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Enantioconvergent Synthesis of Functionalized γ-Butyrolactones via (3 + 2)-Annulation

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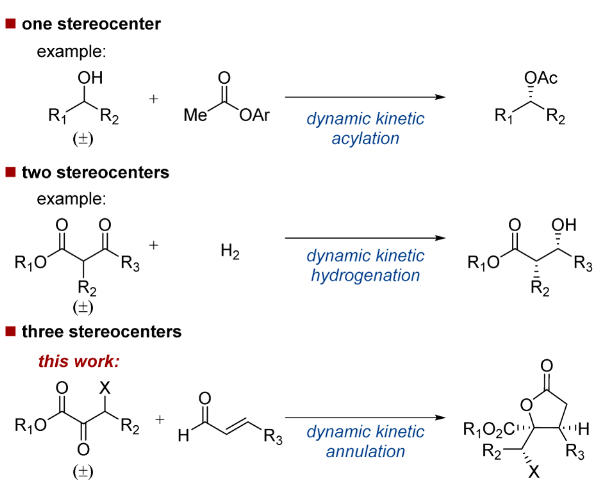
Supporting Information

ABSTRACT: A dynamic kinetic resolution of β-halo α-keto esters in an asymmetric homoenolate reaction is described. A chiral *N*-hetereocyclic carbene catalyzes the $a^3 \rightarrow d^3$-*umpolung* addition of α,β-enals to racemic α-keto esters, forming γ-butyrolactones with three contiguous stereocenters. The addition occurs with high regio-, diastereo-, and enantiocontrol. This methodology constitutes an intermolecular DKR process to set three stereocenters during the key bond forming event.

Dynamic kinetic asymmetric transformations are potent methods to generate functionalized and stereochemically defined products from racemic starting materials, and a number of enzymatic and chemocatalytic reactions have been put forward utilizing this paradigm.[1] Concomitant with the burgeoning number of dynamic methodologies has been an increase in the stereochemical complexity generated in these systems. At the bottom of this gradient resides methods that generate a single stereocenter; a prototypical example is the conversion of racemic alcohols into optically pure acetates enabled by redox processing (Scheme 1).[2] The second echelon in complexity-generation includes dynamic pathways that generate two stereocenters. The asymmetric hydrogenation of configurationally labile α-substituted β-keto esters is the archetypical example.[3]

Scheme 1. Degrees of Stereocomplexity in Dynamic Kinetic Transformations



Stereodynamic methods that generate three stereocenters are limited.[4,5] The preponderance of these methods use catalyst or substrate control to independently establish one stereocenter and dynamic bond formation to furnish the other two. The intramolecular DKR transformation of β-keto esters to β-lactones reported by Scheidt and co-workers serves as a counter-example, whereby simultaneous generation of all three stereocenters can occur during the same step.[6] To the best of our knowledge, an intermolecular DKR or dynamic kinetic asymmetric transformation (DyKAT) that establishes three stereocenters during the key bond-forming event is heretofore unknown. In this communication we describe a DKR utilizing carbene-generated homoenolate equivalents for the chemoselective formation of γ-butyrolactones from α,β-unsaturated aldehydes and racemic α-keto esters with excellent levels of diastereo- and enantiocontrol.

The exploitation of homoenolate (d^3) nucleophiles generated by the union of *N*-heterocyclic carbenes (NHC) and α,β-unsaturated aldehydes has seen widespread use.[7] This method of catalytic *umpolung* (polarity inversion) has grown to include the use of imines,[8] carbonyls,[9] and Michael acceptors[10] as electrophilic components; however, to this point the reaction of enals with linear α-keto esters been reported in only low diasterocontrol (1.5:1) and moderate enantioselectivity (78% ee).[11] In connection with our interest in enantioconvergent carbon–carbon bond constructions involving racemic electrophiles,[12] we sought to develop NHC-catalyzed homoenolate addition of α,β-unsaturated aldehydes to configurationally labile α-keto esters. This endeavor presents a significant challenge in rate constant management: eight stereoisomers are possible and byproducts arising from mechanistically validated cross-benzoin[12c,13] and enal dimerization pathways were a legitimate concerns (Scheme 2).[14]

Our studies began by examining the reaction of cinnamaldehyde and α-keto ester **1a-Me**. A preliminary screen showed that NHC catalyst **A**[12c] delivers γ-butyrolactone **2** in low regio- and diastereoselectivity (Table 1, entry 1).[15] Using **1a**, which has a more sterically demanding *tert*-butyl ester, in combination with **A** yielded **2a** as a single product in a 6:1 diastereomeric ratio (dr) (Table 1, entry 2). Taking this result as an indication that a sterically hindered ester was likely necessary for the efficacy of this transformation, we began a systematic screening of carbene catalysts with **1a**. Catalyst **B** and **C** revealed no marked increase in stereoselectivity (Table 1, entry 3–4). In tandem, these results indicated that increasing the steric bias of phenylalanine

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Scheme 2. Chemoselectivity Challenges for the Carbene Catalyzed Coupling of α,β-Enals (Blue) and Enolizable α-Keto Esters (Red)

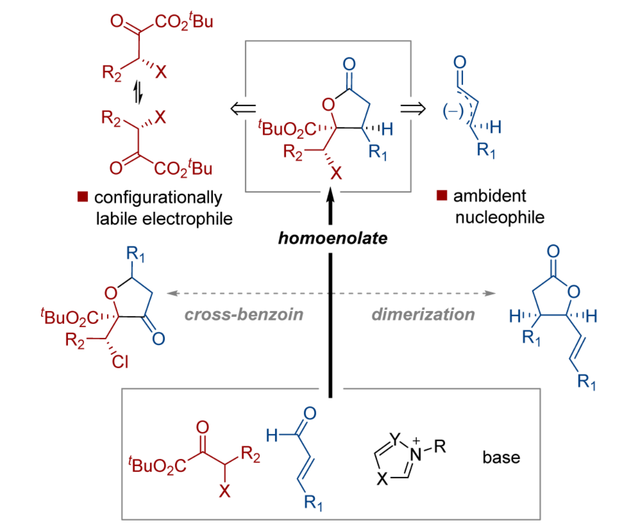
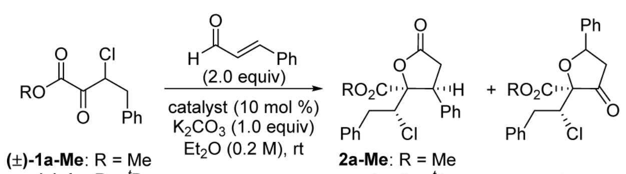
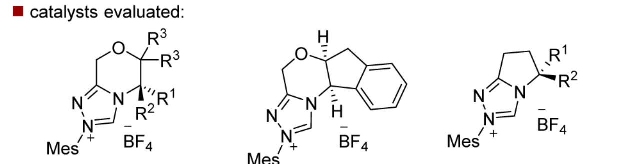


Table 1. Catalyst and Substrate Optimization



catalysts evaluated:



cat.	R^1	R^2	R^3
A	^{i}Pr	H	H
B	Bn	H	Me
C	Bn	H	Ph

D

cat.	R^1	R^2
E	Bn	H
F	H	$C(OTMS)Ph_2$
G	H	$C(OTBS)Ph_2$

entry[a]	R	cat	conv (%)	2a/3a[b]	dr[b,c]	er[d]
1	Me	A	100	5:1	3:1	90:10
2	^{t}Bu	A	100	>20:1	6:1	84:16
3	^{t}Bu	B	88	>20:1	3:1	73:27
4	^{t}Bu	C	64	3.5:1	2:1	85:15
5	^{t}Bu	D	100	2:1	6:1	–
6	^{t}Bu	E	100	>20:1	3:1	78:22
7	^{t}Bu	F	100	>20:1	9:1	93:7
8	^{t}Bu	G	100	>20:1	33:1	99:1
9[e]	^{t}Bu	G	40	>20:1	>20:1	–
10[f]	^{t}Bu	G	100	>20:1	33:1	99:1

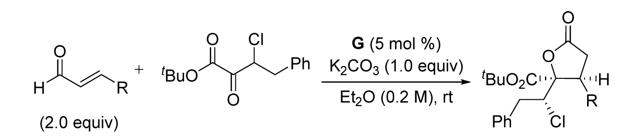
[a]All reactions were run on a 0.10 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]dr is only reported for homoenolate product **2a**. [d]Determined by chiral SFC analysis. [e]Conducted on the corresponding β-bromo analogue of **1a**. [f]Five mol % of catalyst **G**.

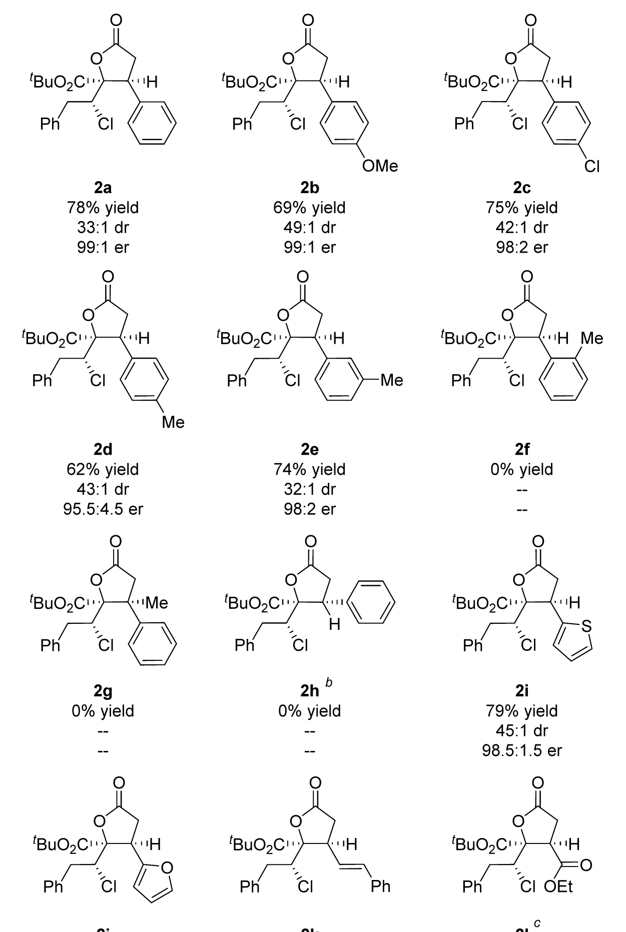
derived NHC catalysts was ineffectual to increasing reaction selectivity. Aminoindanol-derived catalyst **D**[16] showed poor differentiation between the acyl anion and homoenolate pathway yielding a 2:1 ratio of products **2a**/**3a** (Table 1, entry 5). Catalyst **E** provided **2a** as the sole product with a 3:1 dr and an enatiomeric ratio (er) of 78:22 (Table 1, entry 6).

Catalyst **F**,[17] which is a derivative of pyroglutamic acid, delivered exclusively **2a**, in 9:1 dr and 93:7 er (Table 1, entry 7). Deploying catalyst **G** furnished **2a** in 33:1 dr and 99:1 er (Table 1, entry 8). Using the β-bromo α-keto ester of **1a** under identical conditions maintained high levels of isomer selectivity but suffered from poor reactivity (Table 1, entry 9). Lowering the catalyst loading to 5 mol % had no deleterious effects on reaction efficiency or selectivity (Table 1, entry 10).

With suitable conditions in hand we began to probe the allowable steric and electronic parameters of this annulation, initially by varying the identity of the α,β-unsaturated aldehyde (Table 2). Changing the electronic features of the aldehyde delivered **2b** and **2c** without loss of reaction fidelity. While both

Table 2. Variation of α–β Unsaturated Aldehydes in the Homoenolate Addition to β-Chloro-α-Keto Esters[a]





2a 78% yield 33:1 dr 99:1 er	**2b** 69% yield 49:1 dr 99:1 er	**2c** 75% yield 42:1 dr 98:2 er
2d 62% yield 43:1 dr 95.5:4.5 er	**2e** 74% yield 32:1 dr 98:2 er	**2f** 0% yield -- --
2g 0% yield -- --	**2h**[b] 0% yield -- --	**2i** 79% yield 45:1 dr 98.5:1.5 er
2j 86% yield 6:1 dr 95:5 er	**2k** 83% yield 36:1.5:1 dr 97:3 er	**2l**[c] 40% yield 3:1 dr 92.5:7.5 er

[a]All reactions were run on a 0.20 mmol scale at room temperature for 14 h. No acyl anion addition was observed for any example. Diastereomeric ratios were determined by ^{1}H NMR; enantiomeric ratios by chiral SFC. Yields are of isolated products. [b]Using (Z)-cinnamaldehyde. [c]Yield shown is a ^{1}H NMR yield of the major diastereomer utilizing mesitylene as an internal standard.

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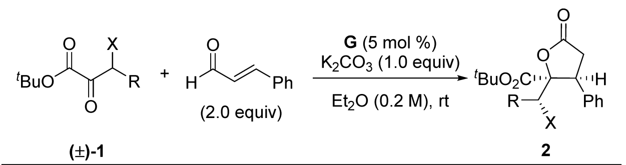
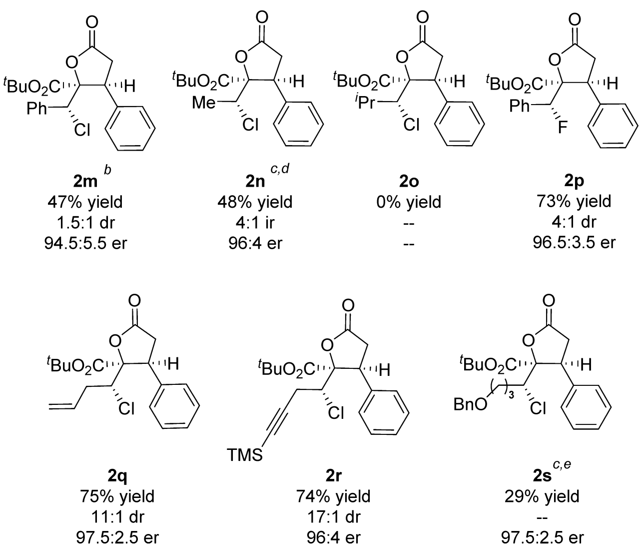
meta- and *para*-toluyl-derived cinnamaldehydes cleanly delivered **2d** and **2e**, the heightened steric encumbrance of *ortho*-methylcinnamaldehyde resulted in no reaction. Similarly, **2g** and **2h**, products that would arise from the addition of a trisubstituted alkene[12d] and (*Z*)-cinnamaldehyde, respectively, were inaccessible. Heteroaromatic **2i** was isolated in 45:1 dr and 98.5:1.5 er, while **2j** was obtained with 6:1 dr and 95:5 er. Products **2k** and **2l** demonstrated the viability of nonaromatic substitution, albeit with low dr for the addition of (*E*)-4-oxobut-2-enoic acid ethyl ester.

Variation of the α-keto ester also provided information regarding reaction scope (Table 3). Reducing the chain length

Table 3. Variation of β-Halo α-Keto Esters in the Homoenolate Addition of Cinnamaldehyde[a]



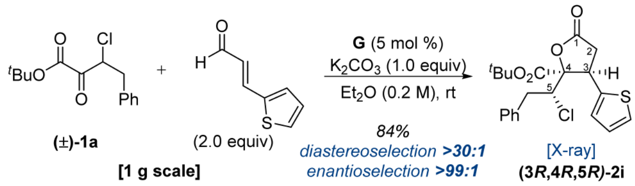


[a]All reactions were run on a 0.20 mmol scale at room temperature for 14 h. Diastereomeric and product ratios were determined by ^{1}H NMR; enantiomeric ratios by chiral SFC. Yields are of isolated products. [b]Using THF as the solvent. [c]Yield shown is a ^{1}H NMR yield of the major diastereomer utilizing mesitylene as an internal standard. [d]Unambiguous differentiation between regioisomers and diastereomers was not feasible; an isomer ratio (ir) is reported. [e]Unambiguous identification of isomer ratios was not possible. Isolation of **2s** was achieved via chromatography.

of the starting α-keto ester delivered **2m** with 1.5:1 dr and 94.5:5.5 er. Similarly, **2n** was isolated with high enantioselectivity but as a 4:1 mix of isomers, while sterically encumbered **1o** resulted in no reaction. Replacing chlorine with fluorine gave **2p** in 4:1 dr and 97:3 er. Products **2q** and **2r** showcase the efficacy of substrates bearing β-propargyl and β-allyl substitution while heteroatom containing **2s** was obtained in low yield but with 97.5:2.5 er.

The reaction of **1a** with (*E*)-3-(thiophen-2-yl)acrylaldehyde on a 1 g scale resulted in 84% yield of **2i** as a single stereoisomer. An X-ray diffraction study was carried out to assign the relative and absolute stereochemistries as (3*R*,4*R*,5*R*) (Scheme 3).[18] The strong stereochemical influence of the β-

Scheme 3. Gram Scale Reaction of 1i and Cinnamaldehyde



chloro substituent is manifested by the conserved anti-relationship between the nascent tertiary alcohol and the resident halogen.[12b,c] This outcome is consistent with stereocontrol based on Felkin-Anh or Cornforth models.[19]

In conclusion, we have developed the first stereoconvergent homoenolate reaction that utilizes racemic electrophiles. This NHC-catalyzed process between β-halo-α-keto esters and α,β-unsaturated aldehydes also constitutes the first intermolecular dynamic kinetic resolution in which three stereocenters are established during the enantiodetermining step. The resultant γ-butyrolactones bear a fully substituted glycolic acid moiety and are often obtained as single products in high diastereo- and enantioselectivity. Further manipulations of this product class and continued expansions of complexity-generating dynamic processes are of ongoing interest in our laboratory.

■ 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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