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RESEARCH ARTICLE

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Catalytic Decarboxylative C–N Formation to Generate Alkyl, Alkenyl and Aryl Amines

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Abstract: Transition-metal catalyzed sp^2 carbon–nitrogen (C–N) formation is a reliable method with which to synthesize aryl amines. Catalytic sp^3 C–N formation reactions have been reported occasionally, and methods which can realize both sp^2 and sp^3 C–N formation are relatively unexplored. Here we address this challenge with a method of catalytic decarboxylative C–N formation which proceeds through a cascade carboxylic acid activation, acyl azide formation, Curtius rearrangement and nucleophilic addition reaction. The reaction uses naturally abundant organic carboxylic acids as carbon sources, readily prepared azidoformates as the nitrogen sources, and 4-dimethylaminopyridine (DMAP) and $Cu(OAc)_2$ as catalysts with as low as 0.1 mol% loading, providing protected alkyl, alkenyl and aryl amines in high yields with gaseous N_2 and CO_2 as the only byproducts. Examples are demonstrated of late-stage functionalization of natural products and drug molecules, stereospecific synthesis of useful α-chiral alkyl amines, and rapid construction of different ureas and primary amines.

Introduction

Construction of the C–N bond is important in organic chemistry because it produces nitrogen-containing motifs which are common in natural products, organic materials, agrochemicals and pharmaceuticals.[1] Significant progress has been made since 1990 in the area of transition-metal catalytic C–N coupling reactions, and reactions such as the Ullmann coupling,[2] the Buchwald–Hartwig amination,[3] and the Chan–Lam amination[4] have been reported. These methods are generally limited to the creation of sp^2 C–N bonds, and sp^3 C–N formation has been developed by several groups[5] as a complementary reaction. The construction of sp^3 C–N bonds relies mainly on traditional reactions such as nitrogen nucleophilic substitution of alkyl electrophiles,[6] Mitsunobu reaction of alcohols,[7] reductive amination of carbonyl compounds[8] and hydroamination of olefins[9] which are not suitable for the construction of sp^2 C–N bonds. Catalytic sp^3 C–N formation reactions are urgently needed in synthetic chemistry, but have not been extensively explored and the development of methods for both sp^2 and sp^3 C–N formation is more challenging.[10]

Organic carboxylic acids are stable to air or moisture, generally non-toxic, and easily prepared. They serve as perfect carbon sources in catalytic decarboxylative cross-coupling reactions,[11] in which most reactions form C–C bonds and there are only a few examples of the formation of C–N bonds.[12] Chan-Evans-Lam reactions feature decarboxylative sp^2 C–N formation of aryl carboxylic acids with amines under oxidative conditions (Figure 1A).[13] The substrate scope in such reactions is limited to electron deficient benzoic acids and the reactions are generally performed at elevated temperatures with 10-20 mol% catalyst loading. Catalytic sp^3 C–N formation reactions have been reported occasionally[14] and a breakthrough was recently reported involving metallaphotoredox catalysis[15] (Figure 1B). Fu et al.[16] developed a photoinduced, copper-catalyzed decarboxylative sp^3 C–N formation of alkyl redox-active esters,[17] and Hu et al.[18] achieved coupling of alkyl redox-active esters and anilines by a tandem photoredox reaction with a copper catalyst. MacMillan et al.[19] achieved a copper-involved metallaphotoredox catalytic sp^3 C–N coupling of iodonium carboxylates and nitrogen nucleophiles. We questioned whether the decarboxylative C–N formation can be achieved with electrophilic nitrogen sources and carboxylic acids rather than with these electrophilic carboxylic acid derivatives and nitrogen nucleophiles.[16-20] With their facile preparation and compatibility with various functional groups,[21] organic azides have been widely used in amination reactions as electrophilic nitrogen atom-transfer reagents.[22] Continuing our work on amination using organic azides as amino sources,[23] we herein explored a catalytic C–N formation reaction between organic carboxylic acids and organic azides (Figure 1C). By taking advantages of the neutral reaction conditions and the clean reaction with N_2 and CO_2 as only byproducts, we hoped to develop a broadly useful reaction that would be able to efficiently construct both sp^2 and sp^3 C–N bonds.

Inspired by the Curtius[24] and the Steglich rearrangement reactions,[25] we envisioned that the electron deficient carbonyl skeleton in azidoformates would be attacked by *N*,*N*-dimethylaminopyridine (DMAP) (Figure 1D), generating an azido anion and an intermediate **I** which reacts with a carboxylic acid, leading to a mixed anhydride complex **III** which is subject to nucleophilic attack by the azido anion and converted to an acyl azide **IV**. This follows a previously unexploited pathway of catalytic acid activation and azido transfer, in which diphenylphosphoryl azide (DPPA) cooperating with a stoichiometric amount of base are known to facilitate such chemical transformations.[26] Curtius rearrangement of the acyl azide **IV** may occur to generate an isocyanate intermediate **V** which is attacked by carbonate anion *via* a cyclic transient state.[27] With loss of CO_2, an intermediate **VI** is generated and protonation of **VI** forms the coupling product, releasing the copper and DMAP catalysts.

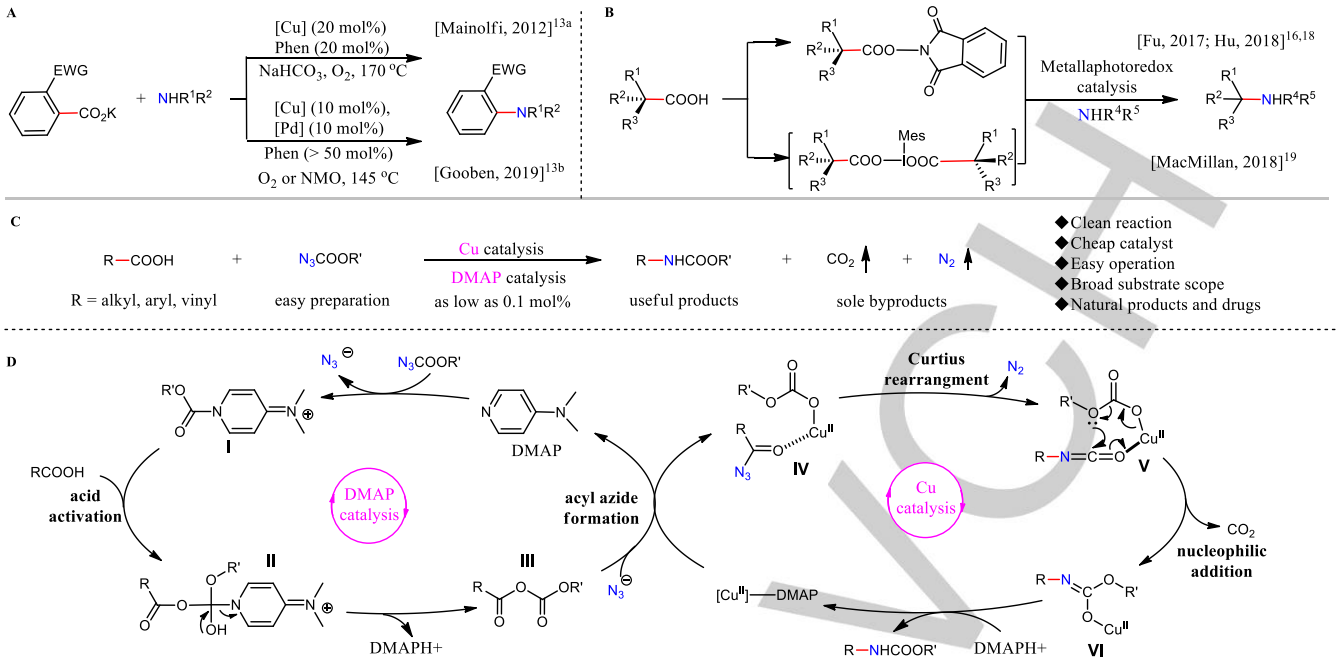
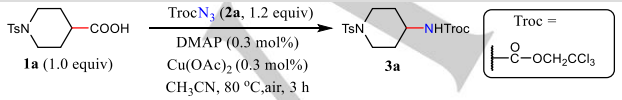


Figure 1. Development of catalytic decarboxylative C–N formation

Results and Discussion

The reactions of 1-tosylpiperidine-4-carboxylic acid (**1a**) with azidoformates were examined, and we found that DMAP in conjunction with $Cu(OAc)_2$ exhibits remarkable catalytic activity for the reaction of **1a** with $TrocN_3$ (**2a**)[28] (Table 1, for the details see Table S1 in SI). Using 0.3 mol% of $Cu(OAc)_2$ and 0.3 mol% of DMAP as catalysts, the reaction yield of the coupling product **3a** reached 99% after 3 h (entry 1). With a 30 min reaction time, **3a** was produced in 89% yield (entry 2). There is no reaction without DMAP or with organic bases such as pyridine replacing the DMAP (entries 3-4), and a diminished yield was obtained in the absence of $Cu(OAc)_2$ (entry 5). DMSO is also a solvent that can be used in this catalytic system (entry 6), and the solvent power of DMSO further extends the applicability of the reaction. If the catalyst loading is increased, the reaction is complete within 10 min (entry 7).

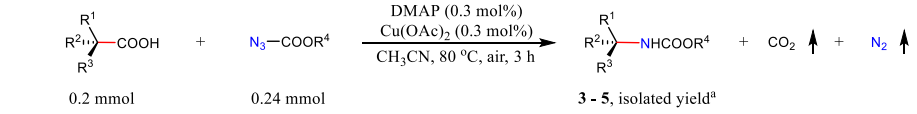
Table 1. Summary of the effects of reaction parameters.



Entry	Variation[a]	Yield[b]
1	--	99%
2	30 min	89%
3	no DMAP	0
4	pyridine instead of DMAP	0
5	No $Cu(OAc)_2$, 30 min	37%
6	DMSO instead of CH_3CN	88%
7	$Cu(OAc)_2$ (5 mol%), DMAP (10 mol%), 10 min	99%

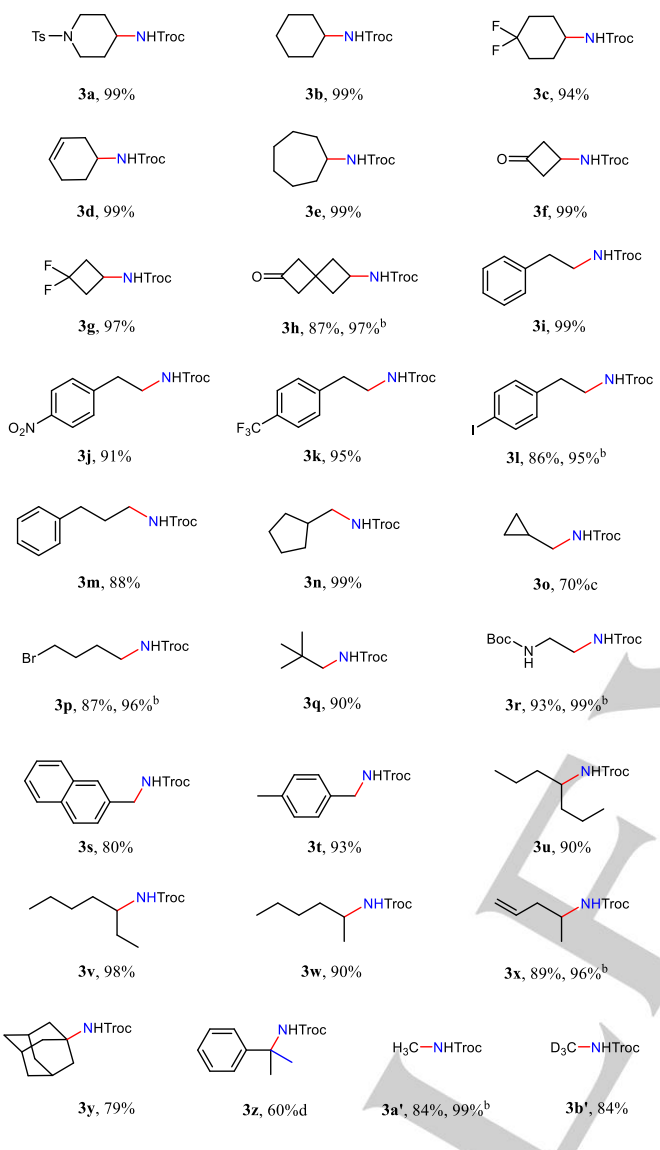
[a] 0.1 mmol of **1a**. [b] Yield determined by crude NMR with CH_2Br_2 as standard.

With the optimal reaction conditions in hand, we explored the scope of this reaction (Table 2). First, we tested the generality of this C–N formation reaction by exploring the scope of alkyl carboxylic acids. Heterocyclic (**3a**), cyclic (**3b**-**3g**), and spiro-cyclic (**3h**) carboxylic acids are all feasible substrates, producing amines containing 6-, 7- and 4-membered rings in 94-99% yields. For linear and branched alkyl carboxylic acids, excellent yields of primary (**3i**-**3t**) and secondary (**3u**-**3x**) alkyl amines are obtained. Tertiary alkyl carboxylic acids, which because of steric hindrance are less reactive than primary and secondary alkyl carboxylic acids, give good yields of the desired *α,α,α*-trisubstituted alkyl amines **3y** and **3z**. Various functional groups such as substituted phenyl (**3j**-**3l**), alkenyl (**3x**), bromo (**3p**), fluoro (**3c**, **3g**), carbonyl (**3f** and **3h**) and amido (**3r**) are tolerated. Compared with common methylating reagents such as the electrophilic MeI and its equivalents or nucleophilic methylmetal compounds, acetic acid is the most stable and cheapest methylating reagent. We therefore, examined the reaction of acetic acid with $TrocN_3$. This reaction proceeded smoothly, and the yield of *N*-methyl carbamate **3a'** was 84%. Commercially available tetradeuteroacetic acid could be used as a convenient trideuteromethylating reagent to form *N*-trideuteromethyl carbamate **3b'**. This is quite interesting since that the *N*-methyl group is common in natural products and drug molecules.[29] Then, we tested the nitrogen coupling partner azidoformates. Aryl azidoformates serve as suitable amine sources and can couple with **1a** to generate the desired products **4a** and **4b** in high yields. Alkyl azidoformates can also be used, and those bearing an electron-withdrawing group (**3a**) serve as a better coupling partner than those with electron-donating groups (**4c** and **4d**). The azidoformate containing a sterically demanding group (**4e**) could also be used. The decarboxylative amination of cyclohex-3-ene-1-carboxylic acid or acetic acid with phenyl or benzyl azidoformate was studied and the amination products **4f**-

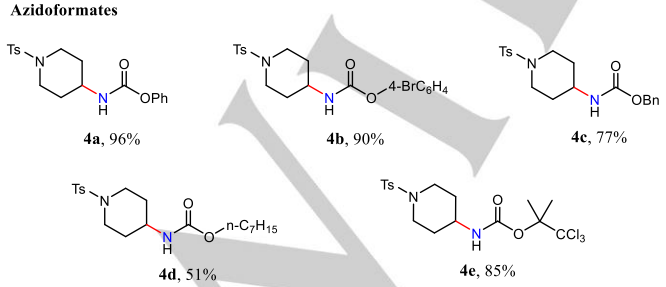


- 1°, 2° and 3° alkyl acids (36 examples)
- Natural products and drugs (15 examples)
- CO_2 and N_2 as sole byproducts
- Neutral and non-additive conditions
- 51 examples, average yield: 89%

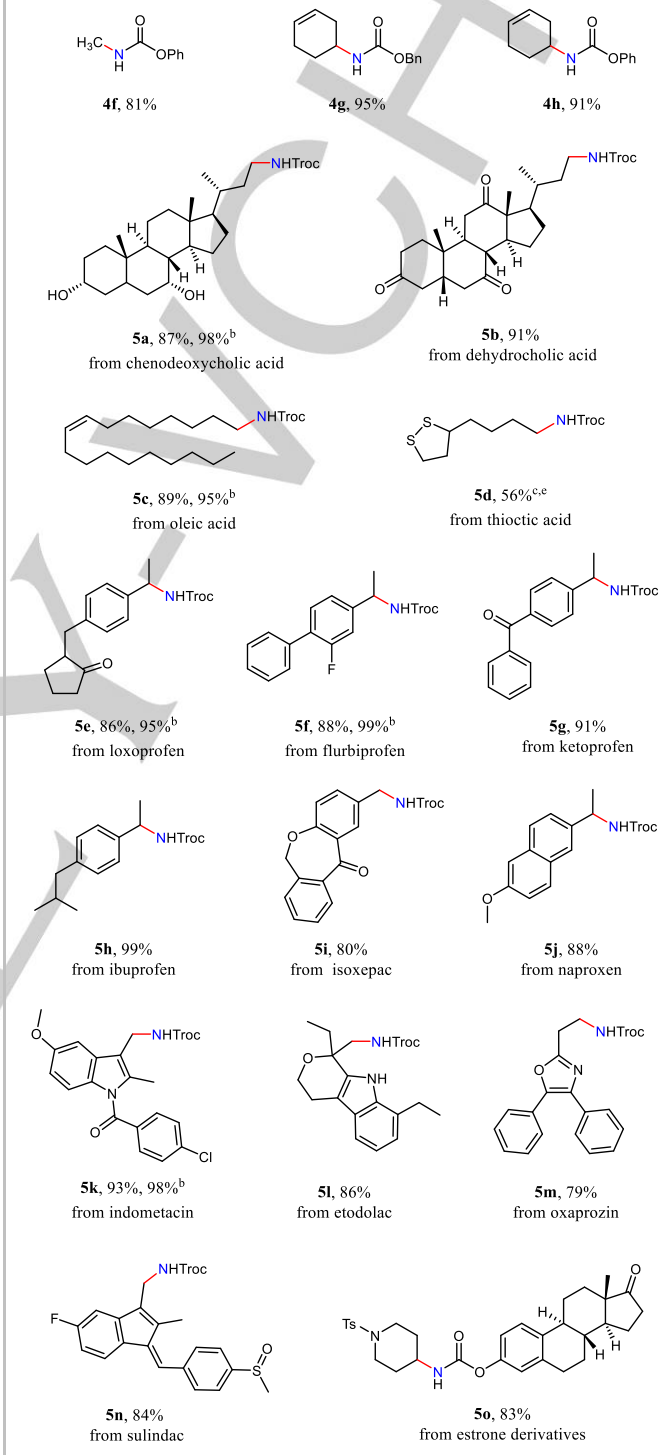
Alkyl carboxylic acids



Azidoformates

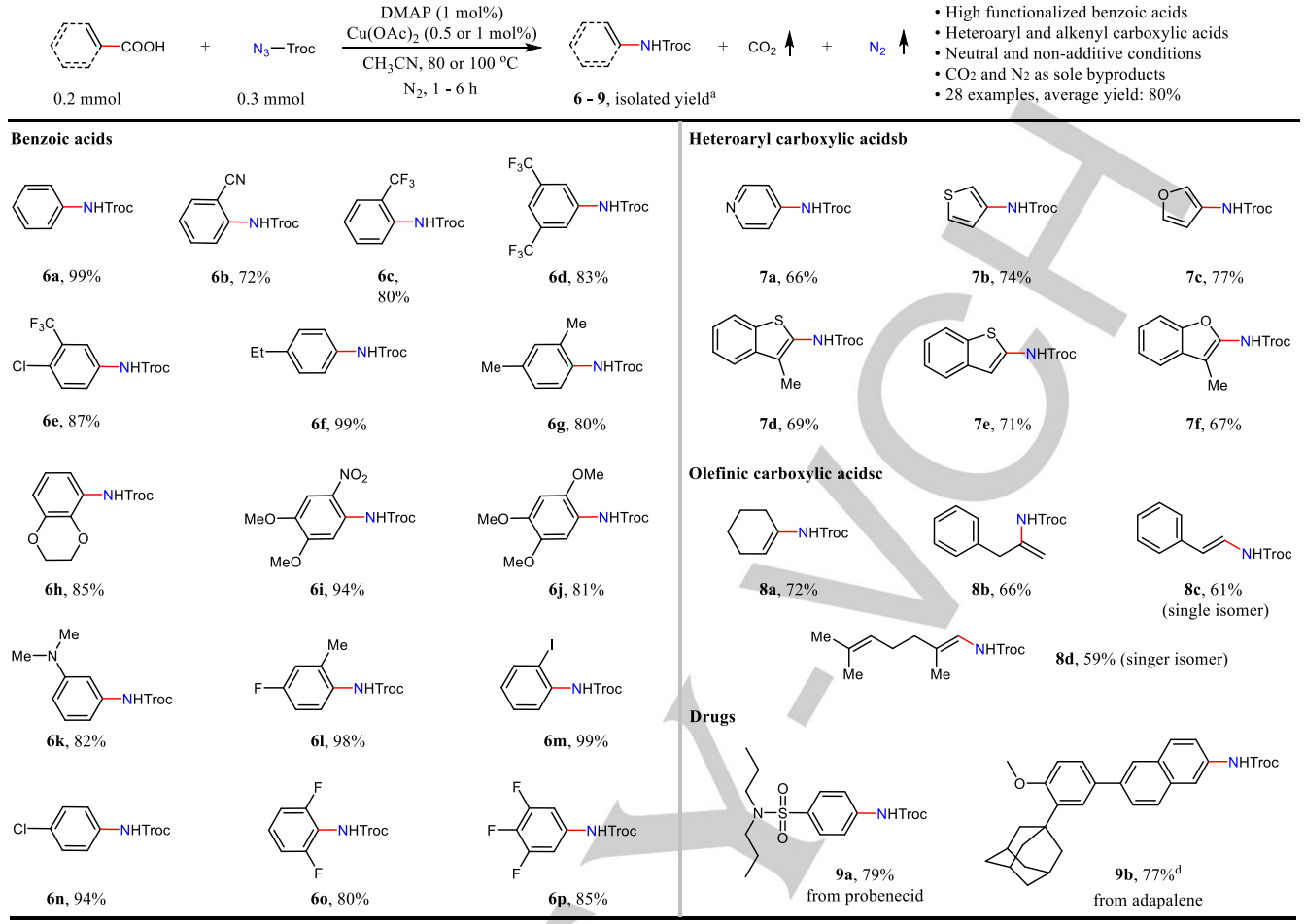


Nature products and drug molecules



[a] General conditions: Carboxylic acid (0.20 mmol), azidoformate (0.24 mmol), CH_3CN (4 mL), DMAP (0.3 mol%), $Cu(OAc)_2$ (0.3 mol%), 80 °C, air, 3 h. [b] DMAP (10 mol%), $Cu(OAc)_2$ (5 mol%), 80 °C, air, 10-25 min, see Supplementary Information for details. [c] DMAP (1 mol%), $Cu(OAc)_2$ (1 mol%), 0.5 h. [d] DMAP (0.5 mol%), $Cu(OAc)_2$ (0.5 mol%), N_2, 15 h. [e] DMSO/CH_3CN (1/1), N_2.

Scheme 1. Scope of alkyl carboxylic acids and azidoformates.

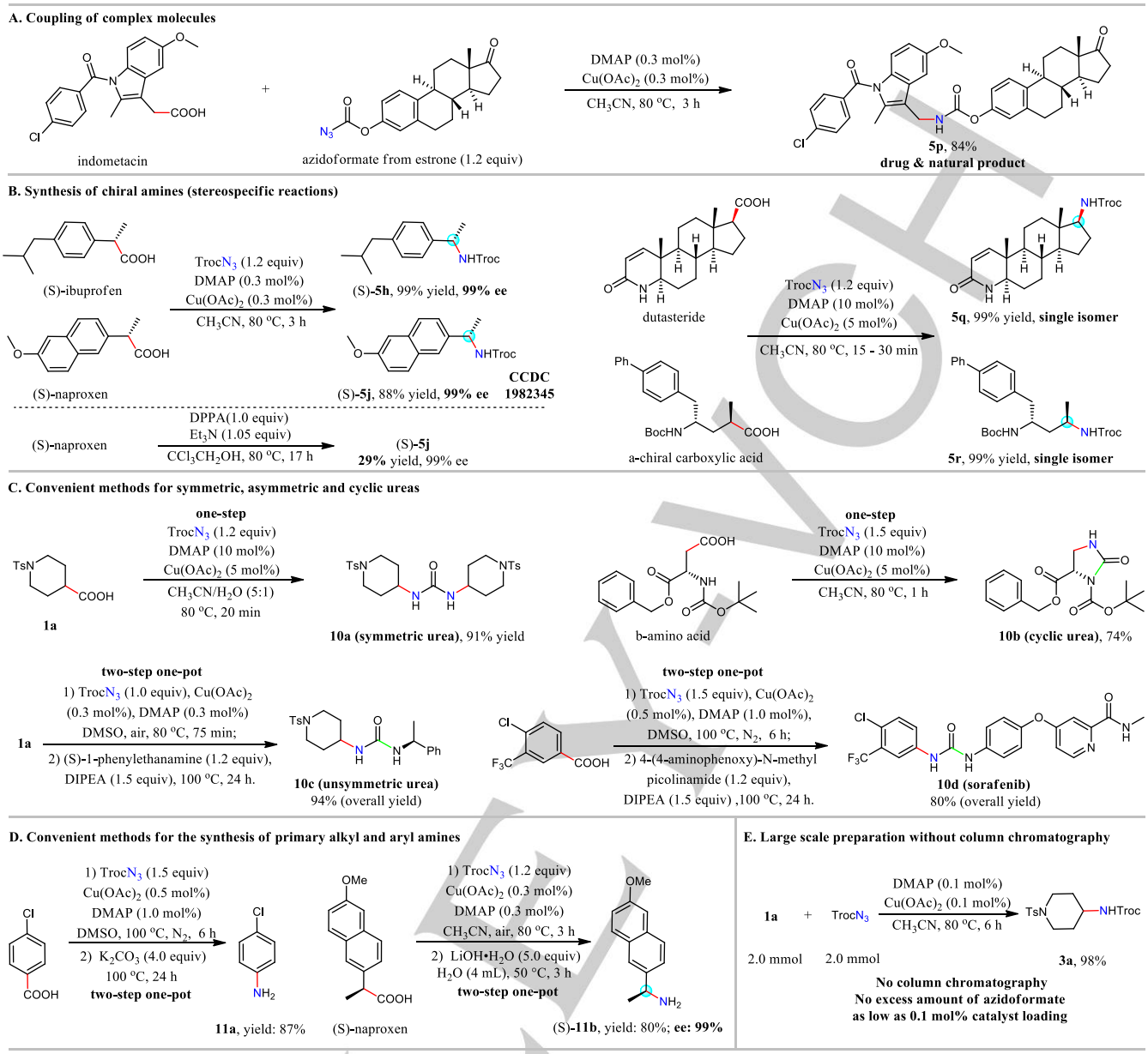


[a] General conditions: Carboxylic acid (0.20 mmol), $TrocN_3$ (0.3 mmol), CH_3CN (4 mL) , DMAP (1 mol%), $Cu(OAc)_2$ (0.5 mol%) , 100 °C, N_2, 6 h. [b] $Cu(OAc)_2$ (1 mol%), 3 h. [c] $Cu(OAc)_2$ (1 mol%), 80 °C, 1 h. [d] DMSO instead of CH_3CN.

Scheme 2. Scope of aryl and alkenyl carboxylic acids.

4h were isolated in good yields. Such experiments demonstrate the universality and efficacy of this catalytic system and it was thought to have great potential in late stage functionalization. Natural products containing hydroxyl, carbonyl and *cis*-olefin groups went through the decarboxylative amination process without need for protection. With chenodeoxycholic acid (**5a**), dehydrocholic acid (**5b**) or oleic acid (**5c**) for example, excellent yields were achieved. Although thioctic acid has poor solubility and a very vulnerable disulfide functional group, the desired amination product **5d** was still produced when the reaction was carried out in the mixture solvent of DMSO and CH_3CN. Several drug molecules were then tested. Nonsteroidal anti-inflammatory drugs such as loxoprofen (**5e**), flurbiprofen (**5f**), ketoprofen (**5g**), ibuprofen (**5h**), isoxepac (**5i**) and naproxen (**5j**) served as perfect substrates, provided the corresponding amine derivatives in 80-99% yields. Drugs containing heteroaryl ring, such as indole (**5k** and **5l**) or oxazole (**5m**) reacted well. In spite of steric hindrance, the anti-inflammatory drug etodolac was converted to the amination product **5l** with a satisfactory yield. Allylic carboxylic acid such as the drug sulindac, which contains an oxidation-sensitive sulfinyl group and a conjugated olefinic structure is a suitable substrate, providing the allyl amine derivative **5n** in high yield. An aryl azidoformate derived from estrone is an acceptable substrate, producing 83% yield of the desired product **5o**. When increasing catalyst loading to 5 mol% of $Cu(OAc)_2$ and 10 mol% DMAP (note b), the reactions were complete within 25 min and the yield of the desired product (**3h**, **3l**, **3p**, **3r**, **3x**, **3a'**, **5a**, **5c**, **5e**, **5f** and **5k**) was at least 95%.

The reaction conditions for the synthesis of aryl amines are optimized as shown in Table S2 in SI. The reactions of aryl carboxylic acids are generally less efficient than that of alkyl carboxylic acids, but when the catalyst loading was increased to 0.5 or 1 mol% of $Cu(OAc)_2$ and 1 mol% of DMAP, satisfactory yields were obtained (Table 3). Aryl carboxylic acids containing electron-withdrawing and electron-donating groups in the phenyl ring produced the desired aryl amine derivatives **6a**-**6p** in good to excellent yields. Functional groups, such as cyano (**6b**), trifluoromethyl (**6c**-**6e**), nitro (**6i**), methoxyl (**6j**), and amino (**6k**) in phenyl rings were tolerated. The aryl carboxylic acids with halogen in various positions on the aryl ring were used, and could provide further transformations of amination products **6l**-**6p**. The reaction efficiency is independent of *para*- and *meta*-substitution in the phenyl ring, and the sterically hindered *ortho*-substituted aromatic carboxylic acids provide the desired products in good yields (**6b**, **6c**, **6g**, **6i**, **6j**, **6l** and **6m**). Carboxylic acids containing heteroaromatic rings such as pyridine (**7a**), thiophene (**7b**), furan (**7c**), benzothiophene (**7d** and **7e**) and benzofuran (**7f**) are well tolerated in this catalytic



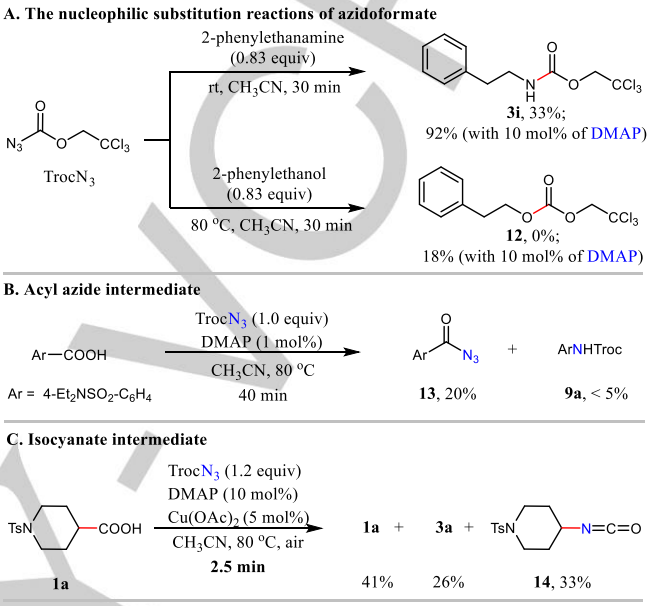
Scheme 3. Synthetic applications.

system, and provide the corresponding protected heteroaryl amines in good yields. In addition to aryl and heteroaryl carboxylic acids, alkenyl carboxylic acids are suited to the catalytic system. For example, cyclic (**8a**), terminal (**8b**), conjugated (**8c**) and trisubstituted (**8d**) olefinic carboxylic acids have been tested and the desired alkenyl amines were obtained in good yields. Only a single isomer of the alkenyl amine (**8c** and **8d**) was isolated from the reactions of *trans* α,β-unsaturated carboxylic acid. These reactions generated some observable side products, possibly due to the instability of the alkenyl amines. The drug probenecid containing a benzoic acid unit is a good substrate, providing the corresponding amination product (**9a**) in 79% yield. The drug adapalene is poorly soluble in CH_3CN, but a satisfactory yield of the amino derivative (**9b**) was achieved when the reaction was performed in DMSO.

Finally, we studied the synthetic applications of the reaction (Scheme 3). As an important chemically stable structure able to permeate cell membranes, the carbamate is widely used in medicinal chemistry as a substitute for peptide linkage.[30] As shown above, this reaction is one of the most efficient and general strategies with which to build carbamates. To further demonstrate the synthetic applications, we applied this method to the coupling of two complex molecules using a carbamate group as the linkage. The coupling of indomethacin with the azidoformate derived from estrone, produced a product **5p** which contained both the natural product and drug moieties (Scheme 3A), suggesting that this method may have potential in medicinal chemistry and new drug discovery. Experiments were performed to evaluate the potential stereospecificity of the catalytic decarboxylative C–N formation (Scheme 3B). To this end, the enantiomerically pure drugs (S)-ibuprofen and (S)-naproxen were used in the reaction, and the desired amination products (S)-**5h** and (S)-**5j** respectively were obtained in high yields and 99% ee. The absolute configuration of (S)-**5j** was

confirmed by X-ray crystallographic analysis (CCDC 1982345). For comparison with DPPA involved Curtius rearrangement, the reaction of (S)-naproxen with DPPA was performed following the reported procedure.[31] As shown in Scheme 3B, only 29% yield of desired product (S)-**5j** was produced while the reaction requires base to neutralize phosphoric acid and uses 2,2,2-trichloroethanol as the solvent. The natural product dutasteride with a chiral cyclic carboxylic acid unit was subjected to the reaction, and the resulting chiral cyclic amine **5q** was obtained quantitatively as a single diastereoisomer. From the reaction of the α-chiral carboxylic acid, an α-chiral amine **5r** was also achieved in 99% yield as a single isomer. These results indicated a full chirality transfer during the catalysis. The urea functionality is present in numerous bioactive compounds, including clinically approved drugs such as sorafenib, lisuride, cariprazine and ritonavir,[32] and we developed several convenient pathways for the synthesis of different ureas (Scheme 3C). When the reaction was performed in aqueous solvent, the symmetrical urea **10a** was generated in 91% yield. From the reaction of a *β*-amino acid, the 5-membered cyclic urea **10b** was prepared in one step through decarboxylation amination followed by intramolecular nitrogen nucleophilic substitution reaction. Two-step one-pot reactions have been developed for the synthesis of unsymmetrical ureas. For example, the catalytic reaction of **1a** with $TrocN_3$ was performed in DMSO, and upon addition of (S)-1-phenyl-ethanamine to conduct the secondary substitution reaction, the unsymmetrical dialkyl urea **10c** was isolated in 94% overall yield. Following a similar two-step one-pot synthetic procedure, a diaryl urea, drug sorafenib **10d** was prepared in 84% overall yield from commercially available 4-chloro-3-(trifluoromethyl)benzoic acid and 4-(4-aminophenoxy)-*N*-methylpicolinamide, further demonstrating the synthetic applications of the reaction. Compounds such as aniline **11a** and chiral alkyl amine **11b** with important primary amine fragments were also achieved with high yields by new developed one-pot processes (Scheme 3D). When gram scale preparations are conducted, the load of catalyst can be further reduced to 0.1 mol% of $Cu(OAc)_2$ and 0.1 mol% of DMAP and one equivalent of the coupling partner $TrocN_3$ can be used (Figure 2e). By being washed with dilute hydrochloric acid to remove trace amount of catalysts, the reaction could produce **3a** in 98% yield, demonstrating the practicality of this method. All carboxylic acids cited in this paper are stable and commercially available. In contrast, common carbon sources such as alkyl halides (tosylates) and organometallic reagents are less frequently available, and some are unstable. Use of carboxylic acids as carbon sources can be extremely efficient and convenient.

Several experiments were conducted to gain a better understanding of the reaction mechanism (Scheme 4). The reactions of **1a** with 2-phenylethanamine or 2-phenylethanol have been conducted (Scheme 4A), and the nucleophilic substitution products **3i** and **12** were isolated in 93% and 18% respectively under DMAP catalysis, while in absence of DMAP, **3i** was produced in only 33% yield and **12** was not produced. These results revealed that DMAP catalyzed the nucleophilic substitution reactions of azidoformate and the azido group acted as a leaving group. When the reaction of aromatic carboxylic acid was performed at lower temperature and in the absence of $Cu(OAc)_2$ (see the details in SI), acyl azide **13** was produced and coupling product **9a** was almost not observed (Scheme 4B). With 5 mol% of $Cu(OAc)_2$ and 10 mol% of DMAP catalyst loading and the reaction time shortened to 2.5 minutes (Scheme 4C), the isocyanate intermediate **14** can be observed in 33% NMR yield. These results indicate that the reaction may proceed through a cascade carboxylic acid activation, acyl azide formation, Curtius rearrangement and nucleophilic addition reaction.



Scheme 4. Mechanism study

Conclusion

In summary, we have developed a general method to achieve the catalytic decarboxylative C–N formation. This protocol tolerates many functional groups and works well with a wide range of organic carboxylic acids including alkyl, alkenyl and aryl carboxylic acids, efficiently providing various useful carbamates. The reaction is stereospecific and leads to the preparation of α-chiral amines from α-chiral carboxylic acids. The additional advantages of this reaction include its utility for natural products and drug molecules, simple operation under redox neutral reaction conditions, lack of additives, cheap and commercial catalysts with low catalyst loading, gaseous N_2 and CO_2 being the only byproducts, and high efficiency with a 87% average yield for all 84 examples. Processes for rapid construction of different ureas and primary amines have also been developed. This is an atom and step economic route for the synthesis of versatile amine derivatives, which has great potential in chemical industry, pharmaceutical chemistry and natural product synthesis.

Acknowledgements

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Keywords: decarboxylative • C–N formation • Curtius rearrangement • azidoformate • amine

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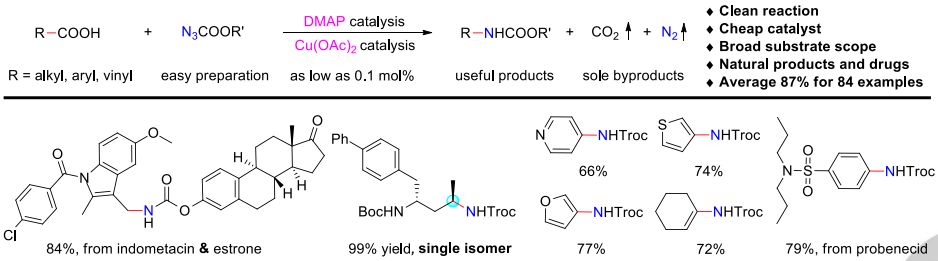

A decarboxylative C–N formation of organic carboxylic acid and azidoformate was achieved with 4-dimethylaminopyridine (DMAP) and $Cu(OAc)_2$ as catalysts, providing various protected amines with gaseous N_2 and CO_2 as the only byproducts.