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Dynamic Kinetic Asymmetric Cross-Benzoin Additions of β-Stereogenic α-Keto Esters

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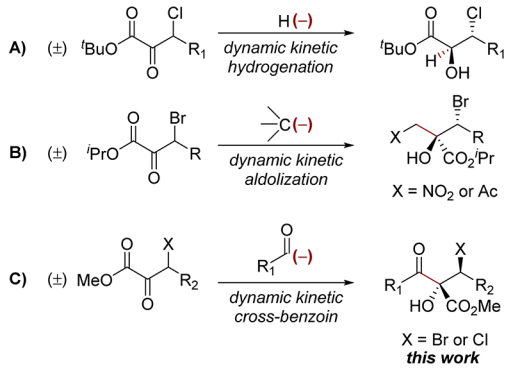
Supporting Information

ABSTRACT: The dynamic kinetic resolution of β-halo α-keto esters via an asymmetric cross-benzoin reaction is described. A chiral *N*-heterocyclic carbene catalyzes the *umpolung* addition of aldehydes to racemic α-keto esters. The resulting fully substituted β-halo glycolic ester products are obtained with high levels of enantio- and diastereocontrol. The high chemoselectivity observed is a result of greater electrophilicity of the α-keto ester toward the Breslow intermediate. The reaction products are shown to undergo highly diastereoselective substrate-controlled reduction to give highly functionalized stereotriads.

The benzoin condensation is a carbene- or cyanide-catalyzed reaction that couples two carbonyl compounds to give α-hydroxy ketones via carbon−carbon bond formation. The reaction proceeds with concurrent generation of a stereogenic center and is the archetype of a catalytic umpolung (polarity inversion) reaction.[1] Its significance and widespread use largely flow from two defining characteristics: (1) its capacity to generate useful and ubiquitous α-hydroxy ketones, and (2) the 100% atom efficiency inherent to the reaction. As a consequence, significant research effort has been devoted to various aspects of the transformation. Methods now exist for the asymmetric homobenzoin reaction (the coupling of two identical aldehydes).[2] The union of two different carbonyls (cross-benzoin addition) provides the possibility of accessing a more diverse set of α-hydroxy ketones;[3] however, controlling the chemoselectivity of these reactions (i.e., constitutional isomer distribution) is difficult, particularly in the intermolecular manifold. Asymmetric cross-benzoin additions have been achieved through the deployment of miscellaneous strategies and reagents using enzymatic,[4] metallophosphite,[5] and carbene[6] catalysis. Despite the aforementioned positive attributes, a limitation present in all of these methods is that they generate only a single stereocenter during the C−C bond forming event. To the best of our knowledge, a cross-benzoin coupling that generates more than one stereocenter, and thus a higher level of complexity, has yet to be reported.[7] In this communication we describe a chemoselective, cross-benzoin dynamic kinetic resolution (DKR) which couples aldehydes and racemic α-keto esters. The reactions generate vicinal stereocenters during the C−C bond construction with excellent levels of diastereo- and enantiocontrol.

The DKR subset of enantioselective transformations is less common than asymmetric reactions of achiral starting materials, but can offer some unique advantages.[8] DKRs utilizing configurationally labile α-keto esters offer the opportunity to generate highly functionalized glycolates. Reactions developed include enantioconvergent transfer hydrogenation (Scheme 1A) and direct aldolization with acetone and nitromethane (Scheme 1B).[9] Seeking to expand this work we envisioned that N-heterocyclic carbene (NHC) catalyzed cross-benzoin of aldehydes and α-keto esters would give access to previously inaccessible products (Scheme 1C).

Scheme 1. DKRs with β-Halo α-Keto Esters



To date, NHC-catalyzed DKR transformations have been described for the formation of β-lactones from β-keto esters[10] and simple kinetic resolutions are known for [3 + 4] cycloadditions of azomethine imines and enals.[11] While cross-benzoin procedures using α-keto esters have been disclosed, all previous asymmetric examples have used ketones bearing aromatic substituents and as such are nonenolizable.[6c,d] For a NHC-catalyzed DKR to be achieved, the heretofore unknown use of enolizable α-keto esters was compulsory. That structural change brings with it the possibility of undesired homo- and cross-aldolization in addition to the known benzoin dimerization (Scheme 2). We were cognizant that our projected reaction conditions were mechanistically viable for promoting all of these processes.[12] Accordingly, we sought to identify conditions that would chemoselectively deliver the cross-benzoin product while fulfilling the required parameters for a DKR.

We began by examining the coupling of benzaldehyde and β-chloro-α-keto ester **1a**. Using catalyst **A**,[13] glycolate **2a** was delivered with 96:4 enantiomeric ratio (er), and 4.5:1 diastereomeric ratio (dr), but only 25% conversion of **1a**

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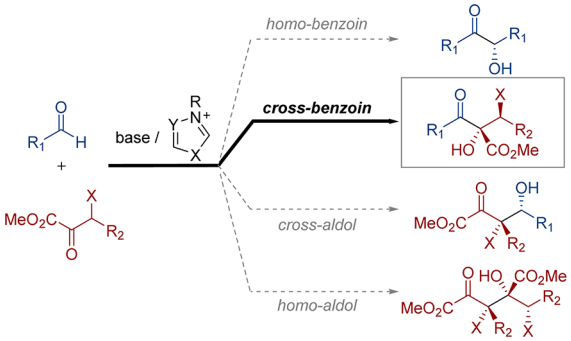
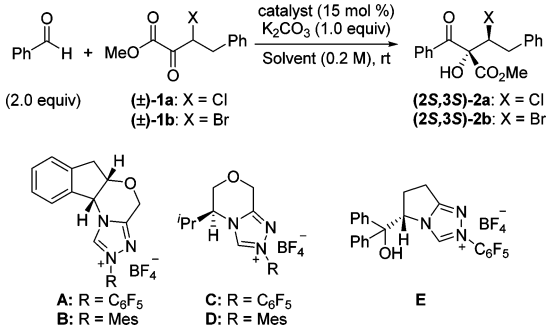
Scheme 2. Chemoselectivity Challenges for the Coupling of Aldehydes (blue) and Enolizable α-Keto Esters (Red) in the Presence of Base and Carbene



(Table 1, entry 1). Using more electron-rich catalyst **B**[14] gave a marked increase in both reactivity and dr without a notable change in er (Table 1, entry 2).[15] The importance of using an electron rich catalyst was observed throughout the screening of conditions, as electron-poor catalysts **C**[6d] and **E**[6b] routinely gave low conversion of starting material (Table 1, entries 3, 5, 7, and 9). Using catalyst **B** with bromo ketone **1b** increased the observed dr with little effect on conversion or er (Table 1, entry 6). Screening the solvent and base[16] revealed that TBME and K_2CO_3 were optimal, providing tertiary alcohol **2b** with >20:1 diastereoselection and 96:4 er (Table 1, entry 10). Efforts to further increase stereoselectivity by introduction of steric bulk at the ester position only resulted in reduced reactivity and stereoselectivity (Table 1, entry 11). Under identical conditions chloro variant **1a** delivered ketone **2a** with identical enantioselectivity, but a dr of 14:1 (Table 1, entry 12). Due

Table 1. Catalyst and Substrate Optimization[a]



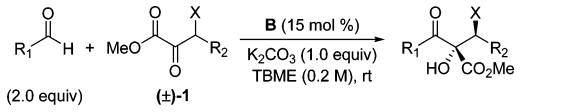
entry	X	catalyst	solvent	conv. (%)	dr[b]	er[c]
1	Cl	A	THF	25	4.5:1	96:4
2	Cl	B	THF	100	14:1	95:5
3	Cl	C	THF	40	1.5:1	98:2
4	Cl	D	THF	100	>20:1	90:10
5	Br	A	THF	<5	-	-
6	Br	B	THF	>95	>20:1	94:6
7	Br	C	THF	<5	-	-
8	Br	D	THF	30	-	-
9	Br	E	THF	<5	-	-
10	Br	B	TBME	100	>20:1	96:4
11[d]	Br	B	TBME	54	17:1	81:19
12	Cl	B	TBME	100	14:1	96:4

[a]All reactions were run on a 0.10 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by chiral SFC analysis. [d]Run with ^{i}Pr as the ester.

to the higher sense of diastereoselection, we elected to examine the scope of the reaction using β-bromo-α-keto esters.

Next we began modifying the structure of **1** in order to probe the allowable steric and electronic parameters of this cross-benzoin process (Table 2). Varying the arene on the α-keto

Table 2. Cross Benzoin Additions of Aldehydes to β-Bromo α-Keto Esters[a]



2a
95% yield
13:1 dr
96:4 er

2b[b]
78% yield
>20:1 dr
96:4 er

2c[b,c]
83% yield
>20:1 dr
95.5:4.5 er

2d[c]
72% yield
18:1 dr
95.5:4.5 er

2e
63% yield
11:1 dr
95:5 er

2f
65% yield
17:1 dr
93.5:7.5 er

2g
68% yield
>20:1 dr
94:6 er

2h[e]
40% yield (63%)
>20:1dr
94:6 er

2i
76% yield
>20:1 dr
97.5:2.5 er

2j
78% yield
>20:1 dr
94.5:5.5 er

2k
0% yield
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2l[d,e]
37% yield (40%)
>20:1dr
98:2 er

2m[c,f]
77% yield
>20:1 dr
98:2 er

2n
70% yield
>20:1 dr
75:25 er

2o
51% yield
14:1 dr
56:44 er

2p[d,g]
61% yield (82%)
10:1 dr
98:2 er

[a]All reactions were run on a 0.20 mmol scale at room temperature for 16 h. Diastereomeric ratios were determined by ^{1}H NMR, enantiomeric ratios by chiral HPLC or SFC. Yields unless otherwise noted are of isolated products; some contain the minor diastereomer. [b]Yield is reported as a ^{1}H NMR yield utilizing ferrocene as an internal standard. [c]The product was reduced with $NaBH_4$ and the e.r. of the diol was analyzed. [d]Yield in parentheses represents a ^{1}H NMR yield utilizing mesitylene as an internal standard. [e]The mass balance is unreacted α-keto ester. [f]Reaction was run using 20 mol % of catalyst **B**. [g]Isolated yield is reported for the diol formed via reduction of **2p** with $NaBH_4$. The enantiomeric ratio was determined via Mosher ester analysis of the isolated diol.

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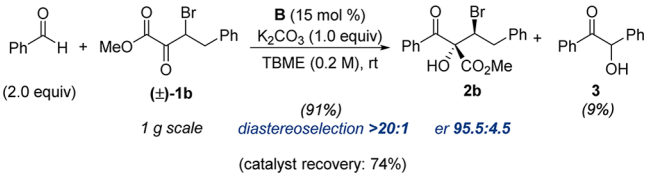
ester delivered **2c** and **2e** without loss of reaction fidelity. Removing the arene as well as changing the carbon chain length provided **2d**, **2f**, and **2g** cleanly with high stereoselectivity. Inclusion of a β-branch point gave product **2h** with >20:1 dr and 94:6 er albeit in only 60% conversion of starting material.[17]

Variation of the aldehyde also provided data regarding reaction generality. While both *para*- and *meta*-tolualdehyde were well tolerated (**2i** and **2j**), *ortho*-tolualdehyde proved to be too sterically encumbered, giving no reaction. Electron-rich and -poor aldehydes were slow to react providing **2l** and **2m** with good stereoselectivity but incomplete conversion after 18 h. While longer reaction time did not increase the yield, a slight increase in catalyst loading provided full conversion of the β-bromo α-keto ester.[18] Heteroaromatic **2n** was isolated in >20:1 dr, and 75:25 er, while indole-derived **2p** was obtained with 10:1 dr and 98:2 er. One limitation of this method at the current level of development is the requirement of aromatic aldehydes in order to achieve high enantioselectivity, highlighted by the use of isobutyraldehyde which provided **2o** with 14:1 diastereoselectivity but only 54:46 er.

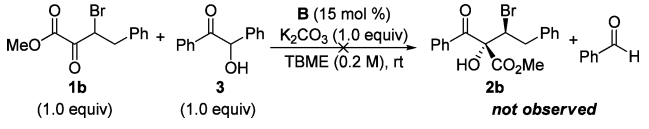
Coupling of **1b** with benzaldehyde on a 1 g scale resulted in 91% yield of **2b** without loss of stereoselectivity and with 74% catalyst recovery. Benzoin (**3**) was also isolated in 9% yield (Scheme 3).

Scheme 3. Gram Scale Reaction of 1b and Benzaldehyde



The obtention of benzoin on larger scale led us to consider the broader question of cross-benzoin chemoselectivity. We considered the possibility that homobenzoin formation was the faster process, but reversible under the reaction conditions. In this scenario, the cross-benzoin reaction would serve as an irreversible trap for the reversibly liberated benzaldehyde, analogous to the observations of Enders et al. in their study of cross-benzoin reactions with 1,1,1-trifluoromethylketones.[6a] To evaluate the mechanism, we subjected **1b** and **3** to the normal reaction conditions (Scheme 4). Neither **2b** nor benzaldehyde

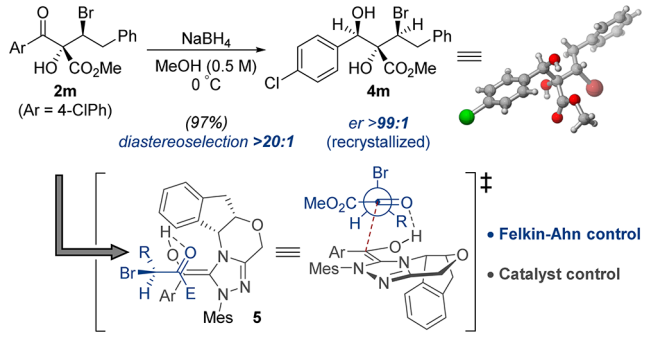
Scheme 4. Determining the Source of the Observed Cross-Benzoin Chemoselectivity



was observed during the course of the reaction, indicating that benzoin formation is irreversible under these conditions. The product distribution observed in Scheme 3 can thus be considered as a reflection of the relative rate constants for capture of the Breslow intermediate by the sterically hindered but electronically activated α-keto ester versus a simple aldehyde. Our results are congruent with those of Murry and Frantz, who observed that benzoin was not a competent donor in carbene-catalyzed additions to *N*-acyl imines.[19]

The cross-benzoin product presents four functional groups that are in principle uniquely addressable. As a first pass to probe the reactivity, ketone **2m** was reduced with $NaBH_4$ to provide diol **4m** with >20:1 diastereoselection (Scheme 5).[20]

Scheme 5. Reduction of the Cross-Benzoin Product and Determination of Relative and Absolute Stereochemistries



Several additional cross benzoin products were also reduced with high diastereoselectivity to their corresponding diols.[21] An X-ray diffraction study of **4m** was carried out to assign the relative and absolute stereochemistries as (1*R*,2*S*,3*S*).[22] By analogy, the cross-benzoin adducts were assigned as (2*S*,3*S*). This configuration implicates the illustrated transition structure **5** as a plausible one to account for the stereochemical outcome of the benzoin addition. In this model the α-keto ester exhibits a strong polar Felkin-Ahn diastereofacial bias.[23] The chiral Breslow intermediate then selects for the reactive α-keto ester enantiomer in part through strong facial bias imparted by the indane subunit, but also through the orienting/activating effect of the hydroxyl group.[24] The precise disposition of the two reactants with respect to the axis of the forming bond (illustrated in red) is not known, but the gross features described above are likely to be relevant.

In conclusion, we have developed the first stereoconvergent cross benzoin reaction that utilizes racemic electrophiles. The addition generates two stereocenters during the C−C bond construction via the dynamic kinetic resolution of β-halo α-keto esters. This NHC-catalyzed process generates a variety of fully substituted β-halo α-glycolic acid derivatives in high diastereo- and enantioselectivity utilizing a variety of aromatic aldehydes and α-keto esters. Subsequent diastereoselective reduction provides access to a number of highly functionalized and stereochemically rich diols. Work is ongoing to define the pK_a limits in the electrophile for stereoconvergent reactions of racemic α-keto esters and to examine other substitution patterns that would broaden the scope of accessible product types.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) See Supporting Information for base and catalyst screen.

(17) As measured by 1H NMR using an internal mesitylene standard.

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(21) For full details see Supporting Information.

(22) CCDC 1009331 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif. The structure in Scheme 5 was generated with CYLview: Legault, C. Y. *CYLview*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, 2009; http://www.cylview.org.

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