The benzoin condensation is a carbene- or cyanide-catalyzed reaction that couples two carbonyl compounds to give $\alpha$-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. Its significance and widespread use largely flow from two defining characteristics: (1) its capacity to generate useful and ubiquitous $\alpha$-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). The union of two different carbonyls (cross-benzoin addition) provides the possibility of accessing a more diverse set of $\alpha$-hydroxy ketones; 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, metallophosphite, and carbene 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. In this communication we describe a chemoselective, cross-benzoin dynamic kinetic resolution (DKR) which couples aldehydes and racemic $\alpha$-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. DKR's utilizing configurationally labile $\alpha$-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). Seeking to expand this work we envisioned that N-heterocyclic carbene (NHC) catalyzed cross-benzoin of aldehydes and $\alpha$-keto esters would give access to previously inaccessible products (Scheme 1C).

To date, NHC-catalyzed DKR transformations have been described for the formation of $\beta$-lactones from $\beta$-keto esters and simple kinetic resolutions are known for $[3 + 4]$ cycloadditions of azomethine imines and enals. While cross-benzoin procedures using $\alpha$-keto esters have been disclosed, all previous asymmetric examples have used ketones bearing aromatic substituents and as such are nonenolizable. For a NHC-catalyzed DKR to be achieved, the heretofore unknown use of enolizable $\alpha$-keto ester 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. 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 $\beta$-chloro-$\alpha$-keto ester 1a. Using catalyst A, glycolate 2a was delivered with 96:4 enantiomeric ratio (er), and 4:5:1 diastereomeric ratio (dr), but only 25% conversion of 1a.
Scheme 2. Chemoselectivity Challenges for the Coupling of Aldehydes (blue) and Enolizable α-Keto Esters (Red) in the Presence of Base and Carbene

Using more electron-rich catalyst B\textsuperscript{14} gave a marked increase in both reactivity and dr without a notable change in er (Table 1, entry 2).\textsuperscript{15} The importance of using an electron rich catalyst was observed throughout the screening of conditions, as electron-poor catalysts C\textsuperscript{6d} and E\textsuperscript{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\textsuperscript{16} revealed that TBME and KHCO\textsubscript{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 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 1. Catalyst and Substrate Optimization\textsuperscript{a} |
| --- |
| entry | X | catalyst | solvent | conv. (%) | dr\textsuperscript{b} | er\textsuperscript{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\textsuperscript{d} | Br | B | TBME | 54 | 17:1 | 81:19 |
| 12 | Cl | B | TBME | 100 | 14:1 | 96:4 |

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

Table 2. Cross Benzoin Additions of Aldehydes to β-Bromo α-Keto Esters\textsuperscript{a})

| Entry | R | X | Y | Z | Solvent | conv. (%) | dr | er |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1a | Cl | Ph | Me | OH | THF | 25 | 4:5:1 | 96:4 |
| 1b | Cl | Ph | Me | OH | THF | 100 | 14:1 | 95:5 |
| 1c | Cl | Ph | Me | OH | THF | 40 | 1:5:1 | 98:2 |
| 1d | Cl | Ph | Me | OH | THF | 100 | >20:1 | 90:10 |
| 2a | Br | Ph | Me | OH | THF | <5 | - | - |
| 2b | Br | Ph | Me | OH | THF | >95 | >20:1 | 94:6 |
| 2c | Br | Ph | Me | OH | THF | <5 | - | - |
| 2d | Br | Ph | Me | OH | THF | 30 | - | - |
| 2e | Br | Ph | Me | OH | THF | <5 | - | - |
| 3a | Br | Ph | Me | OH | THF | 100 | >20:1 | 96:4 |
| 3b | Br | Ph | Me | OH | THF | 54 | 17:1 | 81:19 |
| 3c | Br | Ph | Me | OH | THF | 100 | 14:1 | 96:4 |

\textsuperscript{a})All reactions were run on a 0.20 mmol scale at room temperature for 16 h. Diastereomeric ratios were determined by \textsuperscript{1}H NMR, enantiomeric ratios by chiral HPLC or SFC. Yields unless otherwise noted are of isolated products; some contain the minor diastereomer. \textsuperscript{b})Yield is reported as a \textsuperscript{1}H NMR yield utilizing ferrocene as an internal standard. \textsuperscript{c})The product was reduced with NaBH\textsubscript{4} and the e.r. of the diol was analyzed. \textsuperscript{d})Yield in parentheses represents a \textsuperscript{1}H NMR yield utilizing mesitylene as an internal standard. \textsuperscript{e})The mass balance is unreacted α-keto ester. \textsuperscript{f})Reaction was run using 20 mol % of catalyst B. \textsuperscript{g})Isolated yield is reported for the diol formed via reduction of 2p with NaBH\textsubscript{4}. The enantiomeric ratio was determined via Mosher ester analysis of the isolated diol.

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estor 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. 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. 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).

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. To evaluate the mechanism, we subjected 1b and 3 to the normal reaction conditions (Scheme 4). Neither 2b nor benzaldehyde 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.

Several additional cross benzoin products were also reduced with high diastereoselectivity to their corresponding diols. An X-ray diffraction study of 4m was carried out to assign the relative and absolute stereochemistries as (1R,2S,3S), By analogy, the cross-benzoin adducts were assigned as (2S,3S). This configuration implicates the illustrated transition structure S 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. 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. 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 stereoreconvergent 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 NHCCatalyzed process generates a variety of fully substituted β-halo α-glycolic acid derivatives in high diastereoad and enantioselectivity utilizing a variety of aromatic aldehydes and α-keto esters. Subsequent diasteroselective reduction provides access to a number of highly functionalized and stereochemically rich diols. Work is ongoing to define the pKa limits in the electrophile for stereoreconvergent 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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REFERENCES

(1) For the initial report of a benzoin process see: (a) Liebig, J.; Wöhler, F. Ann. Pharm. 1832, 3, 249–282. For reviews of benzoin condensations see (b) Hasner, A.; Raay, K. M. The Benzoin and Related Acyl Anion Equivalent Reactions. In Comprehensive Organic Synthesis; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 541–577. (c) Ide, W. S.; Buck, J. S. Org. React. 1948, 4, 269–304. (d) Bugaut, X.; Glorius, F. Chem. Soc. Rev. 2012, 41, 3511–3522. (e) Johnson, J. S. Angew. Chem., Int. Ed. 2004, 43, 1326–1328. (f) DiRocco, D. A.; Rovis, T. Asymmetric Benzoin and Stetter Reactions. In Stereoselective Synthesis 2: Stereoselective Reactions of Carbonyl and Imino Groups; Molander, G. A., Ed.; Georg Thieme Verlag: Stuttgart-New York, Vol. 2011; pp 935–862. (g) O’Bryan, E. A.; Scheidt, K. A. Acyloan Coupling Reactions. In Comprehensive Organic Synthesis II; Knochel, P.; Molander, G. A., Eds.; Elsevier: Amsterdam, The Netherlands, 2014; Vol. 3; pp 621–655.

(2) For selected examples see: (a) Enders, D.; Breuer, K.; Teles, J. H. Helv. Chim. Acta 1996, 79, 1217–1221. (b) Knight, R. L.; Leeper, F. J. J. Chem. Soc., Perkin Trans. 1 1998, 12, 1891–1894. (c) Enders, D.; Kallfass, U. Angew. Chem., Int. Ed. 2002, 41, 1743–1745. (d) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. Adv. Synth. Catal. 2008, 350, 2645–2651. (e) Enders, D.; Han, J. Tetrahedron: Asymmetry 2008, 19, 1367–1371. (f) Baragwanath, L.; Rose, C. A.; Gundala, S.; Connon, S. J.; Zeitler, K. J. Org. Chem. 2009, 74, 9214–9217.

(3) For examples of nomenclatureselective carbonylbenzoin reactions see: (a) Rose, C. A.; Gundala, S.; Connon, S. J.; Zeitler, K. Synthesis 2011, 190–198. (b) Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. Org. Lett. 2011, 13, 880–883. (c) Langdon, S. M.; Wilde, M. D.; Tha, K.; Gravel, M. J. Am. Chem. Soc. 2014, 136, 7539–7542.

(4) (a) Iding, H.; Dünnewald, T.; Greiner, L.; Liese, A.; Müller, M.; Siegert, P.; Grötzinger, J.; Demir, A. S.; Pohl, M. Chem.–Eur. J. 2000, 6, 1483–1495. (b) Demir, A. S.; Pohl, M.; Janzen, E.; Müller, M. J. Chem. Soc., Perkin Trans. 1 2001, 633–635. (c) Dünnewald, T.; Koller-Jung, D.; Nitsche, A.; Demir, A. S.; Siegert, P.; Plohl, M.; Müller, M. J. Am. Chem. Soc. 2002, 124, 12084–12085. (d) Pohl, M.; Lingen, B.; Müller, M. Chem.–Eur. J. 2002, 8, 5288–5295. (e) Lehwald, P.; Richter, M.; Röhrl, C.; Liu, H.; Müller, M. Angew. Chem., Int. Ed. 2010, 49, 2389–2392. (f) Beigi, M.; Walter, S.; Fries, A.; Egelging, L.; Sprenger, G. A.; Müller, M. Org. Lett. 2013, 15, 452–455. (g) Linghu, X.; Potnick, J. R.; Johnson, J. S. J. Am. Chem. Soc. 2004, 126, 3070–3071.

(6) (a) Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. Chem. Commun. 2010, 46, 6282–6284. (b) O’Toole, S. E.; Rose, C. A.; Gundala, S.; Zeitler, K.; Connon, S. J. J. Org. Chem. 2011, 76, 347–357. (c) Rose, C. A.; Gundala, S.; Fagan, C.-L.; Franz, J. F.; Connon, S. J.; Zeitler, K. Chem. Sci. 2012, 3, 735–740. (d) Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. Org. Lett. 2013, 15, 2214–2217. (e) Lee, A.; Scheidt, K. A. Angew. Chem., Int. Ed. 2014, 126, 7724–7728.

(7) For an example of an enzymatic benzoin kinetic resolution, see: Müller, C. R.; Pérez-Sánchez, M.; Domínguez de María, P. Org. Biomol. Chem. 2013, 11, 2000–2004.

(8) For reviews on DKR processes see: (a) Noyori, R.; Tomukage, M.; Kitamura, M. Bull. Chem. Soc. Jpn. 1995, 68, 36–56. (b) Huerta, F. F.; Minidis, A. B.; Bäckvall, J.-E. Chem. Soc. Rev. 2001, 30, 321–331. (c) Steinreiber, J.; Faber, K.; Griengl, H. Chem.–Eur. J. 2008, 14, 8060–8072.

(9) (a) Steward, K. M.; Gentry, E. C.; Johnson, J. S. J. Am. Chem. Soc. 2012, 134, 7329–7332. (b) Steward, K. M.; Corbett, T. M.; Goodman, C. G.; Johnson, J. S. J. Am. Chem. Soc. 2012, 134, 20197–20206.