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Controlled β-protonation and [4+2] cycloaddition of enals and chalcones *via N*-heterocyclic carbene/acid catalysis: toward substrate independent reaction control<sup>†</sup>

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A substrate-independent selective generation of enolates over homoenolate equivalents in NHC-catalyzed reactions of enals and chalcones is disclosed. Acid co-catalysts play vital roles in control of the reaction pathways, allowing for individual access to diverse products from identical substrates.

When multiple reactive intermediates generated from the same substrate are possible, the use of identical substrates may allow for individual access to a diverse set of different products. However, controlling these reaction pathways in a precise and selective manner remains challenging, and thus the observed reaction pathways (and products) are often substrate-dependent. In the arena of N-Heterocyclic Carbene (NHC) catalysis,<sup>1</sup> the activation of enals can lead to at least three different reactive intermediates: homoenolates,<sup>2</sup> enolates,<sup>3,4</sup> and acyl anion equivalents.<sup>5</sup> Protonation (on the enal  $\beta$ -carbon) of homoenolate intermediates could produce enolate intermediates for new intra-3 and intermolecular reactions,<sup>4</sup> as envisioned and realized by the groups of Bode,<sup>4a</sup> Glorius,<sup>4b</sup> Scheidt,<sup>3a,b</sup> Nair,<sup>4d</sup> You,<sup>3c</sup> ourselves,<sup>4e</sup> and others.<sup>6-9</sup> As for intermolecular reactions, in 2006, Bode and co-workers reported intermolecular Diels–Alder reactions of  $\alpha$ , $\beta$ -unsaturated imines with enals bearing electron-withdrawing groups (EWGs) (Fig. 1).<sup>4a</sup> In the same year, the Glorius group described the formation of  $\beta$ -lactones in 22–48% yields by reacting enals and activated ketones.4b In 2010, by using enones bearing additional EWGs as the electrophiles, Bode and co-workers developed efficient enolate generation from enals in the presence of weak bases.<sup>4c</sup>



Fig. 1 Substrate combinations in *intermolecular* enal reactions *via* enolate pathways: partially substrate-dependent reaction control.

Nair and co-workers reported enolate products from enals in the reaction with  $\beta$ -unsubstituted vinyl ketones as the electrophiles.<sup>4d</sup> We recently reported that by using alkylidene diketones as the electrophiles, enals predominantly undergo enolate reaction pathways in the presence of strong bases.<sup>4e</sup>

A further analysis of these otherwise very impressive results (Fig. 1) indicated that access to the enolate pathways (competing with the homoenolate pathways) is somewhat substrate-dependent, with respect to either the enals or the electrophiles. For instance, the reactions of simple enals (bearing no EWG) with chalcones predominantly went through homoenolate pathways to give cyclopentenes, as disclosed by the groups of Nair,2b Bode2c and Scheidt,<sup>2g</sup> under NHC or NHC/Lewis acid cooperative catalysis. Here we report selective access to enolate products using similar enals and chalcones as the substrates (Scheme 1). This work was in part encouraged by our recent success in selective generation of enolate and acyl anion intermediates from the same enal for Diels-Alder and Stetter reactions respectively.4e,5e We hope the present study, built on the progress of others,<sup>4</sup> will provide useful insights into substrate-independent control of reaction pathways. On the application side, it is important to note that the enol lactones obtained in this work cannot be easily accessed using other methods. For example, the related enantioselective enamine catalysis approach using aldehyde pre-nucleophiles worked well only with enones bearing additional EWGs as the electrophiles.<sup>10</sup>

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Scheme 1 Control of the reaction pathways of enals and chalcones to give enolate products.

Two apparent approaches may be used to achieve selective access to the enolate pathway products by controlling the two competing reactions of the homoenolate intermediate (Scheme 1). One is to decrease the reactivity of the electrophile (*e.g.*, enone) toward the homoenolate  $\beta$ -carbon by decreasing its electrophilicity and/or increasing the steric bulkiness. We attributed the predominant enolate pathways in our earlier reactions<sup>4e</sup> to the increased steric bulkiness of the alkylidene diketones. Another and more desired approach is to promote the enal  $\beta$ -protonation by increasing the effective proton concentration (Scheme 1).<sup>4c</sup> At the same time, an increase in proton concentration should not lead to NHC deactivation or other undesired side reactions such as enolate protonation and self-redox reaction.<sup>6</sup>

With this qualitative working hypothesis in mind, we first evaluated the reaction between enal **1a** (200 mol%) and chalcone **2a** (100 mol%) using NHC pre-catalyst **A** (12 mol%) (Table 1). In the presence of 50 mol% of HOAc and 200 mol% of DBU, a small but encouraging amount of enolate pathway product **3a** could be obtained, in comparison to no detectable formation of **3a** in the absence of HOAc (entries 1 and 2). Further adjustment of acid loading led to little improvement in the formation of **3a**. It is important to note that the use of stoichiometric amounts of base

Table 1	Model reaction optimiza H NHC (12 mol%), base (200 mol%) acid (50 mol%)	rion	Mes <sup>-</sup> N <sup>-</sup> Me	s Mes CI-N+N
Ph 2a (R =	THF(1.0 mL), RT, 24 h (0.25 mmol) 4-MeO-C <sub>6</sub> H <sub>4</sub> )	(homoenclate prod.) $R \rightarrow Ph$ Ph 4a (homoenclate prod.)	$BF_{4  } \overset{N}{\longrightarrow} B$	$dr^{b}$
	( ) )	00117 (70)	Ju . 4u	ui
1	<b>A</b> , DBU (no acid)	85	<1:99	n.d.
2	A, DBU, HOAc	81	1:13	n.d.
3	<b>A</b> , $K_3PO_4$ (no acid)	>95	1:8	n.d.
4	A, K <sub>3</sub> PO <sub>4</sub> , HOAc	51	1.3:1	n.d.
5	<b>B</b> , K <sub>3</sub> PO <sub>4</sub> , HOAc	>95	9:1	1.7:1
6	C, K <sub>3</sub> PO <sub>4</sub> , HOAc	>95	5.6:1	20:1
$7^c$	C. KOAc (no acid)	>95	4:1	19:1
$8^{c,d}$	C, KOAc, HOAc	>95 (86) <sup>e</sup>	10:1	20 : 1 (>98)

<sup>*a*</sup> Conversion based on 2a, determined *via* <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>*b*</sup> Determined *via* <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>*c*</sup> 20 mol% of cat. C, 250 mol% of KOAc, 4 Å MS, THF (0.5 mL). <sup>*d*</sup> 25 mol% of HOAc. <sup>*e*</sup> The number in parentheses indicates the isolated yield of 3a (single diastereomer). <sup>*f*</sup> ee (%) of 3a, determined *via* chiral phase HPLC analysis; the absolute configuration of the major diastereomer was assigned based on X-ray structure of 3c (Table 2). n.d. = not determined. MS = molecular sieve.

is critical to ensure effective generation of the free NHC catalysts. The use of catalytic amounts (e.g., 20 mol%) of DBU in the presence of various amounts of acid led to little formation of 3a and/or 4a. Weaker organic bases<sup>4c</sup> such as DABCO resulted in improved, but still unsatisfactory formation of 3a after optimization (see ESI<sup>†</sup>). We subsequently found that inorganic bases such as K<sub>3</sub>PO<sub>4</sub>, in combination with HOAc, performed much better (entries 3 and 4). Triazolium-based NHC B led to more selective formation of enolate product 3a (entry 5) than the imidazoliumbased catalyst A, as previously observed by Bode and co-workers.<sup>4c</sup> Finally, a combination of KOAc, HOAc, and chiral NHC pre-catalyst C could afford 3a in excellent yield, high dr and ee (Table 1, entry 8). It is worth noting that Rovis and co-workers<sup>2i</sup> have previously used acetic acid salts as bases in NHC-catalyzed homoenolate addition to imines to form lactams, in which enolate pathway products were not formed and the conjugate acids were believed to activate the imine electrophiles.<sup>11</sup>

Both  $\beta$ -(hetero)aryl and alkyl enals were effective substrates to react with chalcone **2a** to give the enolate products (**3**) with good yields, excellent dr and ee (Table 2). Substitutions on the enal  $\beta$ -aryls were tolerated (entries 1–6). One observation of notable mechanistic interest is the effect of the substituents of the  $\beta$ -aryls on the ratios of enolate/homoenolate products. For example, enal **1d** with an *ortho*-Br-substituent on the  $\beta$ -phenyl group showed a better enolate/homoenolate product ratio than enal **1c** with a *para*-Br-substituted phenyl unit. The *ortho*-Br substituent provides steric bulkiness that makes homoenolate  $\beta$ -addition to the chalcones less favorable than the corresponding  $\beta$ -carbon protonation. Similar trends were observed for enals **1a** and **1b**. Enals with  $\beta$ -alkyl-substituents were effective substrates as well (Table 2, entries 9 and 10). In all these reactions, a combined use of acids and bases is necessary.

Next, chalcones (2) with various Ar and Ar' substituents were examined to react with enals smoothly (Table 3). In general, chalcones with electron-donating substituents (Me or MeO) on Ar or Ar' (entries 1–3 and 6–7) gave higher enolate/homoenolate product ratios than those with slight electron-withdrawing

Table 2 Scope of the enals $1^a$									
C (20 mol%) KOAc (250 mol%) ACOH (25 mol%) Ph Ph 2a(0.25 mmol) C (20 mol%) ACOH (25 mol%) THF(0.5 mL), MS, RT, 24 h Ph <sup>**</sup> 3 Ph (enolate prod.)									
Entry	R	Yield <sup><math>b</math></sup> (%)	dr	ee (%)	3:4				
1	4-MeOC <sub>6</sub> H <sub>4</sub> (1a)	86 ( <b>3a</b> )	20:1	>98	10:1				
2	$2 - MeOC_6H_4$ (1b)	89 ( <b>3b</b> )	20:1	>98	26:1				
3 <sup>c</sup>	$4-BrC_{6}H_{4}(1c)$	73 ( <b>3c</b> )	20:1	>98	6:1				
$4^c$	$2\text{-BrC}_6\text{H}_4$ (1d)	83 ( <b>3d</b> )	20:1	>98	21:1				
5	$4 - Me_2 NC_6 H_4$ (1e)	81 ( <b>3e</b> )	20:1	>98	5:1				
6 <sup><i>c</i></sup>	2-Naphthyl (1f)	84 ( <b>3f</b> )	19:1	>98	9:1				
$7^c$	2-Furyl (1g)	69 ( <b>3g</b> )	20:1	>98	n.d.				
8 <sup>c</sup>	Ph (1h)	88 ( <b>3h</b> )	20:1	>98	10:1				
9 <sup>c</sup>	$n-C_5H_{11}$ (1i)	79 ( <b>3i</b> )	20:1	>98	9:1				
$10^c$	$n-C_3H_7$ ( <b>1j</b> )	77 ( <b>3j</b> )	9:1	>98	10:1				

<sup>a</sup> Reaction conditions similar to Table 1, entry 8: 0.75 mmol of 1 was used except for entries 1, 2 and 5 where 0.5 mmol of 1 was used.
 <sup>b</sup> Isolated yield of 3. <sup>c</sup> THF (0.25 mL) was used. n.d. = not determined.

Table 3 Scope of the chalcones 2<sup>a</sup>



<sup>a</sup> Reaction conditions similar to Table 1, entry 8, except for entries 5 and 9 where 150 mol% of HOAc and 200 mol% KOAc were used.
 <sup>b</sup> Isolated yield. <sup>c</sup> 40 h.

65 (**3q**)

75 (3q)

60 (**3r**)

70 (3s)

 $4-ClC_6H_4$ 

 $4-ClC_6H_4$ 

4-MeC<sub>6</sub>H<sub>4</sub>

2-Furyl

15:1 (>98)

19:1(>98)

16:1(>98)

8:1 (>98)

6:1

8:1

11:1

5:1

groups (entries 4, 8 and 11) under previously optimized conditions used in Table 2. After a brief additional optimization with regard to acid and base loadings, good enolate/homoenolate product ratios were obtained for these substrates by using 2.0 equiv. of KOAc and 1.5 equiv. of AcOH (entries 5 and 9). The diastereomeric ratios of the enolate pathway products (3) were also improved by using a higher acid loading.

In summary, we have achieved a control over reaction pathways in NHC-mediated reactions of enals and chalcones. Acid co-catalysts were used to realize selective homoenolate  $\beta$ -protonation and controlled access to previously unobservable enolate products. The competing enolate/homoenolate pathways were found to be sensitive to the steric bulkiness of the enal and enone substrates, and could be nicely controlled by the acid co-catalysts. The synthetically useful lactone products from our reactions could not easily be prepared using other approaches. We hope this study will initiate further investigations into substrate-independent manipulation of catalytic reaction pathways, and thus allow for individual access to diverse products from identical substrates.<sup>12</sup>

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8

9

10

11

Ph

Ph

Ph

4-BrC<sub>6</sub>H<sub>4</sub>