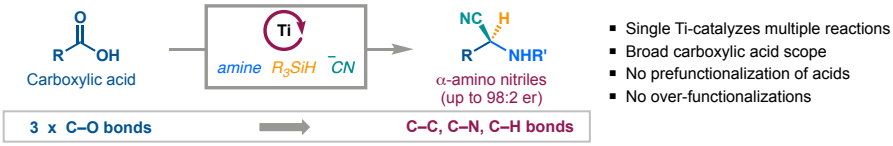
Enantioselective Deoxygenative Amino-Cyanation of Carboxylic Acids via Ti-Multicatalysis

Giovani Gutierrez, Jason A. Wilt, Samirah Muhammad, Emily Girotti, Diego Rodriguez, Byoungmoo Kim*

Department of Chemistry, Clemson University, Clemson, South Carolina 29634, United States.

KEYWORDS: carboxylic acids, enantioselective deoxygenative functionalization, multicatalysis, base metal



ABSTRACT: Carboxylic acids are valued synthetic building blocks that offer shelf-life stability, structural diversity, and wide commercial availability. Despite the remarkable synthetic utility of carboxylic acids, a direct enantioselective deoxygenative functionalization of carboxylic acids remains rare. We present enantioselective deoxygenative amino-cyanation of carboxylic acids using a novel Ti^{IV}-multicatalytic system that catalytically modified each C–O bond of carboxylic acid to C–C, C–N, and C–H bonds, generating enantio-enriched chiral α-amino nitriles (up to 98:2 er).

Carboxylic acids are structurally diverse, bench stable, relatively nontoxic, and abundant in bioactive compounds. Also, the wide commercial availability of carboxylic acid building blocks compared to other carbonyl compounds[1] has been recognized as an essential element for developing novel innovations (Figure 1A), allowing exploration of new chemical space continuously.[2–10] In addition to these advancements, deoxygenative functionalization of a carboxyl group wherein each C–O bond is converted to a new set of bonds to generate a stereocenter enantioselectively is an intriguing fundamental pursuit, yet it remains elusive (Figure 1A). Unlocking this paradigm would enable the rapid and modular buildup of molecular and stereochemical complexity of carboxylic acids.

The challenges of developing an enantioselective deoxygenative functionalization of carboxylic acids stem from their poor electrophilicity and the presence of an acidic proton. Consequently, the use of common organometallic nucleophiles leads to over-functionalized side-products and one sacrificial equivalent of the nucleophile is required due to its incompatibility with the acidic proton. Therefore, the lack of a method for direct deoxygenative functionalization necessitates multi-step synthesis, including redox-manipulations and prefunctionalization of carboxylic acids using harsh reagents or peptide coupling reagents,[11] which is inefficient and wasteful.[12] To our knowledge, there is one report that creates a stereocenter from carboxylic acids via a deoxygenative process, where Adolfsson and co-workers elegantly showcased Mo-catalyzed coupling of enolizable carboxylic acids and secondary amines to produce racemic amines.[13] Despite this breakthrough, a general and enantioselective variant of such a deoxygenative process is elusive.

Herein, we report enantioselective deoxygenative amino-cyanation of carboxylic acids as the first-generation reaction of this platform, where we catalytically modified each C–O bond of carboxylic acid to C–C, C–N, and C–H bonds (Figure 1B). Through the protocol herein, diverse carboxylic acid building blocks are converted directly to enantio-enriched valuable α-amino nitriles (up to 98:2 er), which are biologically active and synthetically versatile compounds shown to be elaborated into various derivatives, such as unnatural amino acids and diamines.[14] Although Strecker reaction is a well-known way to synthesize α-amino nitriles,[15] deoxygenative amino-cyanation of carboxylic acids offer employing widely available, structural diverse, and bench stable building blocks.

As a key design element, we hypothesized that deoxygenation of carboxylic acid towards an imine intermediate would allow employment of enantioselective functionalization to generate chiral amines modularly (Figure 1B). Given the multiple C–O bonds within a carboxyl group, we envisaged combining the hydrosilylation of carbonyls and multicatalysis to solve the unmet challenges in deoxygenative functionalization of carboxylic acids (Figure 1C). Transition metal-catalyzed hydrosilylation is an effective way to deoxygenate various carbonyls.[16–22] Also, multicatalysis has enabled the direct functionalization of unreactive functional groups and the elegant synthesis of complex molecules via multiple bond constructions while minimizing waste and cost.[23–25] We anticipated hydrosilanes would be a suitable mild reductant to i) facilitate

deoxygenation, ii) concomitant removal of the carboxylic proton via a metal-catalyzed dehydrogenative process, and iii) minimize any over-reduction. As outlined in Figure 1C, we envisioned a metal-catalyzed sequential deoxygenation of inert C–O bonds into more stable Si–O bonds will allow: 1) direct amidation of carboxylic acids, 2) chemoselective deoxygenation of the amide **II** to generate an imine intermediate **III**, and 3) the enantioselective functionalization to produce diverse enantio-enriched α-amino nitriles **IV**.

We devised to employ a sustainable metal catalyst and a

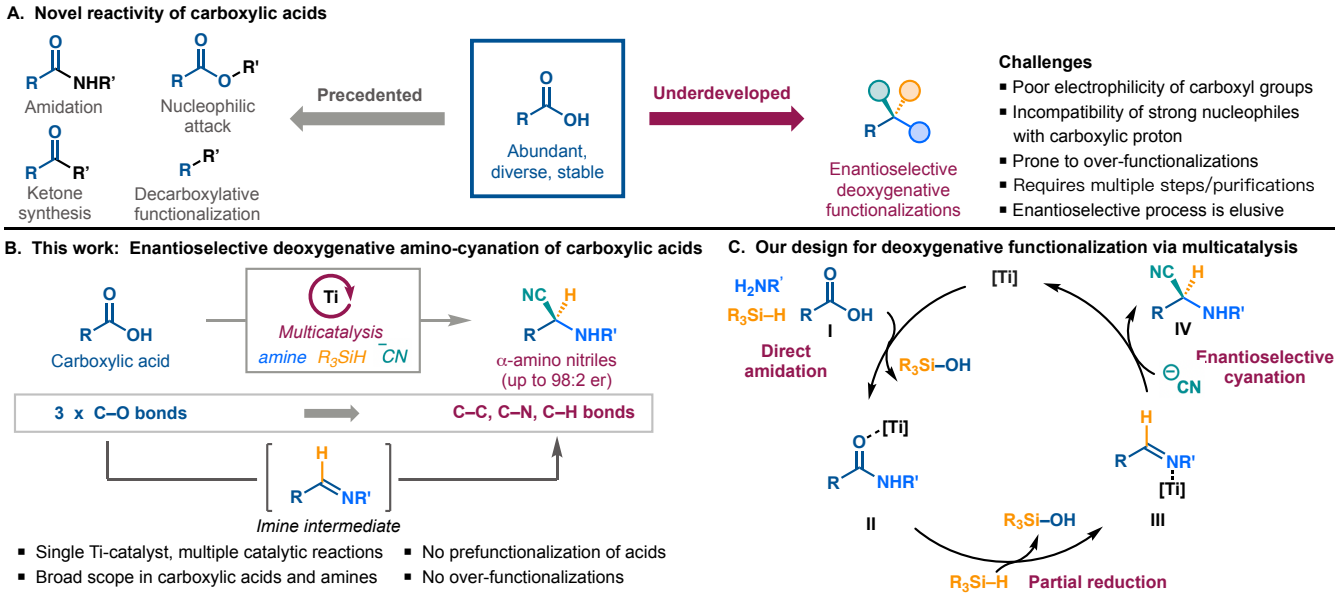
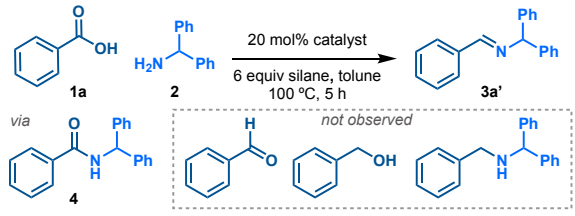


Figure 1. Various application of carboxylic acids and our reaction design in this work.

readily accessible chiral ligand. We were drawn to oxophilic Ti^{IV} species as they are catalytically versatile, earth abundant, and inexpensive metals that are known to house various chiral ligands for enantioselective catalysis, including carbonyl functionalizations[26,27] and enantioselective Strecker reactions.[28–33] Particularly, we were motivated by Buchwald's pioneering report on the partial reduction of enolizable tertiary amides to aldehydes using a stoichiometric amount of Ti^{IV} alkoxide.[34] Although this transformation was rendered catalytic in Ti^{IV}, it requires $(EtO)_3SiH$, which is toxic and generate a pyrophoric side-product, SiH_4.[35] This inspired us to develop a safer and general catalytic variant of the partial reduction that could be employed in our proposed deoxygenative functionalization of carboxylic acids. We focused on using benzoic acid **1a** and

Table 1. Optimization of the direct amidation-partial reduction of carboxylic acid 1a.[a]



Entry	Catalyst	Silane	3a' (%) [b]
1	**$Ti(OnBu)_4$**	**$Me(EtO)_2SiH$**	**>95**
2	-	$Me(EtO)_2SiH$	0
3	$Ti(OnBu)_4$	-	trace

[a]Amine **2** (0.20 mmol), carboxylic acid **1a** (0.22 mmol), $Ti(OnBu)_4$ (20 mol%), $Me(EtO)_2SiH$ (6.0 equiv), toluene (1.0 mL), 100 °C, 5 h. [b] Determined by ^1H NMR analysis.

benzhydryl amine **2** as model substrates to generate an imine product **3a'**. After an examination of various catalysts and hydrosilanes, we identified 20 mol% $Ti(OnBu)_4$ and excess $Me(EtO)_2SiH$ at 100 °C provided the desired imine **3a'** in >95% conversion (Table 1, entry 1 and see SI for further details). Also, amide **4** intermediate was observed, consistent with our proposed pathway (Figure 1C). This is supported by subjecting amide **4** under the Ti-catalysis to generate imine **3a'** in >95% conversion (see SI for details). It is noteworthy that we did not observe the anticipated reduced side-products, including benzyl amine or alcohol (Table 1), which is contrary to the well-established reductive N-alkylation of amines using carboxylic acids.[20] Control experiments revealed that excluding the Ti-catalyst or hydrosilane led to unreacted starting materials (entries 2-3). Our observation is consistent with the dehydrogenative silylation of carboxylic acid towards a silyl ester, followed by amidation to afford an amide intermediate.[36,37]

Then, we investigated if the Ti-catalyst could be recuperated *in situ* toward an enantioselective cyanation of the imine intermediate **3a'**. The wealth of literature on Ti-catalyzed Strecker Reactions[28,29,31,33,38] inspired us to implement chiral Schiff base[39] or amino-alcohols[29,40,41] and for their ease of modularity. *n*BuOH was used to capture TMS group of TMSCN. In our ligand optimization, amino-alcohol **L4a** was found to be the optimal ligand that afforded the α-amino nitrile **3a** in 64% isolated yield and 95:5 er (Figure 2 and see SI for details). Inspired by Chai's work, we employed water additive in the enantioselective cyanation, which is known to form an active oxo-bridged titanium species.[33,42–44] Attempts to add all the required components at the beginning of the reaction yielded a small amount of the desired product **3a** (see SI for details).

We surveyed a variety of carboxylic acids **1**, which gave the

corresponding α-amino-nitriles **3** in moderate to excellent isolated yields and high enantioselectivity (Figure 2, up to 90% isolated yield and 98:2 er). Substrates possessing various electron-donating and withdrawing substituents, including *p*-tert-butyl (**3b**, 76% isolated yield, 93:7 er), *p*-methoxy (**3c**, 68% isolated yield, 97:3 er), *p*-chloro (**3d**, 71% isolated yield, 95:5 er), *p*-bromo (**3e**, 79% isolated yield, 89:11 er), and *p*-dimethylamino group (**3f**, 90% isolated yield, 87:13 er) were well-

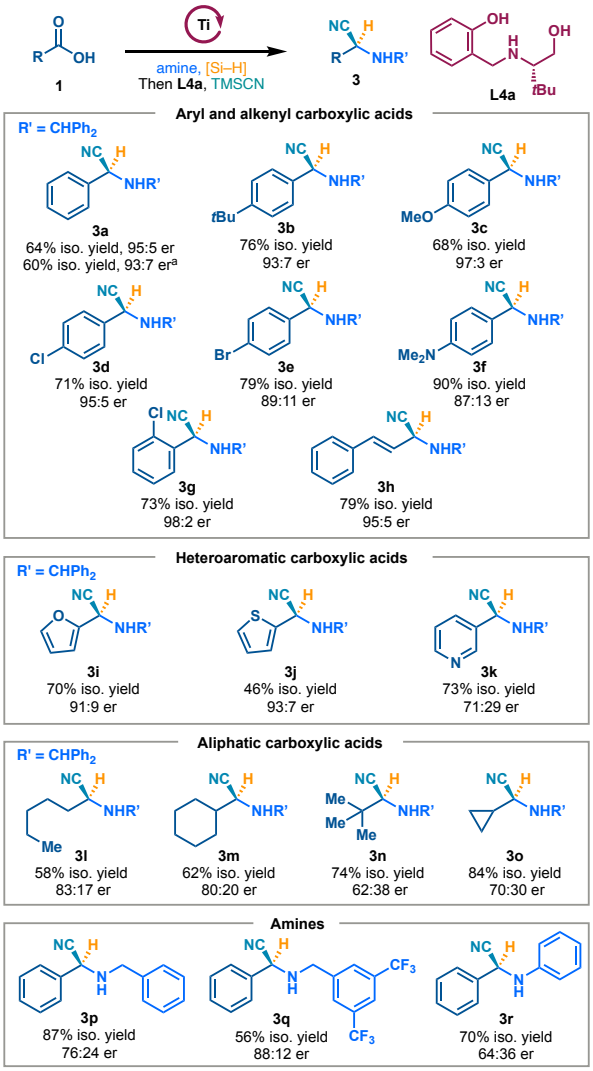
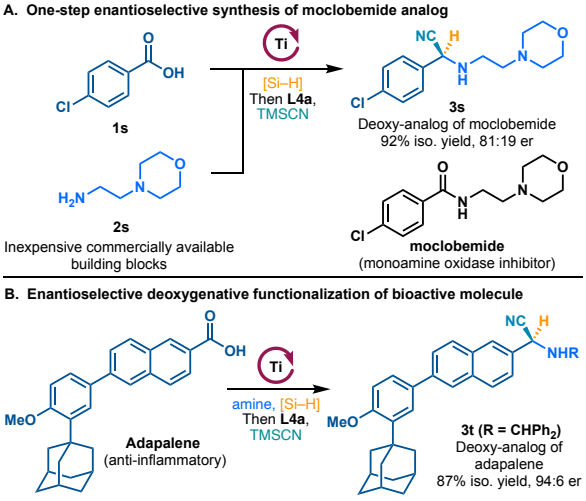


Figure 2. Substrate scope of enantioselective deoxygenative amino-cyanation. Reaction conditions: carboxylic acid (0.22 mmol), amine (0.20 mmol), Ti(O*n*Bu)$_4$ (20 mol%), Me(EtO)$_2$SiH (6.0 equiv), toluene (1.0 mL), 100 °C, 5 h. Then, ligand L4a (22 mol%), TMSCN (3.0 equiv), *n*BuOH (1.5 equiv), H$_2$O (20 mol%), toluene (0.40 mL) rt, 3-8 h. [a]1.1 mmol of 1a and 1.0 mmol of 2 was used. See SI for further details.

tolerated. Benzoic acid bearing an *ortho*-chloro-substituent was not impacted by the steric hindrance, resulting in 73% isolated yield and 98:2 er of the product **3g**. No dehalogenation was observed for all the halogen-bearing substrates. For trans-cinnamic acid substrate, the corresponding conjugated imine intermediate was formed quantitatively without reduction of α,β-unsaturation, followed with highly regio- and enantioselective cyanation to generate the α-amino-nitrile product **3h** in 79% yield and 95:5 er. Heterocyclic acids were well-tolerated to produce amino-nitriles (**3i, 3j**, and **3k**) with moderate to excellent enantioselectivity. Using 2-furonic acid and 2-thiophene carboxylic acids, products **3i** and **3j** were obtained in high enantioselectivities (70% isolated yield, 91:9 er and 46% isolated yield, 93:7 er, respectively). Nicotinic acid substrate gave a reduced level of enantioselectivity in product **3k** (71:29 er) in 73% isolated yield. Linear and cyclic aliphatic acids gave moderate enantioselectivity in product **3l** and **3m** (83:17 er and 80:20 er, respectively). To our surprise, the sterically hindered pivalic acid was converted to corresponding amino-nitrile **3n**, albeit with poor enantioselectivity of 62:38 er. Cyclopropyl carboxylic acid proceeded smoothly with modest enantioselectivity of 70:30 er in good yield (84%, see compound **3o**) and no ring-opened products were observed, suggesting no α-amino radical is formed. Then, we surveyed several amine coupling partners. Benzylamine and bis(3,5-trifluoromethyl)-benzylamine were well-tolerated to give their corresponding products **3p** and **3q** in 87% and 56% isolated yield, respectively, with moderate to good enantioselectivity (76:24 and 88:12 er, respectively). Less nucleophilic aniline was a suitable coupling partner that led to 70% isolated yield and 64:36 er of the product **3r**.

To demonstrate the utility of our protocol, we developed one-step, enantioselective synthesis of deoxy-analogs of pharmaceuticals (Scheme 1). The implementation of our Ti-multicatalysis using commercially available carboxylic acid **1s** and amine **2s** proceeded smoothly to generate a new deoxy-analog of moclobemide **3s** (a known monoamine oxidase inhibitor)[45] in 92% isolated yield and 81:19 er. It is notable that Lewis basic amine **2s** did not inhibit the reaction. In fact, the enantioselective cyanation of the corresponding imine intermediate proceeded faster than other substrates, suggesting that the morpholine moiety may be acting as a directing group for the Ti-center. Next, we investigated the derivatization of adapalene,

SCHEME 1. Synthesis of deoxy-analogs of pharmaceuticals.



For reaction conditions, see SI for details.

a naphthoic acid derivative with retinoid activity.[46] After a solvent optimization, the new deoxy-analog of adapalene **3t** was obtained in 87% yield and 94:6 er. This result highlights a distinct advantage of our method, allowing carboxylic acids as

starting materials. To employ the current Strecker method to prepare product **3t**, the carboxylic acid motif must be converted to its aldehyde analog via redox-manipulation then undergo condensation with an amine followed by cyanation, which is synthetically inefficient.

We propose the multicatalytic cycle outlined in Figure 3. Carboxylic acid **1** undergoes Ti-catalyzed dehydrogenative silylation to form silyl-ester **I** (see SI for detail), which sequentially undergoes Ti-catalyzed amidation to generate amide intermediate **II**. Then, the oxophilicity of the Ti-catalyst and the Lewis basicity of amide facilitate the chemoselective partial reduction to produce a silyl-hemiaminal **III**, which collapses to an imine species **IV**. Lastly, in the presence of the chiral ligand and water additive, an oxo-bridged chiral titanium complex is formed to catalyze the enantioselective cyanation via complex **V**, generating the α-amino-nitrile **3**. We observed a non-linear effect under our optimized condition, which is consistent with the formation of the oxo-bridged chiral titanium complex **V** (see SI for detail).[47] Alternative forms of complex **V** akin to Maruoka's work are also possible.[48]

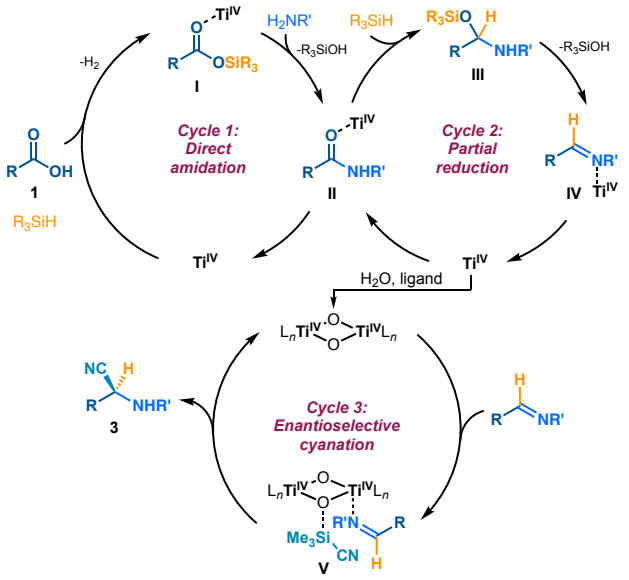


Figure 3. Proposed Ti-multicatalysis.

In conclusion, we have developed a multicatalytic enantioselective deoxy-functionalization of carboxylic acids that directly generate α-amino nitrile products. This reaction is facilitated by an inexpensive, widely accessible Ti^{IV} catalyst and a chiral amino-alcohol ligand that converts each C–O bond of carboxylic acid to C–C, C–N, and C–H bonds via three distinct catalytic transformations. We envision that this multicatalytic strategy will provide a direct approach toward diversifying carboxylic acids. Further mechanistic investigation and application of this platform is currently in progress.

ASSOCIATED CONTENT

Data Availability Statement: The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org. The supporting information includes Experimental procedures and NMR spectra data (PDF)

AUTHOR INFORMATION

Corresponding Author

*Email: byoungk@clemson.edu

Author Contributions

G.G.: Conceptualization, synthesis, compound characterization, writing, and revision. J.A.W., S.M., E.G., D.R. : Synthesis and compound characterization under the guidance of G.G. B.K.: Conceptualization, writing, and revision.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

B.K. gratefully acknowledge the financial support from Clemson University. B.K. thanks Prof. Daniel C. Whitehead (Clemson University) for mentorship. B.K. thanks Prof. Vincent Lindsay (North Carolina State University) and Prof. Daniel Kim (Temple University) for helpful discussions. B.K. and D.R. gratefully acknowledge the financial support from NSF, award CHE-2050042 (2021-2024). B.K. and S.M. gratefully acknowledge the financial support from NSF, award EES-2005030. The authors would like to acknowledge Dr. Rakesh Sachdeva (Clemson University) for helping us acquire HRMS and IR data.

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