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Article

Stereodivergent Nucleophilic Additions to Racemic β-Oxo Acid Derivatives: Fast Addition Outcompetes Stereoconvergence in the Archetypal Configurationally Unstable Electrophile

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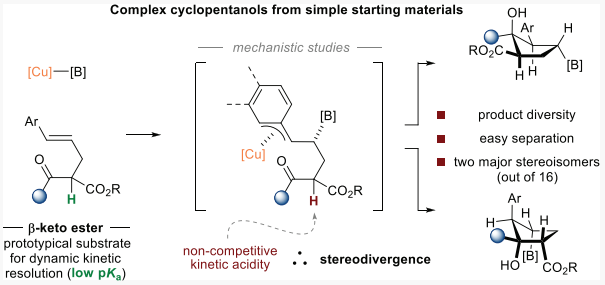
ABSTRACT: Additions of carbon nucleophiles to racemic α-stereogenic β-oxo acid derivatives that deliver enantiomerically enriched tertiary alcohols are valuable, but uncommon. This article describes stereodivergent Cu-catalyzed borylative cyclizations of racemic β-oxo acid derivatives bearing tethered pro-nucleophilic olefins to deliver highly functionalized cyclopentanols containing four contiguous stereogenic centers. The reported protocol is applicable to a range of β-oxo acid derivatives, and the diastereomeric products are readily isolable by typical chromatographic techniques. α-Stereogenic-β-keto esters are typically thought to have extreme or spontaneous configurational fragility, but mechanistic studies for this system reveal an unusual scenario wherein productive catalysis occurs on the same time scale as background substrate racemization and completely outcompetes on-cycle epimerization, even under the basic conditions of the reaction.



INTRODUCTION

The conversion of racemic starting materials to stereochemically complex products through stereoconvergent pathways is a powerful synthetic tool.[1] As the prototypical case, hydrogenative stereoconvergent reactions of α-substituted β-oxo acid derivatives[2] have been widely employed in the scalable production of enantiomerically enriched secondary alcohols.[3] Stereoconvergency is achieved by racemization between substrate enantiomers **1a** and **1b** through an achiral enol(ate) intermediate. Rapid starting material racemization and high selectivity for one substrate enantiomer in the productive catalytic reaction are obligatory conditions for obtaining the product **1c** in high yield and enantiopurity (Scheme 1a).

Despite the theoretical capacity of β-oxo acid derivatives to deliver enantioenriched tertiary alcohols[4] through stereoconvergent processes, non-hydrogenative enantioconvergent reactions of this class of compounds remain rare.[5] Extant methods involve *in situ* activation of a pendant substrate functional group (**1e** → **1g** and **1f** → **1h**) for the intramolecular delivery of a catalytically generated carbon-based nucleophile (Scheme 1b). Two known examples leverage the basic conditions necessary for the generation of chiral *N*-heterocyclic carbene (NHC) catalysts to promote simultaneous generation of the active nucleophile and racemization/epimerization of the electrophiles.[5a,c,d] These methods rely on the assumption that for the archetypal configurationally unstable electrophiles (namely β-dicarbonyl compounds), the rate of interconversion between substrate enantiomers (k_{rac}) and/or activated diastereomers (k_{epim}) is fast and outcompetes the rate of cyclization (k_{cycl}). Scenario 1 in Scheme 1b graphically summarizes the relevant rate requirements. An alternative mechanism for stereoconvergency (Scenario 2) requires that the rate of substrate racemization outcompete enantiomer-selective substrate activation by the chiral catalyst ($k_{rac} > k_{act(R)} > k_{act(S)}$) and the activated intermediate cyclize onto the pendant ketone before epimerization occurs ($k_{cycl(R)} > k_{epim}$). This mode would require high levels of substrate/catalyst stereodifferentiation during the activation event at the distal site and has not, to the best of our knowledge, been unambiguously demonstrated.

In extant cases,[5] some of these stereochemical complications are simplified by the fact that engagement of the substrate with the catalyst (i.e., generation of Breslow intermediates) does not introduce new chiral centers. In the interest of generating a higher level of stereochemical complexity in cyclized products, we wondered if an alternative strategy that involves stereoselective activation of a pronucleophilic olefin tethered within a chiral racemic β-oxo acid derivative (**2a** and **2b**) might advance the art. The *in situ*-generated activated organometallic intermediates **2c** (and **2d**) were hypothesized to serve as competent nucleophiles in complexity-building stereoconver-

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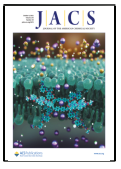

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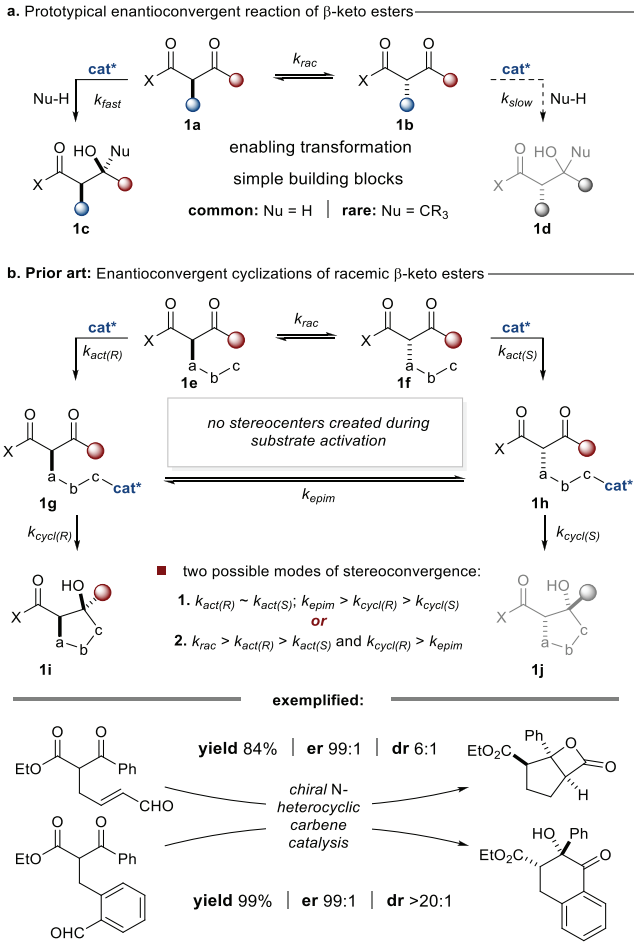
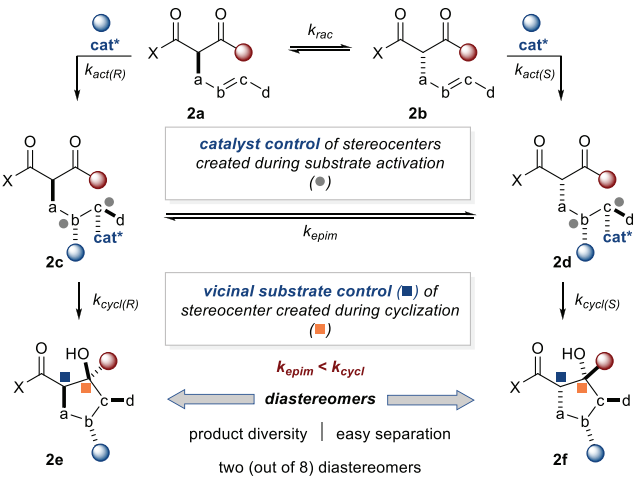
Scheme 1. Stereoconvergent Reactions with β-Oxo Acid Derivatives



gent annulations of β-dicarbonyls (Scheme 2). Transformations in which the generation of the active organometallic intermediate occurs in parallel with the formation of a carbon-heteroatom bond (cf. blue sphere in Scheme 2) could in principle be good candidates for downstream diversification reactions. With this hypothetical approach, two additional stereogenic centers would be created during the substrate activation step. Given the recent success in the development of catalytic stereoselective borylative functionalization of π-bonds,[6] we envisioned a sequenced borylative cyclization in which the resultant alkylmetal intermediate would be trapped by a pendant ketone (**2c** → **2e** or **2d** → **2f**). This approach is reminiscent of one deployed in the desymmetrization of 1,3-diketones;[7] however, to the best of our knowledge, there are no examples of this type of transformation using chiral, racemic electrophiles. This paper describes the development of stereoselective Cu-catalyzed borylative cyclization reactions for the rapid assembly of functionalized cyclopentanols. In contrast to previous methods, we demonstrate through mechanistic studies that substrate-controlled diastereoselective cyclization outcompetes epimerization of the activated complex, thereby delivering a system that exhibits stereodivergent behavior rather than stereoconvergency.[8] The findings provide important cautionary information about assumptions around the configurational lability of β-keto esters.

Scheme 2. This Work: Stereodivergent Cyclization of Racemic β-Oxo Acid Derivatives



RESULTS AND DISCUSSION

Optimization Studies. We began our studies with the reaction of β-keto ester **3a** and the chiral nonracemic copper complex generated from ligand **5a.** While the reaction proceeded in high yield to the desired product, it displayed modest enantioselectivity and ~1:1 diastereoselectivity (Table 1, entry 1). (Negligible quantities of the other six possible diastereomers were observed.) Encouraged by the high yields, various chiral nonracemic ligands were surveyed in an effort to increase the stereoselectivities of the reaction (Table 1, entries 2−6).[9] Employing (1*R*,1′*R*,2*S*,2′*S*)-DuanPhos[10] (**5b**) as a ligand afforded cyclopentanols **4a** and **4a'** in good yield, both with 92:8 er, although the diastereoselectivity remained unchanged (Table 1, entry 2). Other ligands failed to improve the stereoselectivity of the reaction.[9] A screening of different inorganic bases (Table 1, entries 7−9) was performed, and while yields varied, there was no significant impact on the diastereoselectivity. The rate of racemization of configurationally labile substrates can be accelerated in the context of stereoconvergent reactions by using sterically unencumbered organic bases;[11] however, their use here did not result in an improvement of the diastereoselectivity (entry 10).[9] Other parameters such as alcohol additive, temperature, solvent, catalyst loading, identity of the diboron reagent, and Lewis acid additives were evaluated (entries 11−14); the full details for our efforts to optimize the diastereoselectivity of this transformation can be found in the Supporting Information.[9] At this juncture, the use of K_2CO_3 (0.5 equiv), ^{i}PrOH (2.0 equiv), and bis(pinacolato)diboron (B_2pin_2, 1.5 equiv), (Table 1, entry 8) provided cyclopentanols **4a** and **4a'** in 95% yield, and 92:8 er as a 1.1:1 mixture of diastereomers. Under these reaction conditions, *two out of 16* possible stereoisomers were predominantly obtained, and these two were easily isolated by conventional chromatographic techniques. Intrigued by these findings, we sought greater insight to rationalize what microscopic features of this reaction impeded this substrate from undergoing fully stereoconvergent borylative cyclization.

Mechanistic Studies. A number of plausible reaction pathways could account for the initial observations described above. On the basis of literature precedent,[12] a proposed catalytic cycle for the stereodivergent borylative cyclization of β-oxo acid derivatives is depicted in Scheme 3a. The *in situ*-

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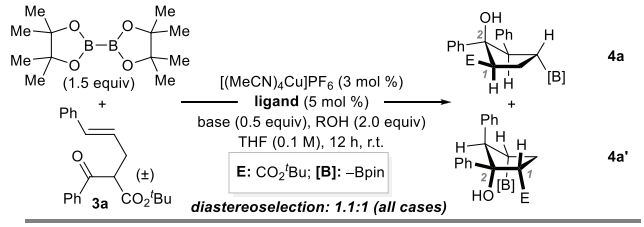
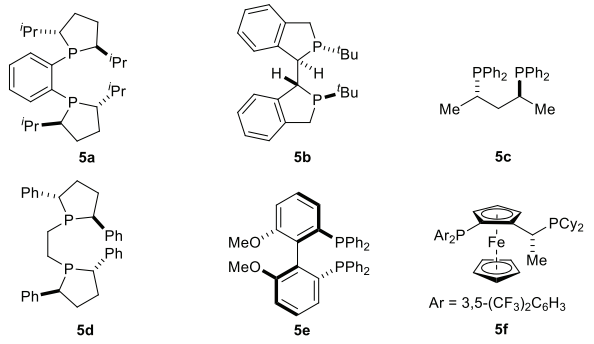
Table 1. Initial Studies and Reaction Optimization





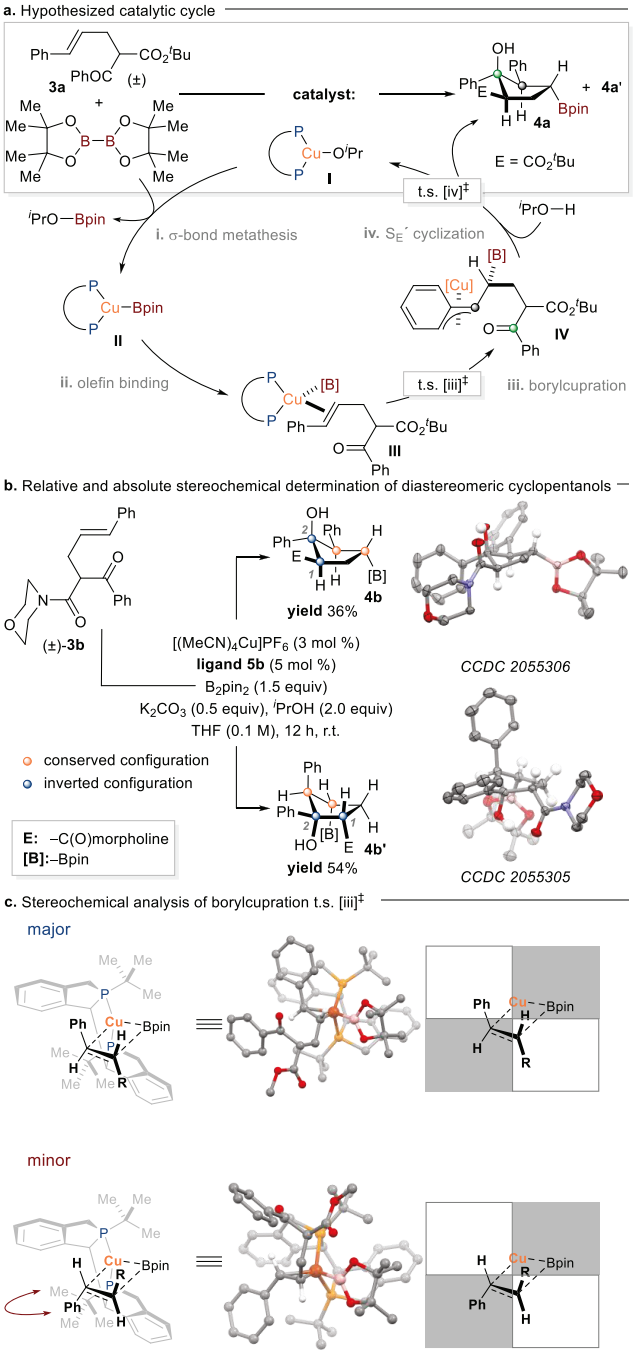
entry[a]	ligand	base	ROH	yield (%)[b]	er[c]
1	5a	KO^{t}Bu	^{i}PrOH	96	70:30
2	5b	KO^{t}Bu	^{i}PrOH	94	92:8
3	5c	KO^{t}Bu	^{i}PrOH	87	65:35
4	5d	KO^{t}Bu	^{i}PrOH	85	85:15
5	5e	KO^{t}Bu	^{i}PrOH	10	54:46
6	5f	KO^{t}Bu	^{i}PrOH	25	60:40
7	5b	NaO^{t}Bu	^{i}PrOH	95	91:9
8	5b	LiO^{t}Bu	^{i}PrOH	60	90:10
9	5b	K_2CO_3	^{i}PrOH	98	92:8
10[d]	5b	NMP	^{i}PrOH	80	85:15
11	5b	K_2CO_3	MeOH	69	92:8
12	5b	K_2CO_3	^{t}BuOH	14	91:9
13[e]	5b	K_2CO_3	^{i}PrOH	10	92:8
14[f]	5b	K_2CO_3	^{i}PrOH	95	92:8

[a]All reactions were carried out on a 0.20 mmol scale. We use prime (′) to denote inversion of configurations for C_1 and C_2 (*vide infra*). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture using phenanthrene as an internal standard. [c]Enantiomeric ratio of the "major" diastereomer determined by HPLC using a chiral stationary phase. See SI for e.r. of both diastereomers [d]NMP = *N*-methylpyrrolidine. [e]Reaction performed at −10 °C. [f]Reaction performed at 50 °C.

generated ligated Cu-^{i}OPr (**I**) undergoes *σ*-bond metathesis with B_2Pin_2 to generate ligated borylcopper intermediate (**II**). After formation of an alkene complex (**III**), regioselective and stereospecific *syn* migratory insertion[13] across the styrene generates benzylic copper intermediate (**IV**), which undergoes S_E' cyclization facilitated by the alcohol additive to release the diastereomeric cyclopentanol products and regenerate the ligated copper alkoxide (**I**).

Mechanistic studies were initiated by first determining the relative and absolute stereochemistry of the diastereomeric cyclopentanols. Single crystals were grown for both diastereomers of the related morpholine-derived *β*-keto amide substrate (**3b**), which exhibited behavior similar to that of *β*-keto ester **3a**. The stereochemistry was corroborated in the ester series through downstream intermediate **4a'** (*vide infra*); all other products were assigned by analogy. The single crystals

Scheme 3. Proposed Catalytic Cycle, Determination of Absolute Stereochemistry, and DFT Analysis of Alkene Borylcupration



used for the X-ray diffraction studies then were independently subjected to chiral HPLC analysis to confirm that the major enantiomers had been analyzed during each of the experiments (see the Supporting Information for additional details). The X-ray crystallographic analysis of morpholinoamides **4b** and **4b'** revealed a conserved *anti*-relationship between the boronic ester and the adjacent aryl ring (orange spheres), and a conserved *syn* relationship between the tertiary hydroxyl group and amide (blue spheres). As revealed in Scheme 3b, the diastereomeric products display conserved absolute configurations that are the same at the boron- and aryl-bearing

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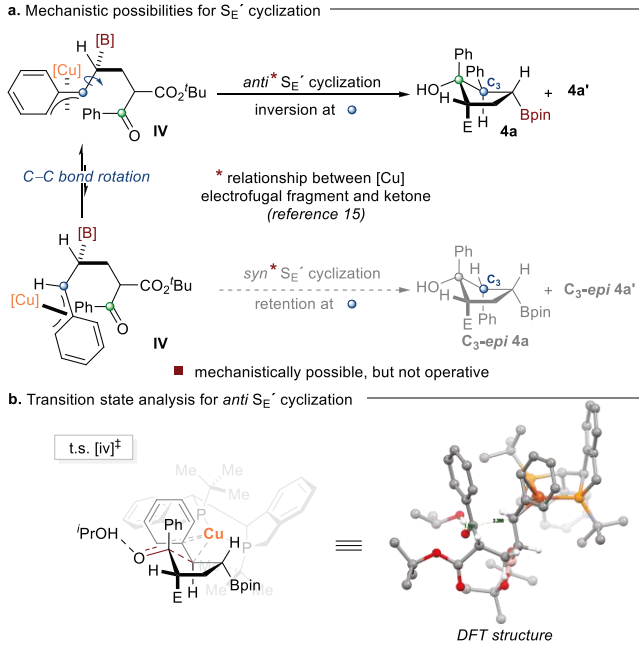
methine stereocenters (orange) but inverted at the alcohol- and amide-bearing stereogenic centers (blue).

In the simplest sense, the structural studies suggest a stereoselective alkene borylcupration step (Scheme 3a, step iii) and a second-stage cyclization (step iv) that selects for two of four possible products. With respect to the former event, the C_2-symmetry of the optimal Duanphos ligand, coupled with the known *syn*-borylcupration mechanism,[13] allows for the construction of an informative quadrant diagram to understand the stereochemical outcome (Scheme 3c). In the preferred diastereomeric transition structure, the (*E*)-alkene inserts into the Cu−B bond in an orientation that places the aryl and alkyl substituents of the olefin in the quadrants unoccupied by the ligand's *tert*-butyl group. The minor transition structure would be expected to suffer the illustrated unfavorable steric interactions when the opposite alkene diastereoface binds to copper. These results were further confirmed by density functional theory (DFT) studies at the level of M062X[14a] approximate functional and a compound Pople basis set (see the Supporting Information for additional details).[14b,c]

To account for the conserved *anti*- relationship between the boronic ester and the aryl group after *syn*-migratory insertion, the illustrated benzylcopper species **IV** is proposed to undergo *anti* S_E''' cyclization, where the electrofugal copper fragment is released peripherally from the C−C bond forming event (Scheme 4).[15] Mechanistically, both *anti* (stereoinvertive) or

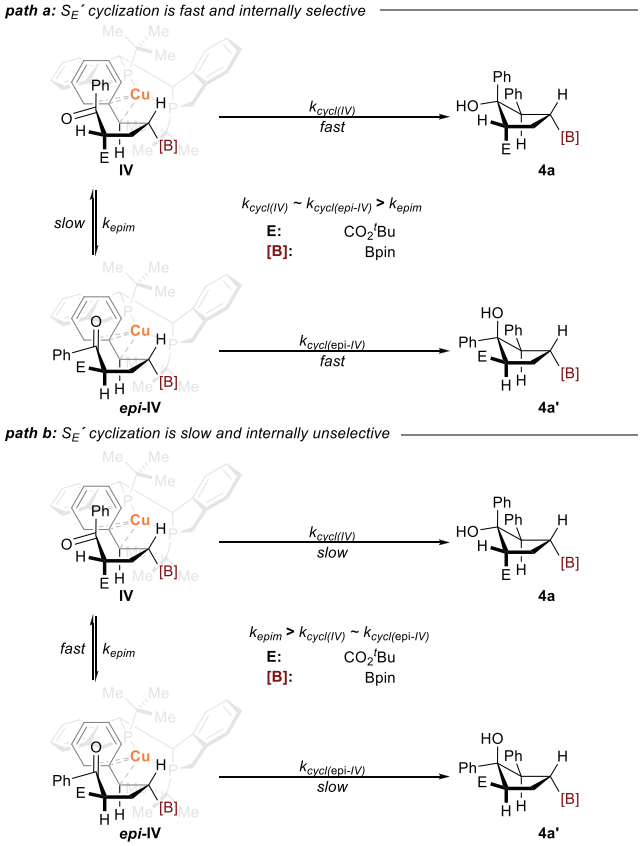
Scheme 4. Stereochemical Analysis for S_E' Cyclization[15]



syn (stereoretentive) pathways are possible,[13d,15d−f] but stereoisomers arising from a *syn* mechanism were never observed, regardless of the steric and electronic parameters of the substrates and the catalyst (Scheme 4a). For clarity, an optimized DFT transition state structure that accounts for one of the diastereomeric products via an *anti* S_E''' cyclization mechanism is depicted in Scheme 4b (see the Supporting Information for additional details).

We then turned our attention to understanding the effect of enolization rate on the stereochemical outcome of the reaction. Two reasonable mechanisms for this reaction can be evaluated in the context of these experimental observations (Scheme 5): an S_E'' cyclization that is fast and internally selective (path a),

Scheme 5. Plausible Mechanisms to Account for Stereodivergency



or an S_E' process that is slow relative to equilibration, and completely internally unselective (path b). To distinguish between these two possibilities, chirality was use as a probe.[16] The synthesis of trifluoromethylphenyl ketone (*R*)-**3c** allowed us to track changes in the stereoisomeric composition of the starting material and products *in situ* using ^{1}H and ^{19}F NMR spectroscopy (Scheme 6). (−)-Menthol was incorporated into the substrate design to allow spectroscopic differentiation of intermediates. The stereochemical information on the menthol auxiliary does not affect the stereochemical outcome of the reaction: a 1.1:1 mixture of diastereomeric products was generated from the 1:1 epimeric mixture of starting *β*-keto ester **6** (Scheme 6a). The synthesis of diastereoenriched *β*-keto ester (*R*)-**3c** was straightforward (Scheme 6b). Aldol reaction between menthyl ester **6** and 4-trifluoromethyl benzaldehyde afforded a mixture of all four diastereomeric *β*-hydroxy esters. A single diastereomer of *β*-hydroxy ester (**7**, CCDC 2087120) was isolated by flash column chromatography and oxidized using Dess-Martin periodinane.[16b,17] The stereodefined *β*-keto ester (*R*)-**3c** was obtained in high yield without erosion on the diastereomeric composition (as determined by ^{1}H and ^{19}F NMR spectroscopic analysis).

The borylative cyclization reaction of ketone (*R*)-**3c** was conducted under standard conditions and monitored by ^{19}F NMR spectroscopy. In contrast to reactions of (±)-**3a** and (±)-**3b**, at low conversion, the product **4c** was formed with a diastereomer ratio of 19:1 (Scheme 6c). As the reaction

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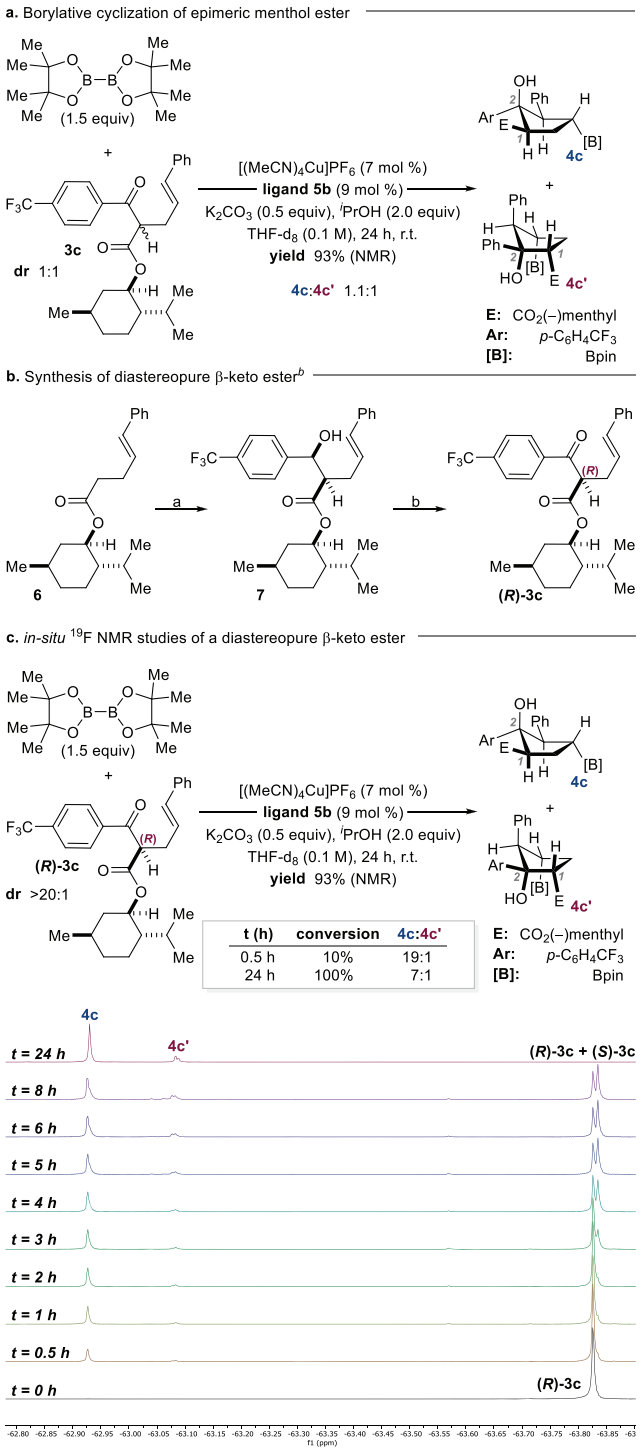
Scheme 6. Experiments to Examine the Origin of Diastereodivergency[a]

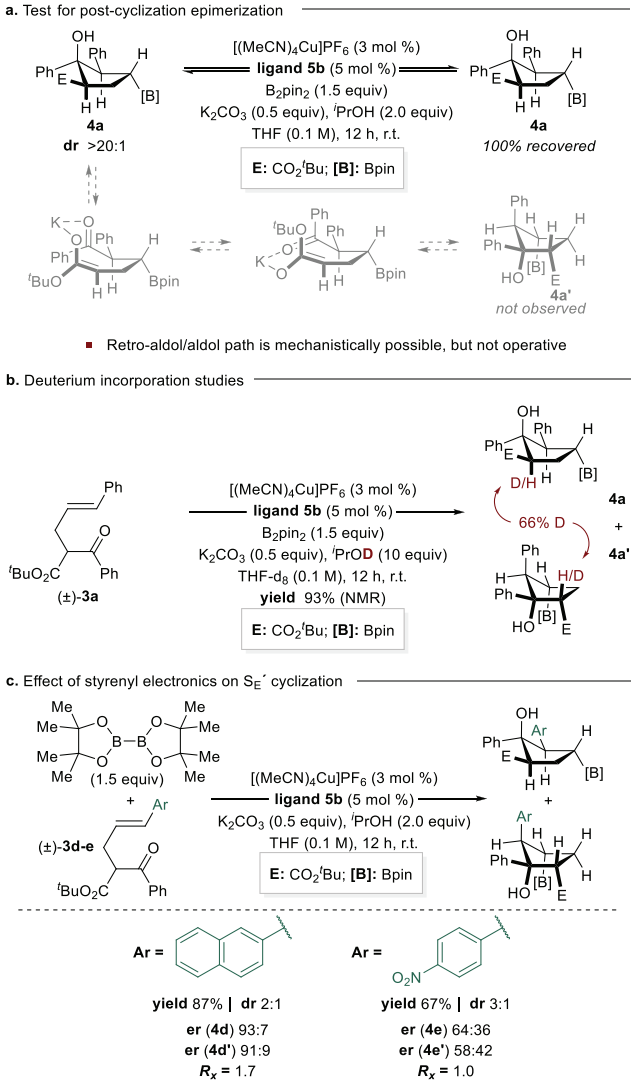


[a]We use prime (′) to denote inversion of configuration for C_1 and C_2. [b](a) LDA (1.1 equiv), p-$C_6H_4CF_3CHO$ (1.0 equiv), 89% yield (dr 1.5:1.4:1.1:1); 18% isolated yield of 7 (dr >20:1) (b) DMP (2.0 equiv), 95% yield, dr >20:1.

progressed and background epimerization of the starting material emerged ((*R*)-**3c** ⇆ (*S*)-**3c**), the second diastereomeric cyclopentanol product began to form, leading to a final product ratio at full conversion of 7:1. We independently studied the diastereomerization of (*R*)-**3c** in the presence of K_2CO_3 (0.5 equiv), ^{i}PrOH (2.0 equiv), and B_2pin_2 (1.5 equiv), in THF; in contrast to related systems,[5a,c,d] equilibration to a 1:1 mixture of epimeric β-keto esters (*R*)-**3c** and (*S*)-**3c** required 4 h under these basic conditions. These experiments are internally consistent with the hypothesis that cyclization is fast relative to epimerization of the β-keto ester intermediate bearing a pendant benzylcopper (**IV**).

To corroborate these results, several control experiments were performed (Scheme 7). To rule out the possibility of

Scheme 7. Control Experiments to Corroborate Origin of Diastereodivergency



product diastereomerization via a retro-aldol/aldol mechanism,[18] a single diastereomer of the product **4a** was resubjected to the standard reaction conditions (Scheme 7a). After 12 h, cyclopentanol **4a** was recovered quantitatively without degradation of the diastereomeric composition. This result excludes the possibility of postcyclization product diastereomerization. We then turned our attention to the racemization process. Under similar conditions, an isotopic labeling study was performed in the presence of 2-propanol-d_8 (10 equiv) to evaluate qualitatively the rates of racemization/epimerization (Scheme 7b). In accordance with the *in situ*

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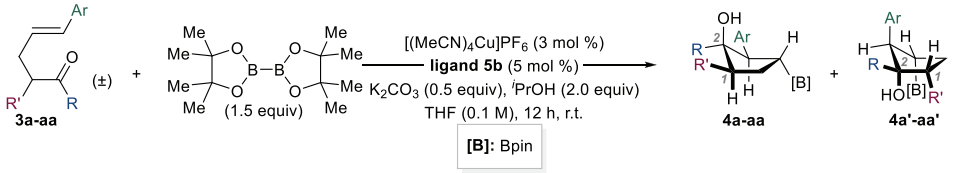
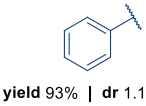
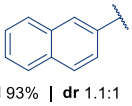
Table 2. Scope of Stereodivergent Borylative Cyclization[a]



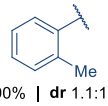
Scope of ketone substituents (R)[b]



yield 93% | dr 1.1:1
er (4a) 92:8
er (4a') 91:9
R_x = 1.6

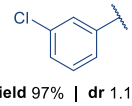


[b]yield 93% | dr 1.1:1
er (4f) 90:10
er (4f') 93:7
R_x = 1.5

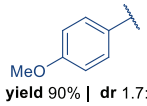


yield 90% | dr 1.1:1
er (4g) 91:9
er (4g') 90:10
R_x = 1.5

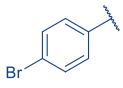
yield 89% | dr 1.1:1
er (4h) 91:9
er (4h') 91:9
R_x = 1.6



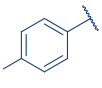
yield 97% | dr 1.1:1
er (4i) 92:8
er (4i') 91:9
R_x = 1.4



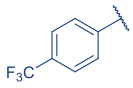
yield 90% | dr 1.7:1
er (4j) 90:10
er (4j') 93:7
R_x = 1.4



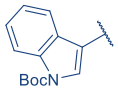
yield 92% | dr 1.2:1
er (4k) 91:9
er (4k') 92:8
R_x = 1.4



yield 94% | dr 1.1:1
er (4l) 90:10
er (4l') 92:8
R_x = 1.6



[c]yield 86% | dr 1.1:1
er (4m) 93:7
er (4m') 92:8
R_x = 1.6



[c]yield 95% | dr 1.2:1
er (4n) 92:8
er (4n') 92:8
R_x = 1.3

[c]yield 82% | dr 1:1
er (4o) 90:10
er (4o') 90:10
R_x = 1.2

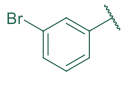
yield 95% | dr 1.1:1
er (4p) 92:8
er (4p') 92:8
R_x = 1.2

Scope of alkenyl substituents (Ar)[e]

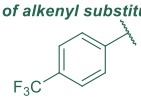
yield 96% | dr 1.1:1
er (4q) 91:9
er (4q') 92:8
R_x = 1.4

[d]yield 80% | dr 2.5:1
er (4r) 85:15
er (4r') 85:15
R_x = 1.5

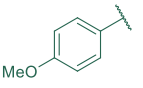
[d]yield 86% | dr 2:1
er (4s) 85:15
er (4s') 86:14
R_x = 1.0



yield 66% | dr 1.5:1
er (4t) 81:19
er (4t') 81:19
R_x = 1.0



yield 83% | dr 1.9:1
er (4u) 91:9
er (4u') 91:9
R_x = 1.2

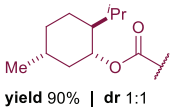


[c]yield 89% | dr 1:1.2
er (4v) 91:9
er (4v') 91:9
R_x = 2.0

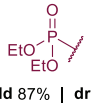
Scope of α - substituents (R')[f]

yield 98% | dr 1.1:1
er (4w) 91:9
er (4w') 90:10
R_x = 1.4

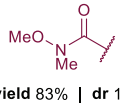
yield 93% | dr 1.1:1
er (4x) 92:8
er (4x') 92:8
R_x = 1.4



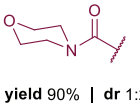
yield 90% | dr 1:1
dr (4y) 8.8:1
dr (4y') 8.8:1
R_x = 1.3



[c]yield 87% | dr 1.5:1
er (4z) 88:12
er (4z') 92:8
R_x = 1.4



yield 83% | dr 1:1
er (4aa) 92:8
er (4aa') 90:10
R_x = 1.3



yield 90% | dr 1:2
er (4b) 87:13
er (4b') 90:10
R_x = 1.8

[a]Reactions performed on 0.2 mmol scale for 16 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture; the er was determined by HPLC using a chiral stationary phase. $R_x = R_{f(\text{diast }2)}/R_{f(\text{diast }1)}$. "(')" denotes inversion of configuration for C_1 and C_2. [b]Ar = Ph, R' = $CO_2{}^t$Bu. [c]Reaction performed with 7 mol % $[Cu(MeCN)_4]PF_6$ and 9 mol % of ligand **5b**. [d]Reaction performed with 7 mol % $[Cu(MeCN)_4]PF_6$ and 9 mol % of ligand **5d**. [e]R = Ph, R'= $CO_2{}^t$Bu. [f]Ar = Ph, R = Ph.

NMR studies for (*R*)-**3c** (*vide supra*), only partial deuterium exchange (66%-*d*) was observed in products **4a** and **4a'**.

The foregoing analysis suggests that if the benzylcopper intermediate **IV** could be stabilized, thereby slowing ketone addition, epimerization might become competitive with cyclization. Indeed, preliminary progress toward stereoconvergence is revealed in Scheme 7c, wherein a 2-naphthyl derivative (**3d**) does provide a modest increase in diastereocontrol (2:1) relative to our prior results. A 4-nitrophenyl (**3e**) activating group gave products in a 3:1 dr, but low enantioselectivity (see the Supporting Information). For similar reasons, and as demonstrated in the ensuing substrate scope (vide infra), reducing the electrophilicity of the ketone leads to similar diastereomer ratio perturbations away from unity.

Collectively, these experimental findings suggest that for benzylcopper **IV** (Scheme 5a), the rate of cyclization ($k_{cycl(IV)}$) is faster than that of the activated substrate epimerization (k_{epim}). These results reveal important differences with prior art involving carbene-aldehyde adducts[5a,c,d] (Breslow intermediates) where, in the presence of an exogenous inorganic base, the rate of epimerization of the activated substrate is greater than the rate of cyclization. In the current reactions, productive catalysis occurs on the same time scale as background substrate racemization (as revealed by deuterium incorporation studies), and completely outcompetes on-cycle epimerization (as revealed by reactions of isomerically pure starting material), even under basic conditions. In this case, complete vicinal substrate control of the stereocenter created during the 5-*exo*-trig cyclization step is observed. We can conclude that for alkylative dynamic kinetic resolution (DKR) cyclizations of β-keto esters, the identity of the transient nucleophile is critical for determining whether enantioconvergency or diastereodivergency will predominate.

Substrate Scope. With mechanistic evidence that rationalizes the observed stereoselectivity of this transformation, we began to probe the allowable steric and electronic parameters of this process, initially by varying the ketone substituents (Table 2). 2-Naphthyl derived β-keto esters undergo efficient borylative cyclization to produce cyclopentanol products **4f** and **4f'** in high yield and enantioselectivity. Aryl β-keto esters bearing electron donating groups (**3g**, **j**), electron-withdrawing

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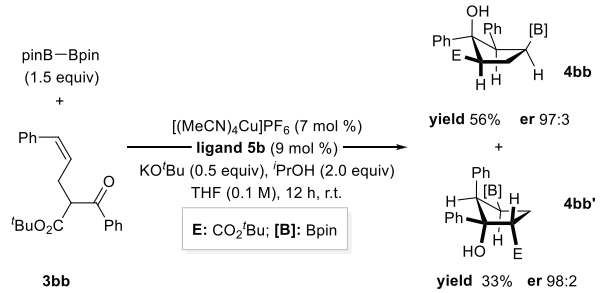
groups (**3m**), and halogens (**3h**, **i**, **k**, **l**) in various positions are suitable substrates in this transformation. A variety of heteroaryl β-keto esters (**3n**-**3q**), including Boc-protected indol-3-yl **3n**, pyrid-3-yl **3o**, furan-2-yl **3p** and thien-2-yl **3q**, result in equally efficient and enantioselective reactions. Alkyl β-keto esters **3r** and **3s** failed to provide the desired cyclopentanols using the Cu−Bpin complex generated from ligand **5b**; however, the copper(I)-complex generated from ligand **5d** was catalytically active in these transformations providing the cyclopentanol products in good yield and enantioselectivity, with a moderate increase in the diastereoselection (2.5:1 and 2:1 dr, respectively). Considering that ligand **5d** (Table 1, entry 4) did not provide an enhancement in the diastereoselectivity when aryl β-keto esters were employed, we hypothesize that for less electrophilic alkyl β-keto ester electrophiles, a slower rate for the 5-*exo*-trig cyclization allows intervention of some β-keto ester equilibration, enabling either the catalyst or substrate to impart partial stereocontrol during the cyclization step. These results from the electrophile side are congruent with those observed in the nucleophile component in Scheme 7c.

Several alkenyl substituents were tested in this reaction (Table 2). These results highlight the sensitivity of the reaction to electronic characteristics on the arene. Bromophenyl substrate **3t** can be employed in this transformation without affecting the efficiency of the reaction. In congruence with the results observed for **3d** and **3e**, the 4-trifluoromethylphenyl derivative **3u** gave the derived cyclopentanol **4u** with higher diastereoselectivity. *Para*-electron donating substituents such as substrate **3v** gave the desired product in good yield as a 1:1.2 mixture of diastereomers, although it was necessary to increase the catalyst loading to achieve full conversion. We believe the lower reactivity observed for **3v** can be rationalized by the poor electrophilicity of the styrenyl electrophile and destabilization of the benzylic copper intermediate by electron-rich arenes.[19]

Lastly, the scope of α-substituents was evaluated. A variety of β-keto esters were tolerated under the reaction conditions without a significant effect on the stereoselectivity (**3w**-**3y**). β-keto phosphonate **3z** successfully delivered β-hydroxy phosphonates **4z** and **4z'** in good yields and enantioselectivities. Given the *syn* relationship between the phosphonate and hydroxyl groups, it was surprising that Horner-Wadsworth-Emmons (HWE)-type elimination products were not observed for this substrate, highlighting the mildness of the reaction conditions. Synthetically useful Weinreb amide **3aa** substrate delivered cyclopentanols **4aa** and **4aa'** in good yields and enantioselectivities. The diastereomeric pairs shown in Table 2 display consistent, distinct chromatographic elution patterns (mean R_x = 1.4), enabling straightforward obtention of diastereomerically pure materials by flash column chromatography.

Finally, the collective mechanistic results suggest that the use of a (*Z*)-alkene starting material would provide complementary access to epimeric cyclopentanols based on the stereospecificity of the *syn*-borylcupration. Catalyzed borylative cyclization of the racemic *cis*-olefin **3bb** delivered the stereodivergent pair **4bb** and **4bb'** (Scheme 8), which are diastereomers of the previously synthesized **4a** and **4a'**. The alkene diastereofacial discrimination is enhanced for the (*Z*)-alkene: the products were obtained with enantiomer ratios of 98:2 and 97:3, respectively.

Scheme 8. (*Z*)-Alkene Starting Material Enables Complementary Access to Epimeric Products



Synthetic Utility. To assess the scalability of this platform, a 10 mmol scale reaction was performed using β-keto ester **3a** (Scheme 9a). Under identical reaction conditions, cyclopentanol products **4a** and **4a'** were isolated in excellent yields and enantioselectivities. With significant amounts of enantioenriched cyclopentanols **4a** and **4a'** in hand, we explored the synthetic viability of the products in further transformations (Scheme 9b). Diol **8** was obtained in 93% yield as a single diastereomer by stereospecific perborate oxidation of **4a'**.[20] Single crystal X-ray crystallographic analysis revealed that the stereochemical arrangement of the substituents around the cyclopentane scaffold agree with the results obtained for compound **4b'**. We next aimed to examine the synthetic utility of the boronate in the formation of carbon−carbon bonds. Under the conditions reported by Aggarwal and co-workers,[21] a Zweifel-type vinylation[22] delivered cyclopentanol **9** in excellent yield and diastereoselectivity.

Reactions of the carboxylate fragment were also fruitful (Scheme 9c). Under gentle heating in the presence of iodine, cyclopentanol **4a** was converted to the derived β-hydroxy acid **10** in good yield.[23] Reaction of the latter with diphenylphosphoryl azide (DPPA) in refluxing benzene provided oxazolidinone **11** in excellent yield via Curtius rearrangement.[24] Alternatively, activation of the carboxylic acid with HATU[25] delivered β-lactone **12** whose isolation was prevented due to the facile extrusion of CO_2.[26] Cyclopentene **13** was isolated upon stirring with silica gel at ambient temperature. By leveraging the reactivity/electrophilicity of lactone **12**, we have shown incorporation of benzylamine as a representative heteroatom nucleophile: secondary amide **14** was obtained in 85% yield without erosion in diastereomeric composition.

■ CONCLUSION

In summary, we have developed a stereodivergent borylative cyclization of racemic β-oxo acid derivatives, catalyzed by a chiral bis(phosphine) copper(I)-complex. A range of stereochemically complex enantiomerically enriched cyclopentanols containing a boronate functional handle can be synthesized from this method. These highly functionalized building blocks can be further manipulated to generate protected 1,2-amino alcohols, 1,3-diols, alkenes, and secondary amides with excellent efficiency. Mechanistic studies employing a stereodefined β-keto ester suggested a scenario wherein the generation of a tethered, reactive organometallic nucleophile is able to outcompete background substrate racemization and on-cycle epimerization during the 5-*exo*-trig cyclization step. In this scenario, vicinal substrate control of the nascent stereocenter created during the cyclization is observed. The results presented in this article contrast the traditional

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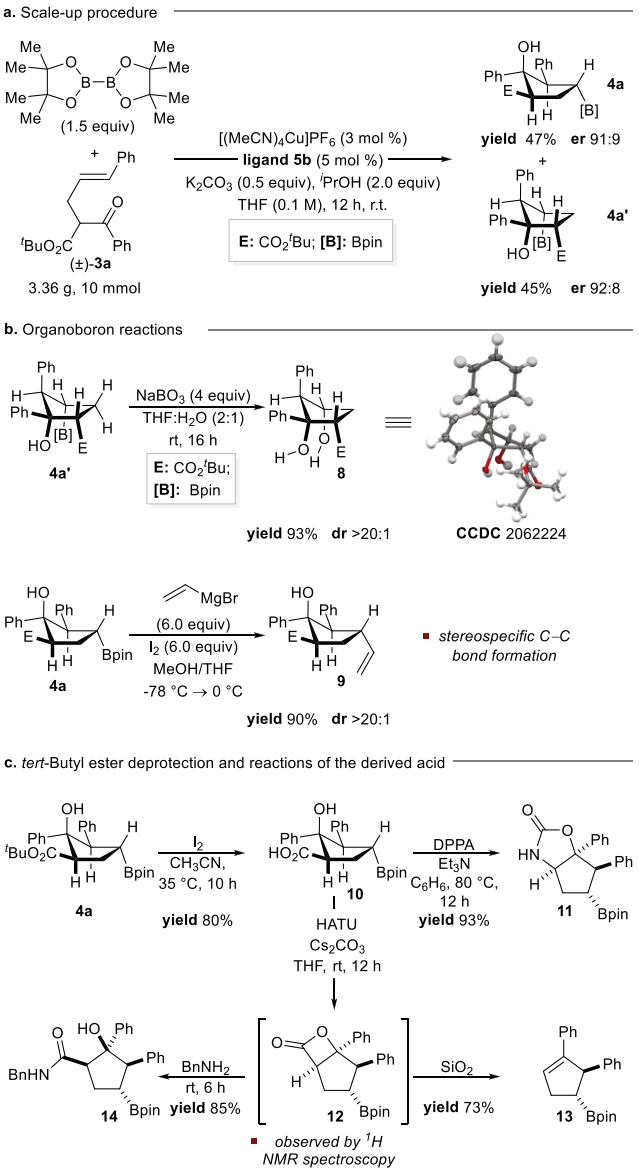
Scheme 9. Scale Up Procedure and Selected Secondary Transformations[a]



[a]All reported yields are after isolation; dr determined by ^{1}H NMR analysis of the crude. See the Supporting Information for details.

assumption that the configurational fragility of the archetypal substrates for enantioconvergent reactions (1,3-dicarbonyl compounds) can automatically be exploited in stereoconvergent processes. The application of these mechanistic insights to the development of stereoconvergent borylative cyclization reactions is currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c07702.

Experimental details, materials and methods, characterization data, NMR spectra for all compounds, chromatograms for chiral separations, DFT calculations, information on X-ray diffraction experiments (PDF)

Accession Codes

CCDC 2055305−2055306, 2062224, and 2087120 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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