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Enantioselective Oxidative Coupling of Carboxylic Acids to α-Branched Aldehydes

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Supporting Information

ABSTRACT: A new reactivity in organocatalysis is proposed to account for the coupling of carboxylic acids to α-branched aldehydes by combining primary amine catalysis and an oxidant. The developed methodology is an enantioselective α-coupling of aromatic and aliphatic carboxylic acids to α-branched aldehydes and proceeds in high yields (up to 97%) and for most examples good enantioselectivities (up to 92% ee). On the basis of experimental and mechanistic observations, the role of the primary amine catalyst is discussed.

The direct addition of carboxylic acids to the α-position of an aldehyde is challenging as it involves nucleophilic addition of the carboxylate to the nucleophilic enolate. To achieve such a reaction design, one has to overcome the challenge of coupling two nucleophilic centers.[1]

During the last decades, the use of chiral amine catalysts has become an important tool for functionalizing carbonyl compounds. Secondary amines have been applied in enamine catalysis for incorporation of electrophiles in the α-position of aldehydes (Figure 1a).[2] This HOMO-raising strategy allows for incorporation of common functionalities, but the concept is limited to coupling of electrophiles. A further development in organocatalytic activation of aldehydes was disclosed by MacMillan through oxidative α-coupling of aldehydes to allylsilanes by SOMO-activation of the enamine (Figure 1b).[3] In the following, we present a novel concept in organocatalysis demonstrating the enantioselective oxidative coupling of carboxylic acids to α-branched aldehydes. To account for the reaction pathway, we propose it might proceed via an intermediate other than a radical cation (Figure 1c).

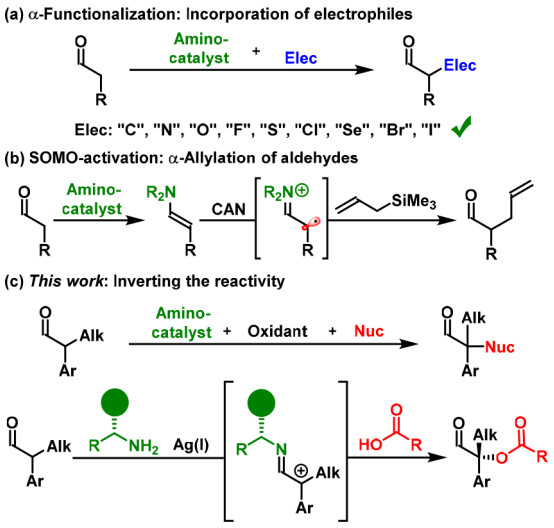

Figure 1. (a) Organocatalytic electrophilic α-functionalization of aldehydes. (b) α-Allylation of aldehydes by SOMO-activation. (c) Inversion of reactivity by enamine oxidation allowing for α-coupling of nucleophiles, such as carboxylic acids, to aldehydes.

Despite the apparent simplicity of an ester bond, the construction of complex ester functionalities is a challenge in synthesis.[4] The Mitsunobu reaction is a fundamental reaction for constructing carboxylate esters allowing primary and secondary alcohols to react with carboxylic acids.[5] Additionally, stereospecific versions have been reported starting from chiral secondary alcohols.[6] The preparation of chiral *tert*-alkyl carboxylates is challenging as the reaction does not proceed with tertiary alcohols. In this context, a variant of the Mitsunobu reaction was developed where chiral tertiary alcohols react with alkoxydiphenylphosphines.[7]

Herein we disclose the organocatalytic enantioselective coupling of carboxylic acids to the α-position of α-branched aldehydes, thereby inverting the reactivity compared to classic enamine catalysis (Figure 1c). This strategy provides direct access to chiral *tert*-alkyl carboxylates. The concept relies on condensation of a chiral primary amine with an α-branched aldehyde forming an enamine that is subsequently oxidized.[8] We propose that the oxidized enamine upon deprotonation might undergo further oxidation generating a cationic intermediate that reacts with the carboxylic acid.

We initiated the investigation of the oxidative coupling by treating α-branched aldehyde **1a** and 4-nitrobenzoic acid **2a** with Ag_2CO_3 in the presence of pyrrolidine-based aminocatalyst **3a** (Table 1, entry 1). These conditions afforded complete conversion into the homocoupled product **5** (7:1 d.r.; 92% ee).[9] Switching to a primary amine catalyst was key for achieving the acid-coupling and product **4a** was formed in 39% product selectivity applying cinchona-alkaloid derived aminocatalyst **3b** (entry 2). Further improvement in product selectivity was obtained when aminocatalyst **3c** was applied and **4a** was isolated in 67% yield and 86% ee (entry 3). Next, different silver salts were tested as oxidants. Applying $AgNO_3$ decreased the conversion to **4a** (entry 4), whereas employing

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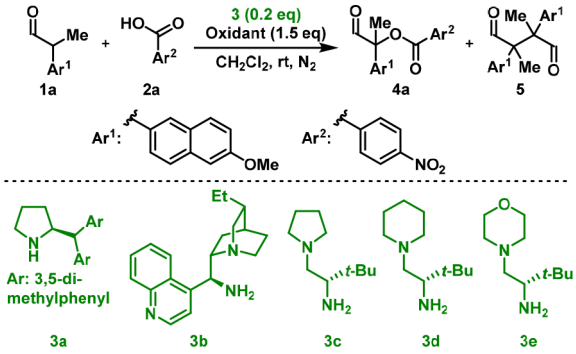
Table 1. Optimization of Reaction Conditions



entry[a]	3	oxidant	4a [%][b]	5 [%][b]	ee (4a) [%][d]
1	**3a**	Ag_2CO_3	0	100	–
2	**3b**	Ag_2CO_3	39	43	–
3	**3c**	Ag_2CO_3	96 (67)	2	86
4[e]	**3c**	$AgNO_3$	20	20	–
5[e]	**3c**	AgOAc	68 (52)	0	79
6	**3c**	Ag_2O	100 (38)	0	85
7[f]	**3c**	Ag_2CO_3	82(70)	0	84
8[g]	**3c**	Ag_2CO_3	87 (47)	0	77
9[h]	**3c**	Ag_2CO_3	91 (50)	5	72
10[i]	**3c**	Ag_2CO_3	91 (59)	5	89
11	**3d**	Ag_2CO_3	70 (53)	13	88
12	**3e**	Ag_2CO_3	100 (78)	0	87
13[j]	–	Ag_2CO_3	0	0	–
14[j]	**3e**	–	0	0	–

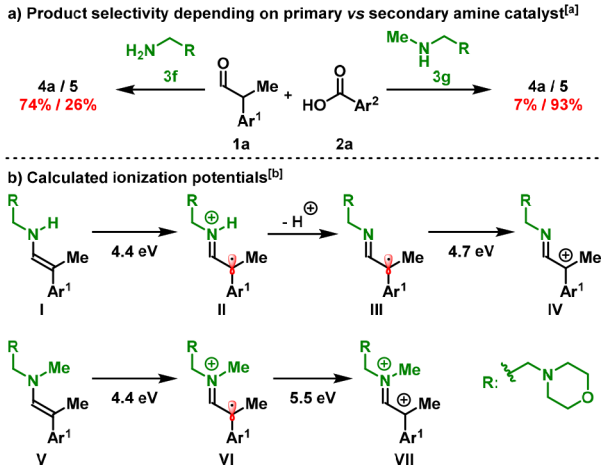
[a]Performed on 0.1 mmol scale with 1.0 equiv of **1a** and 1.5 equiv of **2a** in 0.6 mL of solvent. [b]Conversion measured by ^{1}H NMR of the crude reaction mixture by integration of all aldehyde peaks at full consumption of **3**. [c]Isolated yield in parentheses. [d]ee determined by chiral stationary phase UPC^2. [e]3 equiv of oxidant. [f]$CHCl_3$ as solvent. [g]Toluene as solvent. [h]CH_3CN as solvent. [i]Performed at 5 °C for 30 h. [j]No conversion observed after 7 h.

AgOAc afforded **4a** in 52% yield and 79% ee (entry 5). Using Ag_2O favored the acid-coupling, however, **4a** was isolated in only 38% yield (entry 6). Ag_2CO_3 was found to be the best oxidant and a screening of solvents was initiated. In $CHCl_3$ similar results compared to CH_2Cl_2 were obtained (entry 7), whereas toluene and CH_3CN gave a decrease in yield and enantioselectivity (entries 8 and 9).

To increase enantioselectivity, the reaction was carried out at 5 °C. Although the enantioselectivity was improved to 89% ee, the reaction time was prolonged leading to increased decomposition of **4a** (entries 3 and 10). Finally, we examined the effect of the tertiary amine moiety in the aminocatalyst. Moving from pyrrolidine to piperidine resulted in more homocoupling (entry 11). Interestingly, the morpholino-based catalyst **3e** provided selectively **4a** in 78% yield and 87% ee (entry 12). Finally, control experiments demonstrated both aminocatalyst and Ag_2CO_3 to be essential for the reactivity (entries 13 and 14).

To gain mechanistic insight and explore the influence of a primary vs a secondary amine catalyst, we performed experimental investigations and calculated ionization potentials (IPs) for relevant intermediates (Scheme 1). For this purpose, 2-morpholinoethan-1-amine **3f** was tested in the reaction of **1a** and **2a** providing **4a** in 74% selectivity. In contrast, applying the methylated version of the catalyst (**3g**) under identical conditions, the homocoupled product **5** was formed in 93%

Scheme 1. Investigating the Role of a Primary vs Secondary Amine Catalyst



[a]Performed on 0.1 mmol scale. Product ratios measured by ^{1}H NMR on the crude reaction mixture. [b]For calculation of IPs, see SI.

selectivity (Scheme 1a). This highlights the importance of the aminocatalyst to be primary compared to secondary. Therefore, we decided to investigate the IPs for enamines derived from primary and secondary amine catalysts (Scheme 1b).

The calculated IP of enamine **I** derived from **1a** and primary amine catalyst **3f** is 4.4 eV. The resulting radical cation **II** can be deprotonated forming radical **III** leading to the cationic species **IV** with a similar IP of 4.7 eV. Applying secondary amine catalyst **3g**, the enamine **V** has an IP of 4.4 eV; however, in this case the radical cation **VI** cannot be deprotonated and further oxidation affording the double cationic species has an IP of 5.5 eV. For the primary amine catalyst, the two oxidations have similar IP, whereas for the secondary amine catalyst, a second oxidation step leading to dicationic species **VII** has a higher IP. In related studies on oxidative cyclization of carboxylic acids via benzylic oxidation, formation of a benzylic carbocation is supported by Hammett analysis.[10] This example might indicate the preference for carboxylates to react with the carbocation rather than the transient radical intermediate. We performed competition experiments and the results show that aromatic aldehydes having electron-donating substituents react faster than their more electron-poor counterparts (see SI). Furthermore, the product selectivity decreases, by favoring homocoupling, for electron-poor aldehydes, indicating two different reaction pathways. On the basis of these results, it is not unlikely that the reactive intermediate could be cationic species **IV**. However, coupling of radical **II** or **III**[11] with the carboxylic acid cannot be excluded.

Next, we turned attention toward exploring the substrate scope. The reaction with 4-nitrobenzoic acid **2a** on a 0.2 mmol scale improved the yield of **4a** to 97%, maintaining enantioselectivity (Scheme 2). Nitro substituents in the 2- and 3-position of the benzoic acid were tolerated providing the respective products in 91% yield, 86% ee (**4b**) and 68% yield, 72% ee (**4c**). Benzoic acid derivatives bearing electron-withdrawing groups in the 4-position reacted smoothly, providing the acid-coupled adducts **4d–f** in good yields and enantioselectivities. Despite the moderate yields, we were satisfied that benzoic acid, as well as the derivative bearing a 4-methyl substituent, could be applied forming **4g** and **4h**, in 77% and 74% ee, respectively. For more electron-rich benzoic

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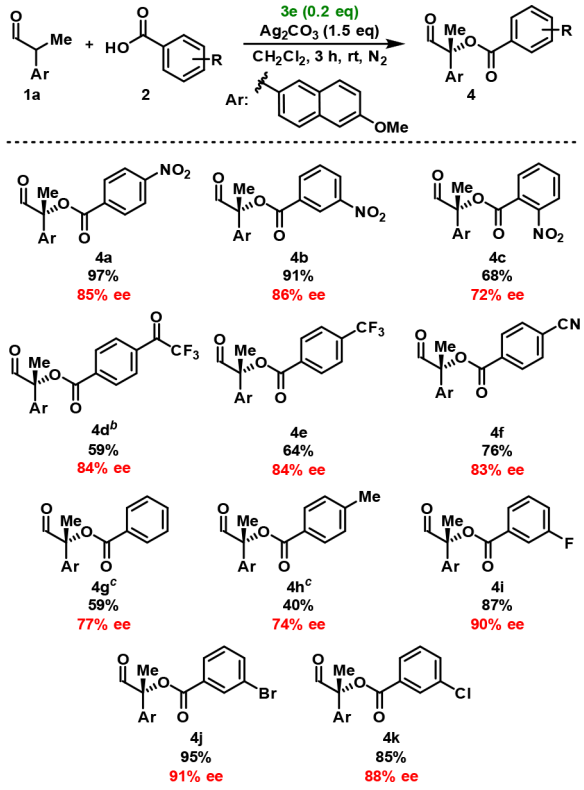
Scheme 2. Enantioselective Oxidative Coupling of Benzoic Acid Derivatives to 1a[a]



[a]Performed on 0.2 mmol scale with 1.0 equiv of **1a** and 1.5 equiv of **2**. ee determined by chiral stationary phase UPC^2. Absolute stereochemistry determined by analogy to X-ray structure of **4k**. [b]Reaction time 8 h. [c]3 equiv of carboxylic acid and 0.5 equiv of 4-hydroxybenzonitrile were added.

acids, the homocoupling becomes a competing pathway. Halogen substituents were tolerated as 3-fluoro-, 3-bromo- and 3-chlorobenzoic acids provided **4i** (87% yield, 90% ee), **4j** (95% yield, 91% ee) and **4k** (85% yield and 88% ee). The absolute configuration of **4k** was determined by X-ray crystallography (Figure 2).

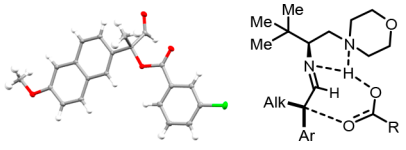
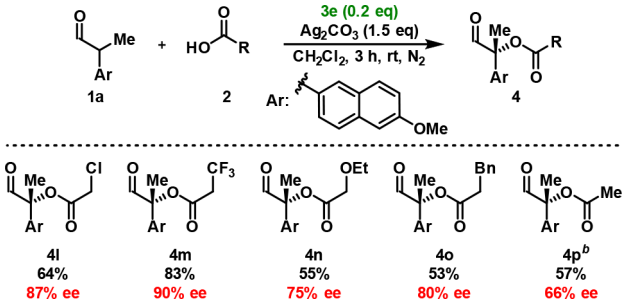


Figure 2. Left: X-ray crystal structure of **4k**. Right: Proposed transition-state structure.

Next, the applicability of aliphatic carboxylic acids was explored. Beside the synthetic value, implementation of aliphatic carboxylic acids indicate that no oxidation of the acid occurs as these can be prone to decarboxylation upon oxidation.[12] Scheme 3 shows that different carboxylic acids are converted smoothly into the corresponding chiral esters.

Chloroacetic acid and trifluoropropanoic acid afforded **4l** (64% yield, 87% ee) and **4m** (83% yield, 90% ee). Ethoxyacetic acid provided **4n** in moderate yield and enantioselectivity. Unactivated substrates, such as hydrocinnamic acid and acetic acid, gave **4o** and **4p** in moderate yields and 80% and 66% ee, respectively. In the coupling of acetic acid, AgOAc was used as

Scheme 3. Enantioselective Oxidative Coupling of Aliphatic Carboxylic Acids to 1a[a]

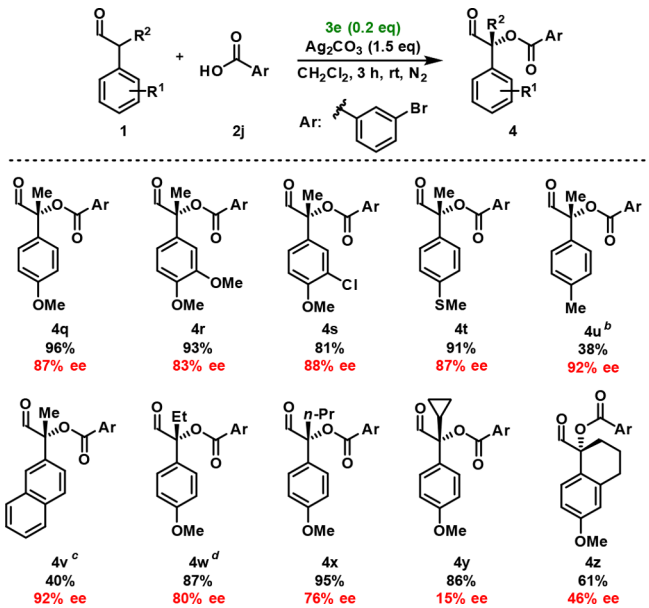


[a]Performed on 0.2 mmol scale with 1.0 equiv of **1a** and 3.0 equiv of **2**. ee determined by chiral stationary phase UPC^2. Absolute stereochemistry determined by analogy to **4k**. [b]5.0 equiv of acetic acid and **3c** as catalyst.

oxidant. To further investigate the origin of the incorporated acetic acid, we performed an experiment with CD_3CO_2D (1.5 equiv) in combination with nondeuterated AgOAc (3.0 equiv). The isolated product revealed a 69% integration of CD_3CO_2D and considering the 2:1 ratio between AgOAc and CD_3CO_2D, this indicates that CD_3CO_2D is preferentially incorporated compared to the acetate bound in AgOAc.

Scheme 4 shows the reaction of different α-branched aldehydes with 3-bromobenzoic acid **2j**. Aldehydes having a

Scheme 4. Enantioselective Oxidative Coupling of α-Branched Aldehydes 1 with 3-Bromobenzoic Acid 2j[a]



[a]Performed on 0.2 mmol scale with 1.0 equiv of **1** and 1.5 equiv of **2j**. ee determined by chiral stationary phase UPC^2. Absolute stereochemistry determined by analogy to **4k**. [b]5 equiv of **2j**. [c]3 equiv of **2j**. [d]Reaction time was 6 h.

methoxy-substituted phenyl provided **4q** (96% yield, 87% ee) and **4r** (93% yield, 83% ee). Similar results were obtained for a 3-chloro-substituted aldehyde **4s** (81% yield, 88% ee). A thioether functionality showed compatibility to the oxidative reaction conditions as **4t** was obtained in 91% yield and 87% ee. Aldehydes bearing electro-neutral aromatic substituents,

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such as 4-methyl and naphthyl, also afforded the products **4u** and **4v** in high enantioselectivities (both 92% ee), however in lower yields (38% and 40%, respectively). Subsequently, aldehydes with different aliphatic moieties in the α-position were tested. Aldehydes with α-ethyl and -*n*-propyl provided **4w** (87% yield, 80% ee) and **4x** (95% yield, 76% ee), whereas an α-cyclopropyl aldehyde gave **4y** in 86% yield and low enantioselectivity. Perhaps, the decrease in enantioselectivity for aldehydes having bulky α-substituents may be explained by the *E*/*Z*-configuration of the enamine. Finally, a cyclic aldehyde was applied in the reaction and afforded **4z** in 61% yield and 46% ee.

The absolute configuration of the acid-coupled adduct **4k** was determined to be *R* by X-ray analysis (Figure 2). On this basis, and computed intermediate structures (see SI), we propose that the tertiary amine may direct the oxidative coupling of enamine and carboxylic acid via N−H−O hydrogen bonding, which facilitates the *Re*-face attack providing the observed adduct.

Encouraged by the results for coupling of carboxylic acids to α-branched aldehydes using a primary amine catalyst, we set out to explore the possible extension of the reactivity to a more remote position of an α,β-unsaturated aldehyde. To our delight, subjecting α,β-unsaturated aldehydes and carboxylic acid **2j** to the standard reaction conditions yielded the γ-acid-coupling products in moderate yields and low enantioselectivities (see SI, page S14). It should be noticed that similar conditions, but with a secondary amine catalyst afforded the γ-homocoupling.[13] This result further highlights the importance of the primary amine catalyst and supports the hypothesis that homocoupling and acid-coupling proceeds via different reactive intermediates.

In summary, we have demonstrated that a chiral primary amine catalyst in combination with α-branched aldehydes and an oxidant generates an intermediate that reacts with carboxylic acids affording a nucleophilic α-coupling to the aldehydes. The methodology proceeds for aromatic and aliphatic carboxylic acids giving access to chiral *tert*-alkyl carboxylates in high yields and for most examples high enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b07394.

Experimental and computational details (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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