Organocatalysis

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β-Functionalization of Carboxylic Anhydrides with β-Alkyl Substituents through Carbene Organocatalysis**

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Abstract: *The first NHC-catalyzed functionalization of carboxylic anhydrides is described. In this reaction, the β carbon behaves as a nucleophilic carbon and undergoes asymmetric reactions with electrophiles. Anhydrides with challenging β-alkyl substituents work effectively.*

Carbonyl compounds are readily available and inexpensive raw materials. The direct functionalization of β carbon atoms of saturated carbonyl compounds can provide a shortcut for the rapid installation of useful functional units, and therefore received intense attention in recent years. Similar to the development of other types of inert chemical bond activations, success in the matter came from transition metal catalysis.[1] In recent years, also organocatalysis was established in the area of inert chemical bond functionalizations. The β carbon atom of a saturated carbonyl compound can be possibly activated as a reactive electrophilic carbon, radical carbon, or nucleophilic carbon. In 2011, the groups of Hayashi and Wang reported the amino-catalyzed oxidation of saturated aldehydes to the corresponding α,β-unsaturated iminium intermediates, in which the formal aldehyde β carbon behaved as an electrophilic reactive carbon (Figure 1 a).[2] With an N-heterocylic carbene (NHC) as the organic catalyst under oxidative conditions the β carbon of a saturated aldehyde can also be activated as an electrophilic carbon, as disclosed in our earlier studies (Figure 1 a).[3] MacMillan's group has pioneered the activation of the β carbon of saturated aldehydes and ketones as reactive radical carbon through amino catalysis in a single-electron transfer process (Figure 1 b).[4]

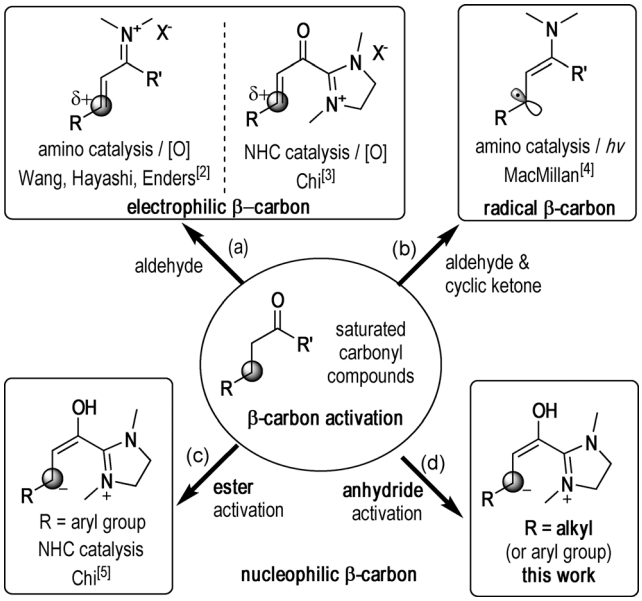

Figure 1. Organocatalytic β-functionalization of carbonyl compounds.

We were interested in the organocatalytic activation of readily available and inexpensive substrates. In 2013, we reported the first catalytic reaction of the β carbon of a saturated ester as a reactive nucleophilic carbon through NHC organocatalysis (Figure 1 c).[5] The reactions are effective with respect to stereoselectivity and several electrophile substrates work well. However, an aryl substituent is required at the β carbon of the ester to enable effective reactions and acceptable yields. Esters with a β-alkyl substituent remain challenging with that strategy, affording products in 8–40 % yields.[5] Here we report a solution to this challenging problem (Figure 1 d). Our new approach involves a carbene-catalyzed β carbon functionalization of anhydrides bearing β-alkyl substituents. The present study also represents an important success in using NHC organocatalysts to activate anhydrides for asymmetric reactions.[6] As a note, Smith and co-workers have pioneered the use of carboxylic anhydrides as enolate precursors (α carbon functionalization) by using isothiourea as organocatalysts.[7] During the submission of this manuscript, Scheidt and co-workers reported an NHC-catalyzed enolate formation using carboxylic acid substrates.[8]

Results of our initial studies and the optimization of the reaction conditions are summarized in Table 1. Anhydride **1a**

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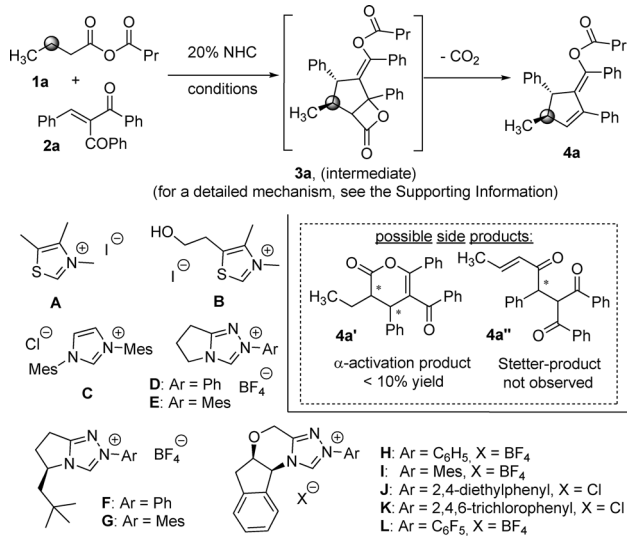
Table 1: Optimization of the reaction conditions.[a]



Entry	NHC	Base	Solvent	Yield [%][b]	e.r.[c]
1	**A, B** or **C**	Cs_2CO_3	ether	0 or < 5	–
2	**D**	Cs_2CO_3	ether	< 10	–
3	**E**	Cs_2CO_3	ether	54	–
4	**F**	Cs_2CO_3	ether	< 10	94:6
5	**G**	Cs_2CO_3	ether	73	88:12
6	**H**	Cs_2CO_3	ether	< 10	87:13
7	**I**	Cs_2CO_3	ether	74	81:19
8	**J**	Cs_2CO_3	ether	60	81:19
9	**K**	Cs_2CO_3	ether	22	98:2
10	**L**	Cs_2CO_3	ether	0	–
11	**K**	DMAP	ether	28	96:4
12	**K**	DMAP	hexane	36	94:6
13	**K**	DMAP	cyclohexane	44	96:4
14[d]	**K**	**DMAP**	**cyclohexane**	**61(62)**	**95:5**

[a] 4 equiv of **1a**, 1 equiv of **2a** (0.1 mmol), 20 mol% of NHC, 3 equiv of base, and 1 mL of solvent at RT (24 °C) for 24 h. [b] Yield was determined by ^{1}H NMR spectroscopy, and the yield in parenthesis was of the isolated product after column chromatography. [c] e.r. of **4a**, determined by HPLC on a chiral stationary phase. [d] The reaction was performed using 2 equiv of **1a** and 4 equiv of DMAP in 0.2 mL cyclohexane at 30 °C for 36 h. DMAP = 4-(dimethylamino)pyridine.

with a β-methyl substituent was chosen as the model carbonyl substrate. We chose α,β-unsaturated ketone **2a** with an electron-withdrawing substituent at the α carbon (benzylidene diketone) as a model electrophile. It is worth noting that this type of electrophiles were challenging to react with the β carbon of similar homoenolate intermediates generated from enals.[9] In our earlier studies, **2a** either reacted with the enal α carbon or carbonyl carbon (see the Supporting Information (SI) for details). Screening of catalysts showed that the use of neither thioazolium (entry 1, **A**, **B**) nor imidazolium (entry 1, **C**) NHC precursors could afford the desired product **4a**. When triazolium salt **D**, bearing a *N*-phenyl group was used as catalyst, product **4a** was formed with a low but encouraging yield (entry 2). Upon switching the phenyl group on the triazolium salt to an electron-rich mesityl group, **4a** was formed with 54% yield (entry 3). Further screening of chiral NHC catalysts showed similar trends: for reaction efficiency (yields), it appeared that triazolium NHC catalysts with an electron-rich *N*-aryl substituent worked significantly better than those analogues with an electron-deficient aryl substituent (e.g., comparison of entry 5 with entry 4, and entries 6–10). Attempts to improve the enantioselectivity of this reaction by using bulkier NHC catalysts (e.g., **J**, entry 8) was unsuccessful. When catalyst **K** with an *N*-trichlorophenyl substituent was used, the reaction afforded **4a** in 22% yield and excellent 98:2 e.r. (entry 9). We then decided to further optimize the reaction using catalyst **K** (entries 11–14) and found that with DMAP as a base and cyclohexane as the solvent, **4a** was isolated in 62% yield and 95:5 e.r. (entry 14). As carboxylic anhydride is easily hydrolyzed under our basic reaction conditions, an excess amount of anhydride is required. This drawback could be partially compensated by the lower price of the corresponding aliphatic carboxylic anhydrides compared with enals as the homoenolate synthetic equivalents (e.g., butyric acid anhydride **1a** at $43/500 mL versus crotonaldehyde at $141.4/500 mL from Alfa Aesar). Notably, product **4a** was obtained as a single diastereomer under our conditions, and the possible by-products **4a′** and **4a″** (formed by reaction between the anhydride-derived enolate or the Breslow intermediate with **2a**) were hardly observed.

With the optimized conditions (Table 1, entry 14) in hand, we next examined the reaction scope (Table 2). The benzylidene diketones with different substitution patterns are tolerated, affording the desired products in excellent enantioselectivities and moderate to good yields (entries 1–15). The β-methyl substituent of **1a** can be replaced with other alkyl substituents such as ethyl and propyl units without affecting the reaction outcomes (entries 16–23). Notably, our present anhydride approach also worked for substrates bearing β-aryl substituents (entries 26–28), although the enantioselectivities of corresponding products were only moderate. Replacement of either R^1 or R^2 group in the diketone substrate **2** to an aliphatic group would result in no product formation (entries 24 and 25).

Next we examined the generality of the anhydride approach using simple chalcones as the electrophile substrates (Table 3). The NHC catalyst **K** for the benzylidene diketone reaction (Table 1, entry 14) gave only trace amounts (< 5% yield) of product for the chalcone electrophile. We then found that by using catalyst **I**, the desired β-carbon functionalization products (cyclopentenes **6a–6k**) could be obtained with good yields and excellent diastereo- and enantioselectivities. It should be noted that the formation of similar substituted cyclopentenes from enals under NHC catalysis has been pioneered by Nair.[10a] The groups of Bode[10b] and Scheidt[10c] also obtained excellent enantioselectivities using enals with β-aryl substituents. On the other hand, for enals with β-alkyl substituent, it still remains challenging to achieve acceptable reaction yields or enantioselectivities.[10]

Isatins as electrophile substrates were also examined.[11] In this case, the NHC precatalyst **J** was found to be optimal. The corresponding spiro-lactone products (Table 3, **8a–8h**) were obtained in moderate to excellent yields and with good to excellent stereoselectivities. As a note, electron-withdrawing substituents seriously decreased the product yields (condi-

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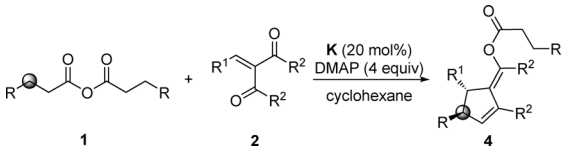
Table 2: Scope of anhydrides and alkylidene diketones.[a]

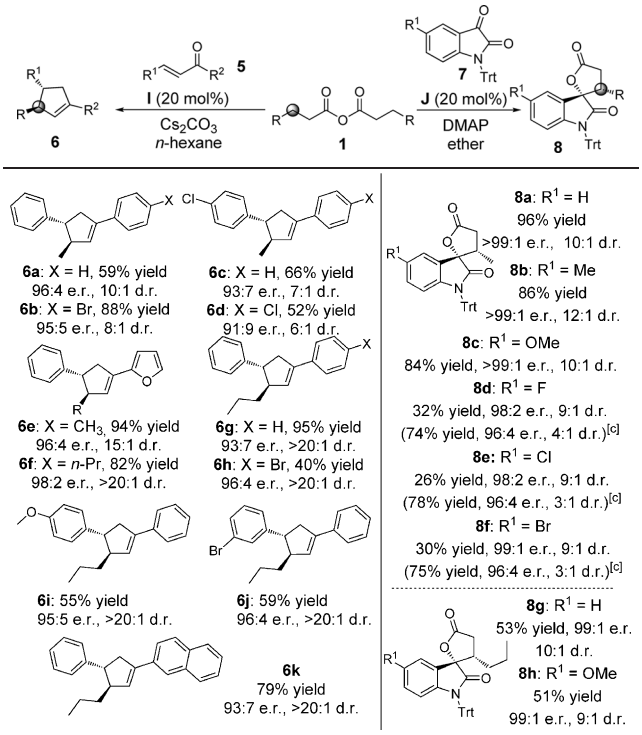


1 2 4

Entry	R	R^1	R^2	4	Yield [%][b]	e.r.[c]
1	Me	Ph	Ph	**4a**	62	95:5
2	Me	3-BrC_6H_4	Ph	**4b**	75	97:3
3	Me	2-ClC_6H_4	Ph	**4c**	52	98:2
4	Me	3-FC_6H_4	Ph	**4d**	73	96:4
5	Me	4-FC_6H_4	Ph	**4e**	60	94:6
6	Me	3-$MeOC_6H_4$	Ph	**4f**	65	96:4
7	Me	4-MeC_6H_4	Ph	**4g**	71	96:4
8	Me	4-$NO_2C_6H_4$	Ph	**4h**	58	97:3
9	Me	2-naphthyl	Ph	**4i**	53	95:5
10	Me	2-furanyl	Ph	**4j**	47	97:3
11	Me	2-thiophenyl	Ph	**4k**	64	98:2
12	Me	4-pyridinyl	Ph	**4l**	62	98:2
13	Me	3-pyridinyl	Ph	**4m**	60	98:2
14	Me	Ph	4-FC_6H_4	**4n**	62	94:6
15	Me	3-$MeOC_6H_4$	4-BrC_6H_4	**4o**	64	95:5
16	Et	Ph	Ph	**4p**	50	97:3
17	Et	3-BrC_6H_4	Ph	**4q**	68	98:2
18	Et	4-MeC_6H_4	Ph	**4r**	68	98:2
19	*n*Pr	Ph	Ph	**4s**	63	98:2
20	*n*Pr	3-BrC_6H_4	Ph	**4t**	67	98:2
21	*n*Pr	3-$MeOC_6H_4$	Ph	**4u**	61	99:1
22	*n*Pr	Ph	4-FC_6H_4	**4v**	68	97:3
23	*n*Pr	3-$MeOC_6H_4$	4-BrC_6H_4	**4w**	67	97:3
24	Me	Me	Ph	–	0	–
25	Me	Ph	Et	–	0	–
26[d]	Ph	Ph	Ph	**4x**	60	84:16
27[d]	Ph	4-ClC_6H_4	Ph	**4y**	72	87:13
28[d]	Ar[e]	3-BrC_6H_4	Ph	**4z**	60	81:19

[a] 2 equiv of **1**, 1 equiv of **2** (0.1 mmol), 20 mol% of **K**, 4 equiv of DMAP, and 0.2 mL of solvent at 30°C for 36 h. [b] Yield of the isolated product. [c] e.r. is determined by HPLC on a chiral stationary phase. [d] 2 equiv of **1**, 1 equiv of **2** (0.1 mmol), 20 mol% of **I**, 1 equiv of K_3PO_4, and 1 mL of MTBE at rt (24°C) for 36 h. [e] Ar = 4-BrC_6H_4. MTBE = methyl *tert*-butyl ether.

Table 3: Reactions of anhydrides with chalcones[a] and isatins.[b]



[a] 3 equiv of **1**, 1 equiv of **5** (0.1 mmol), 20 mol% of **I**, 3 equiv of Cs_2CO_3, and 1 mL of hexane at 50°C for 36 h. [b] Condition A: 3 equiv of **1**, 1 equiv of **7** (0.1 mmol), 20 mol% of **J**, 4 equiv of DMAP, and 2 mL of ethyl ether at RT (24°C) for 12 h. [c] Condition B: 2 equiv of **1**, 1 equiv of **7** (0.1 mmol), 10 mol% of **J**, 2 equiv of DIEA, and 2 mL of dioxane at RT (24°C) for 12 h. DIEA = *N*,*N*- diisopropylethylamine.

tion A, **8d**–**8f**). These lower yields could be compensated by applying other catalytic conditions, which led to some decrease of the d.r. values (condition B, **8d**–**8f**). Again, it is important to note that such optically enriched spiro-lactone products derived from β-alkyl carbonyl compound have not been effectively obtained with NHC catalysis. In previous approaches with β-alkyl enal substrates, similar products were obtained with low enantiomeric excess.

To view the strengths and limitations of our earlier ester approach[5] and the present anhydride method, we systematically compared the two reaction systems (see SI, Table S1). The optimal condition for β-alkyl anhydrides did not work well for β-aryl anhydrides or esters with β-alkyl and aryl substituents. Similarly, the optimal condition for β-aryl esters did not work well for β-alkyl esters or anhydrides with β-alkyl or aryl substituents. The mechanistic origins accounting for these differences are rather complicated and currently under investigation. Our preliminary studies at this point suggest that the anions (4-nitrophenolate and alkylcarboxylate) released by the addition of the carbene catalyst to the substrates could affect multiple steps during the reaction.

The chiral cyclopentene product (**4o**, Table 1) from our catalytic reaction is amenable for further transformations by simple protocols (Figure 2). The enol ester group in product **4o** could be removed through reduction with $LiAlH_4$ to afford cyclopentene **9** without erosion of e.r. Expoxidation of **9** using *m*-CPBA gave oxabicyclo[3.1.0]hexane **10** in optically pure form. The oxabicyclic structure of **10** could be found as basic core structures in several antibiotic molecules such as methylenomycin A.[12] Oxidative carbon–carbon double bond cleavage of cyclopentene **9** by using ozone afforded δ-keto carboxylic acid **11** as a single diastereomer with excellent e.r.

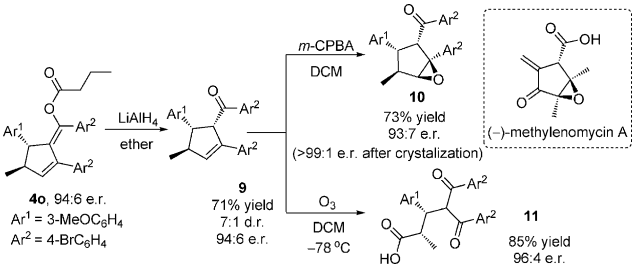


Figure 2. Synthetic transformations.

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In summary, we have developed the first NHC-catalyzed functionalization of carboxylic anhydrides. The β carbon behaved as a reactive nucleophilic carbon and underwent asymmetric reactions. With this approach, anhydrides with β-alkyl substituents work effectively. We expect this study to encourage further explorations in the area of inert chemical bond activations by organocatalysis and to provide additional options for synthetic C–H bond activations.

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