacolato)boron.

Reliable, efficient, and selective catalytic methods for the synthesis of organoboron compounds are of considerable importance.[1] A challenge in organoboron chemistry is the development of catalytic protocols that furnish C–B bonds enantioselectively. There are enantioselective protocols for boron hydride,[2] diboron,[3] proto-boryl,[4] and conjugate additions[5] to unsaturated compounds as well as allylic substitutions[6] that form B-substituted stereogenic centers and are promoted by transition-metal-containing catalysts; related boryl additions to imines have been introduced as well.[7] In the case of boron conjugate addition (BCA) reactions, chiral Lewis base catalysts provide effective alternatives to the Cu-based complexes (Scheme 1);[8] chiral N-heterocyclic carbenes (NHCs) promote enantioselective BCA[9] and offer distinctive chemoselectivity profiles that are otherwise unavailable (Scheme 1).[8d] The large majority of the above protocols, however, lead to products having tertiary boron-substituted carbon centers, and the small number of disclosures focused on the difficult enantioselective BCA processes that generate boron-substituted quaternary carbon centers[10,11] have remained in the domain of Cu catalysis.[12] The lone report on allylic substitutions furnishing allyl-B(pin) products relies on the use of an enantiomerically pure Cu-containing complex.[6b] To the best of our knowledge, there are no examples of Lewis base catalyzed enantioselective reactions that furnish products with a quaternary B-substituted carbon center; such transformations would constitute a notable addition to the collection of catalytic enantioselective C–B bond-forming processes.

Herein, we disclose the first instances of Lewis base catalyzed enantioselective BCA transformations that deliver cyclic or acyclic products with a boron-substituted quaternary carbon; products are obtained in 63–95% yield and 91:9 to >99:1 enantiomeric ratio (e.r.). The catalytic method's unique features are highlighted by an enantioselective synthesis of natural product crassinervic acid.

We first probed a number of easily accessible chiral NHCs that might be used to catalyze the formation of **4a** efficiently and enantioselectively (Table 1). C_2-Symmetric carbenes derived from **1a**,**b** promote the BCA in moderate yield and enantioselectivity (entries 1 and 2, Table 1). There is complete substrate consumption in 14 h when C_1-symmetric **2a**[13] is used; **4a** is obtained in 88:12 e.r. (entry 3, Table 1). Reaction with the *m*-*i*Pr-substituted derivative **2b** is less efficient and selective (68% conv., 67:33 e.r.; entry 4, Table 1). When the NAr moieties of the NHC catalysts are dissymmetric (i.e., **3a–c** in entries 5–7, Table 1), BCA is efficient (>90% conv.) and highly enantioselective (>90:10 e.r.). Transformation with **3c** furnishes **4a** in 90% yield and 96:4 e.r. Additional noteworthy points are:

1) When the reaction is carried out with 1.0 mol% **3c** and 5.0 mol% dbu, under conditions otherwise identical to those

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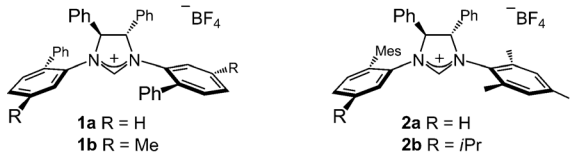
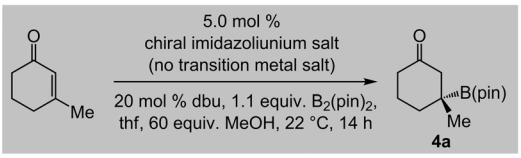
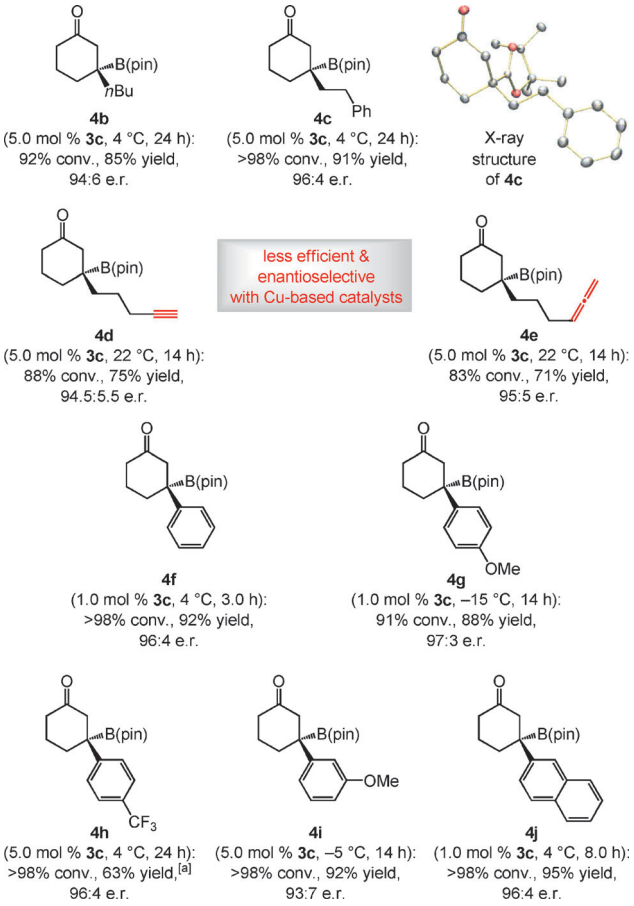
Table 1: Examination of chiral imidazolinium salts as catalyst precursors.[a]





Entry	Imidazolinium salt	Conv. [%][b]	Yield [%][c]	e.r.[d]
1	**1a**	53	46	84:16
2	**1b**	96	85	84:16
3	**2a**	>98	79	88:12
4	**2b**	68	54	67:33
5	**3a**	>98	74	91.5:8.5
6	**3b**	91	82	90:10
7	**3c**	>98	90	96:4

[a] Reactions were performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^{1}H NMR spectra of unpurified mixtures (±2%). [c] Yields of isolated and purified products (±5%). [d] Determined by GC analysis (±2%); see the Supporting Information for details. dbu = 1,8-diazabicyclo[5.4.0]undec-7-ene; Mes = 2,4,6-$Me_3C_6H_2$.



Scheme 2. β-Boryl cyclohexenones can be accessed efficiently and enantioselectively. For general conditions see Table 1. [a] Proto-deboration byproduct formed (ca. 30%); 63% is the yield of pure **4h**.

in entry 7, there is 87% conversion to **4a** (84% yield, 95:5 e.r.).

2) Rigorous exclusion of air and moisture is not required with the NHC-catalyzed transformations; **4a** can be isolated in 92% yield and 95:5 e.r. when the reaction is performed in a typical fume hood.[14]

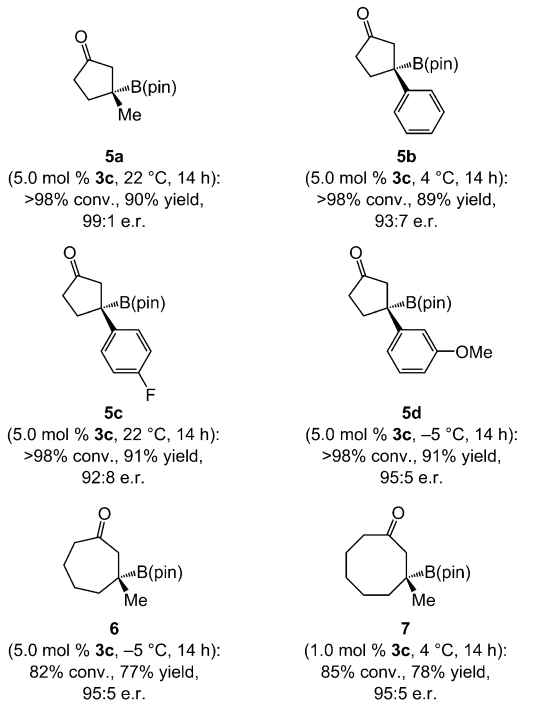
3) Preparation of **3c** is more efficient[15] than the synthesis of the catalyst precursor identified previously as optimal for BCA of the disubstituted cyclic enones.[8d]

4) Generally, NHC-catalyzed BCA processes that furnish products that contain B-substituted quaternary carbon stereogenic centers are more enantioselective than than the analogous reactions with disubstituted cyclic enones (e.g., β-B(pin)-substituted cyclohexanone formed in 87:13 e.r. vs. 96:4 e.r. for **4a**).

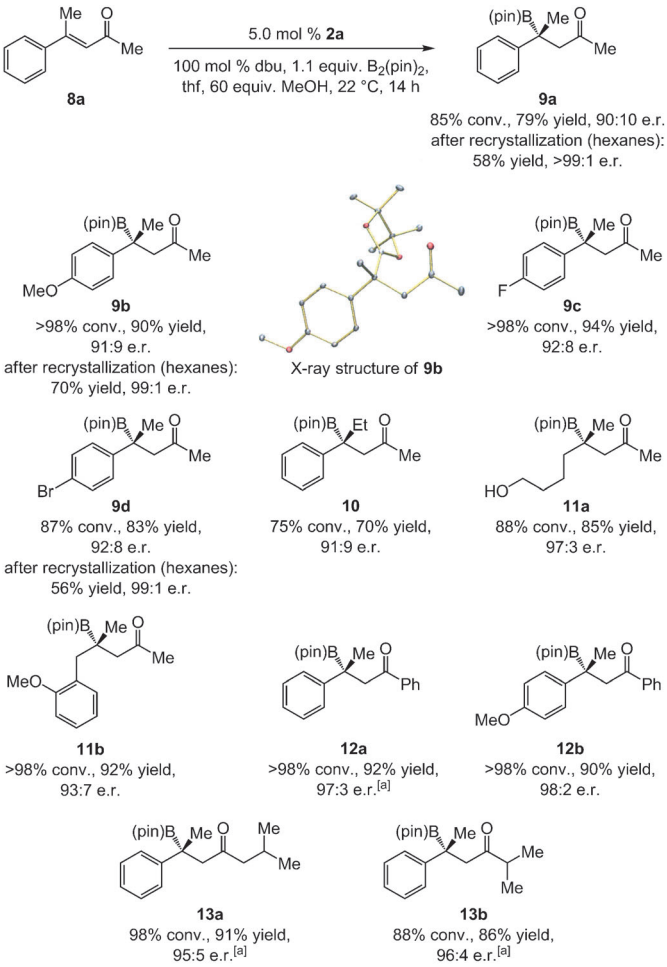
5) When the transformation in entry 7 of Table 1 is carried out with 5.0 mol% CuCl, **4a** is obtained in only 67:33 e.r. (>98% conv., 89% yield), underscoring the disparate mechanistic attributes of the NHC-catalyzed pathways.

β-Substituted cyclohexenones, including those containing an alkyl (cf. **4b–e**) or different aryl groups (cf. **4f–j**), undergo NHC-catalyzed BCA to afford products in 63–95% yield and 93:7–97:3 e.r. (Scheme 2).[16] Alkyl-substituted cyclic enones with a terminal alkyne (cf. **4d**) or an allene (cf. **4e**) are effective substrates. As the data for **4f,g** and **4j** indicate, 1.0 mol% **3c** and 5.0 mol% dbu may be used with similar effectiveness. Catalytic BCA to enones with a relatively bulky substituent is somewhat less enantioselective; for example, the transformation of β-*i*Pr-cyclohexenone delivers the expected β-boryl-cyclohexanone in 71% yield (75% conv.) and 86:14 e.r. (at 4 °C). The X-ray structure of **4c** establishes the absolute configuration of the BCA product.[14] When enantioselective synthesis of alkyne-containing **4d** was attempted under the Cu-catalyzed conditions introduced by Shibasaki (12 mol% (*R*,*R*)-QuinoxP*, 10 mol% $CuPF_6$-$(MeCN)_4$, 15 mol% LiO*t*Bu, 1.5 equiv $B_2(pin)_2$, dmso, 22 °C, 12 h),[12a] the product was isolated in 45% yield and 88:12 e.r.; with allene-bearing **4e**, a complex mixture of unidentified products was formed. Such discrepancies are likely rooted in the competitive reaction of the Cu-B(pin) complex with alkyne[17] and allene moieties.[18]

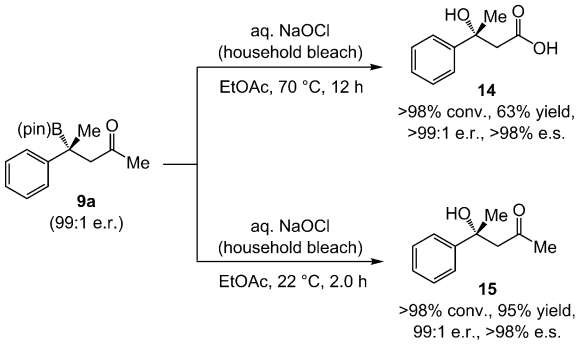
β-Substituted cyclopentenones undergo reaction to furnish **5a–d** in 89–91% yield and 92:8–99:1 e.r. (Scheme 3). Additions to cycloheptenone (cf. **6**) and (for the first time) cyclooctenone (cf. **7**) afford the desired products in 77–78% yield and 95:5 e.r.



Scheme 3. NHC-catalyzed BCA reactions can be performed with five- or seven- and eight-membered-ring enones.



Scheme 4. Efficient and highly enantioselective NHC-catalyzed BCA reactions of acyclic enones. [a] Performed at 35 °C.



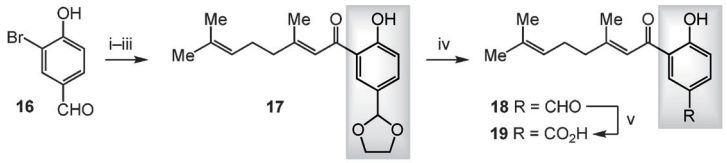
Scheme 5. Subjection of an enantiomerically enriched BCA product to common bleach at room temperature affords the ketone aldol product or the derived β-hydroxy carboxylic acid (e.s. = product enantiomeric excess/substrate enantiomeric excess × 100).

Transformations of acyclic aryl- or alkyl-substituted enones[19] deliver linear β-boryl ketones in 56–94% yield and up to >99:1 e.r. (Scheme 4). In some cases, simple recrystallization delivers materials of exceptional enantiomeric purity. Unlike the BCA of cyclic enones, reactions proceed most enantioselectively with imidazolinium salt **2a**.[20] For example, when **3c** is used in the NHC-catalyzed BCA to enone **8b**, β-boryl ketone **9b** is isolated in 69% yield and 89:11 e.r. (vs. 90% yield and 91:9 e.r.). We have shown that BCA promoted by a chiral NHC-Cu complex leading to phenylketone **12a** proceeds with lower selectivity[12b] even though it is performed at −30 °C (82.5:17.5 in 24 h vs. 97:3 e.r. with **2a** at 35 °C in 14 h).

A deficiency of the NHC-catalyzed BCA is its ineffectiveness with enoates. We have established that treatment of a β-boryl product with common household bleach for 12 h at 70 °C[21] converts the C–B bond to a tertiary alcohol and the methyl ketone to a carboxylic acid (Scheme 5). At room temperature, β-hydroxyl ketone **15** is obtained in 95% yield after two hours.[22]

Our enantioselective synthesis of the antifungal natural product (−)-crassinervic acid[23] demonstrates the advantages of the present approach (Table 2 and Scheme 6).[24] It should be noted that generally efficient and enantioselective aldol additions to ketones are yet to be developed.[25] Under NHC catalysis and two of the more effective sets of conditions involving phosphine- and NHC-Cu complexes (conditions A–C, respectively), there is complete consumption of acetal-containing enone **17**, but it is the NHC-catalyzed BCA that delivers the highest e.r. (84:16 vs. 60:40 and 69:31). Subjection of **18**, containing a phenol and an aldehyde group, to the NHC-catalyzed BCA conditions affords **23** in 72% yield and 95:5 e.r. In contrast, treatment with the chiral Cu complex derived from diamine **17**, effective for BCA to linear β,β-disubstituted ketones,[12c] affords the desired product in only 19% yield; with **21**[12b] as the catalyst source, <2% conversion is observed.[26] Finally, when **19**, containing a phenol and a carboxylic acid is used, only the NHC-catalyzed process

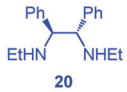
Table 2: Comparison of the BCA step with different substrates en route to (−)-crassinervic acid.[a]

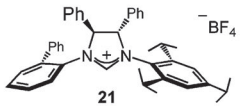


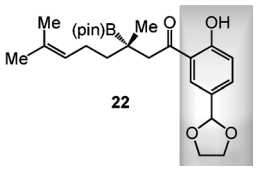
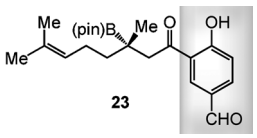
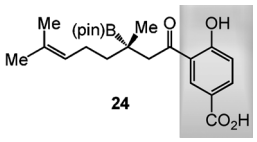
BCA Conditions A (NHC-catalyzed): 5.0 mol % **2a**, 0.40–1.40 equiv. dbu, 1.1 equiv. $B_2(pin)_2$, thf, 60 equiv. MeOH, 22–35 °C, 8.0–14 h

BCA Conditions B (phosphine–Cu-catalyzed): 12 mol % **20**, 10 mol % $CuPF_6(MeCN)_4$, 0.15–1.15 equiv. LiO*t*Bu, 1.5 equiv. $B_2(pin)_2$, 2.0 equiv. *i*PrOH, dme, 22 °C, 24 h

BCA Conditions C (NHC–Cu-catalyzed): 5.0 mol % **21**, 5.0 mol % CuCl, 0.13–1.13 equiv. NaO*t*Bu,1.1 equiv. $B_2(pin)_2$, 1.2 equiv. MeOH, thf, –30 °C, 24 h; HCl workup

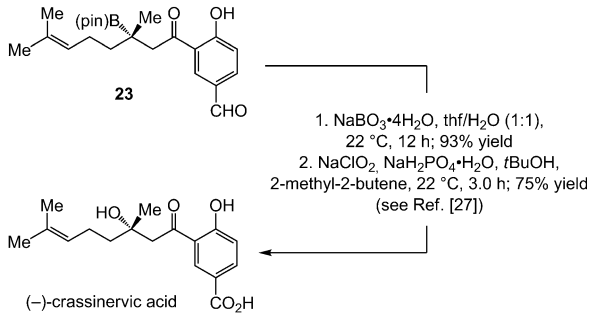




Product	Conditions	Conv. [%][b]	Yield [%][c]	e.r.[d]
	**A**; 0.4 equiv dbu, 22 °C, 14 h	>98	63	84:16
	B; 0.15 equiv LiO*t*Bu, 22 °C, 24 h	87	78	60:40
	C; 0.13 equiv NaO*t*Bu, −30 °C, 24 h	>98 (to **23**)	82 (of **23**)	69:31
	**A**; 0.4 equiv dbu, 35 °C, 8.0 h	>98	72	95:5
	B; 0.15 equiv LiO*t*Bu, 22 °C, 24 h	>98	19	n.d.
	C; 0.13 equiv NaO*t*Bu, −30 °C, 24 h	>98	<2	n.a.
	**A**; 1.4 equiv dbu, 35 °C, 8.0 h	>98	70	88.5:11.5
	B; 1.15 equiv LiO*t*Bu, 22 °C, 24 h	>98	<10	n.d.
	C; 1.13 equiv NaO*t*Bu, −30 °C, 24 h	>98	22	n.d.

[a] General synthesis conditions: i) $HO(CH_2)_2OH$, 10 mol% *p*TsOH·H_2O, tol., reflux, 12 h; 90% yield. ii) 3.0 equiv *t*BuLi, thf, −78 °C; geranial, −78 °C, 2.0 h. iii) 1.0 mol% $(n\text{-}Pr)_4NRuO_4$, *N*-methylmorpholine *N*-oxide, CH_2Cl_2, 22 °C, 2.0 h. iv) 10 mol% *p*TsOH, acetone, 22 °C, 10 min.; 63% overall yield for three steps. v) $NaClO_2$, NaH_2PO_4·H_2O, *t*BuOH, H_2O, 2-methyl-2-butene, 22 °C, 3.0 h; 82% yield. Reactions were performed under N_2 atmosphere. [b] Determined by analysis of 400 MHz ^1H NMR spectra of unpurified mixtures (±2%). [c] Yields of isolated and purified products (±5%). [d] Determined by GC analysis (±2%). See the Supporting Information for details. n.a. = not available, n.d. = not determined.

is efficient. Oxidation of **23** with $NaBO_3$ affords the tertiary alcohol in 93% yield (Scheme 6), which has been converted to the target molecule (75% yield).[27]



Scheme 6. Conversion of organoboron compound **23** to (−)-crassinervic acid.

Investigations regarding the elucidation of mechanistic details of the NHC-catalyzed reactions are in progress and will be reported shortly.

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