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Repurposing amine and carboxylic acid building blocks with an automatable esterification reaction†

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New methodologies to unite amines and carboxylic acids that complement the popular amide coupling can significantly expand accessible chemical space if they yield products distinct from the classic R–NHC(O)–R′ amide arrangement. Here we have developed an amine–acid esterification reaction based on pyridinium salt activation of amine C–N bonds to create products of type R–OC(O)–R′ upon reaction with alkyl and aryl carboxylic acids. The protocol is robust and facile as demonstrated by automation on open-source robotics.

The exploration of chemical space is fuelled by diverse building blocks.[1–3] Traditionally, these building blocks are coupled together through known, robust reactions to generate combinatorial libraries.[4] We hypothesize that the accessible chemical space of a building block collection can be expanded by repurposing them using unconventional reactions that forge moieties not traditionally associated with the functional groups involved. We have been exploring the repurposing of amine and carboxylic acid building blocks using new amine–acid transformations that complement the popular amide coupling.[5] A variety of amine activation strategies currently exist to enable use of C–N bonds[6–9] as a handle for synthesis. While significant progress has recently been made in the field of C–N to C–C bond conversion, comparatively little work has been reported in C–N to C–O bond conversion, leading us to consider utilizing amines as substrates for esterification reactions with acids (Fig. 1A). Esters are among the most prevalent functional groups in natural products, pharmaceuticals, plastics, fragrances, and agrochemicals (Fig. 1B). In medicine, the ester functionality is widely used in prodrug strategies and as a metabolically stable functionality with unique properties. For instance, esters typically exhibit improved membrane permeability over analogous amides.[10] While the venerable coupling of alcohols and acids *via* the Fischer esterification provides a simple access to esters,[11] there are many instances where alcohol building blocks are unavailable, or where regiochemical esterification is challenged by the presence of other unprotected alcohol functionalities on the substrate. In contrast, a wide diversity of amines is available from natural and synthetic sources, so an amine–acid esterification would be a valuable complement to the classic alcohol–acid esterification. We have recently developed a protocol for esterification from arylamine-derived diazonium salts and carboxylic acids.[12] Here we report a complementary esterification from alkylamine-derived pyridinium salts.

Alkyl pyridinium salts have seen recent development for C–C bond formation,[6,13–18] but considerably less for carbon–heteroatom bond formation.[19–22] Available methods for carbon–heteroatom bond formation typically use specialized substrates or extreme reaction conditions, such as heating above 175 °C with molten Katritzky salt as the reaction medium. As part of our effort in identifying new C–O bond formation tactics, we sought to discover reaction conditions for C–N to C–O bond conversion using Katritzky salts, targeting conditions mild enough to enable automation, and with broad substrate scope for effective amine–acid building block repurposing in medicinal chemistry (Fig. 1C).

We began our investigation by coupling **8** with **9** to form **10** (Fig. 2) and identified malonate **11** as a capable promoter at 20 mol% loading. We used the potassium salt of **9**, producing **10** in 73% NMR yield (entry 1), and subsequently found that free acid substrates could be used with one equivalent of potassium *tert*-butoxide for *in situ* deprotonation (entry 2). Use of triethylamine as a base led to lower yields (entry 3), however diisopropylethylamine (DIPEA) was a viable base (entry 6). Only trace product was observed in the absence of **11** (entry 4). Further studies revealed that when dioxane was used as the solvent, potassium iodide was an excellent promoter of the reaction (entry 5 and 6) and greatly simplified product isolation since most reaction by-products could be removed with an aqueous workup. Based on these studies, we moved

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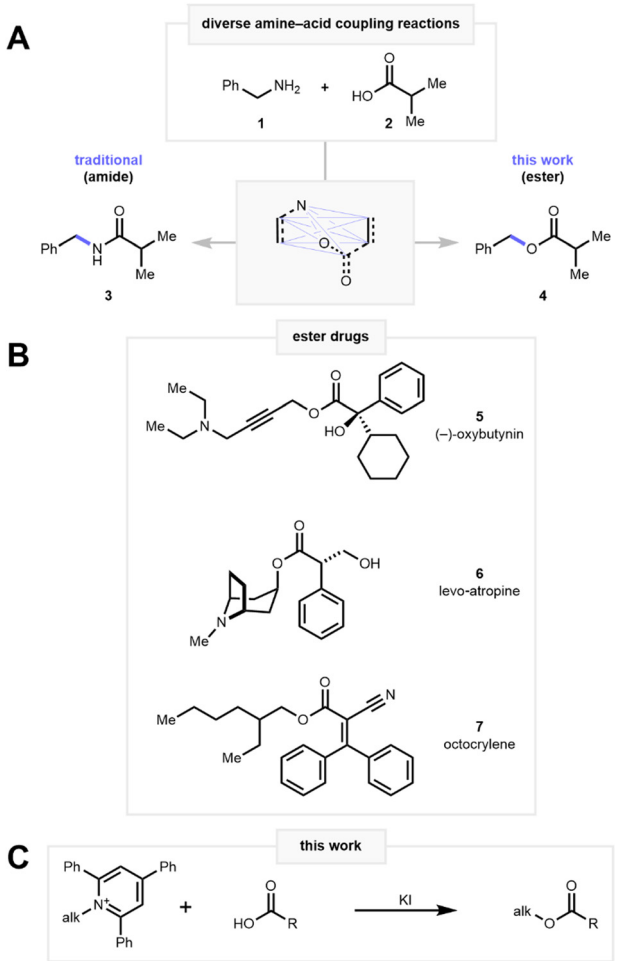
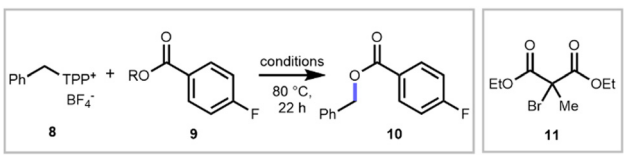


Fig. 1 (A) Diverse amine–acid coupling reactions complement the amide coupling. (B) Selected examples of esters in pharmaceuticals. (C) This work: a carboxylic acid–Katritzky salt deaminative esterification.

forward with dioxane as the solvent (0.3 M), using 1.0 equivalent each of KI, DIPEA, and free acid relative to the Katritzky



entry	9 (eq.)	R	base	additive	solvent	% yield (isolated)
1	1.2	K^+	–	0.2 eq **11**	DMF	73
2	1.2	H	1.2 eq KO^{t}Bu	0.2 eq **11**	DMF	76 (76)
3	1.2	H	1.2 eq Et_3N	0.2 eq **11**	DMF	27
4	1.2	H	1.2 eq KO^{t}Bu	–	DMF	trace
5	1	H	1 eq KO^{t}Bu	1 eq KI	DMF	41
6	1	H	1 eq DIPEA	1 eq KI	dioxane	75 (73)

Fig. 2 Reaction optimization table. All reactions were performed at 0.2 mmol scale under an atmosphere of N_2. KI = potassium iodide, DMF = *N*,*N*′-dimethylformamide, KO^{t}Bu = potassium *tert*-butoxide, Et_3N = triethylamine. [a] Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard, values in parentheses are isolated yields.

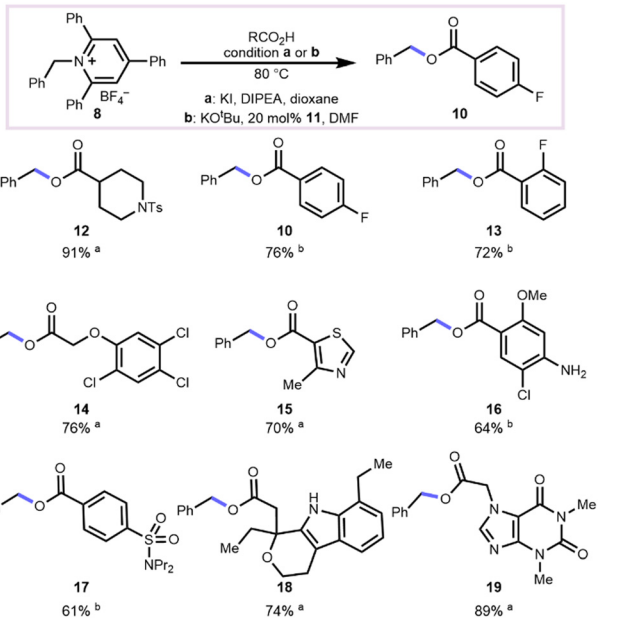


Fig. 3 Acid substrate scope. Reactions were run with pyridinium salt 0.2 mmol (1 equiv.). For condition a, reactions were run with one equivalent each of carboxylic acid, KI, DIPEA, pyridinium salt in anhydrous dioxane at 0.3 M. For condition b, reactions were run with carboxylic acid (1.2 equiv.) and **11** (0.2 equiv.) in anhydrous DMF at 0.1 M.

salt as our preferred conditions. With optimized conditions in hand, we began exploring the generality of the reaction of **8** with various acids (Fig. 3). The reaction is tolerant of aliphatic (**12**, **14**, **18**, **19**) as well as aromatic (**10**, **13**, **15**, **16**, **17**) acids, giving yields ranging from 61–91%. For example, the herbicide 2,4,5-T delivered ester **14** in 76% yield. Electron-poor (**10**, **13**, **17**), electron-rich (**16**), and heterocyclic (**15**, **18**, **19**) acids with various substitution patterns also performed well. Notably, densely functionalized acids such as probenecid (**17**), etodolac (**18**) and theophylline-7-acetic acid (**19**) are smoothly esterified. Selectivity for esterification over aniline alkylation is also achievable using this method (**16**) (Fig. 3 and 4).

Our scope studies were expanded (Fig. 4) to include Katritzky salts derived from primary aliphatic amines (**22**, **24**, **26–27**, **30–33**, **36**), as well as electron-poor or heterocyclic benzylic amines (**23**, **28**, **37**), although these substrates required heating to 110 °C. The method is quite general, tolerating basic amines (**32–33**, **36**), amides (**25**), esters (**26–27**, **30**), Michael acceptors (**37**), acetals (**26–27**), protecting groups including Boc and tosyl (**22–23**, **26**, **29–30**), and oxime ethers (**31**) as well as polyfunctionalities seen in drug molecules such as levofloxacin (**35**), Boc-lysine methyl ester (**30**) enoxolone (**37**), and fluvoxamine (**31**). **32** and **33** are matched molecular pairs of moclobemide and metoclopramide, respectively, wherein the nitrogen atom has been replaced by an oxygen. In addition to anilines, selective esterification was achieved in the presence of other alcohols (**24** and **37**). These latter results showcase the ability to regioselectively esterify without the need for alcohol protecting groups, in contrast to the classic alcohol–acid esterification.

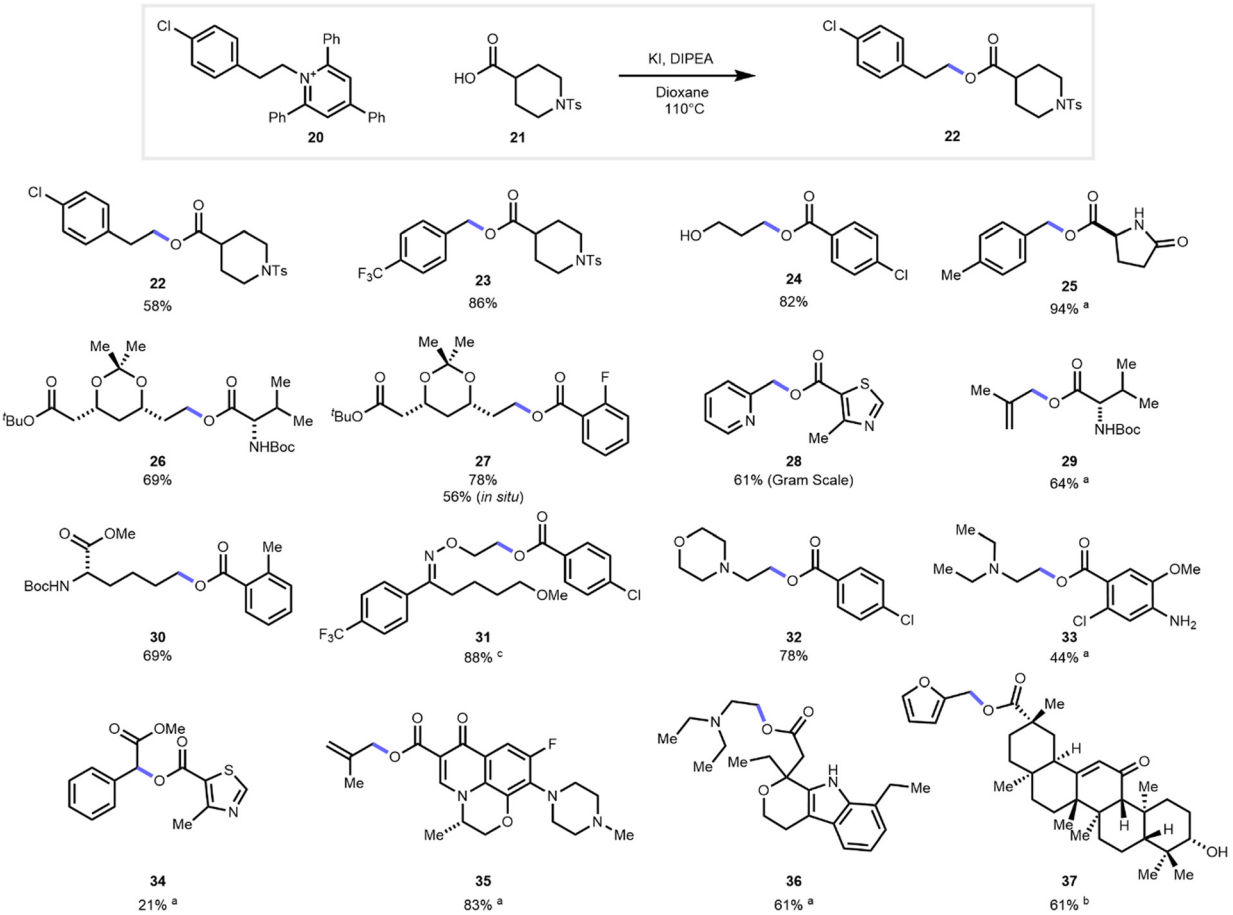


Fig. 4 Substrate scope. Reactions were run with one equivalent each of carboxylic acid, KI, DIPEA, and pyridinium salt in anhydrous dioxane at 0.3 M. (A) 80 °C instead of 110 °C. (B) 60 °C instead of 110 °C. (C) 2 equiv. of KI.

To fully realize the scope of this method and highlight its utility in late-stage diversification, we sought to develop a platform for concise library synthesis (Fig. 5A–C). We envisioned that the Opentrons OT2 liquid handling robot could be used for library generation by speeding up dosing and stock solution preparation. Amlodipine (*cf.* **38**) was chosen as a substrate for the library synthesis campaign. 96 acids were weighed into a source plate which was brought into a nitrogen filled glovebox (Fig. 5E), along with solvent and stock solutions of Katritzky salt **38** and finely ground potassium iodide. To vastly simplify the preparation of stock solutions, acids were weighed quickly into glass shell vials – targeting 0.300 mL of 0.30 M stock solution – with a tolerance of ± 10 mg. The weight was accurately recorded in a spreadsheet, and the appropriate solvent volume for each well computed and written into an OT2 script, which could then automatically direct the autopipetter to dose the correct volume of solvent to produce a 0.30 M stock solution. This protocol greatly simplifies the preparation of stock solutions from diverse substrates with the robotic dilution obviating the need to accurately weigh each substrate to the 0.1 mg accuracy typically associated with library preparation. The roughly weighed but accurately documented acid samples were placed on the robot deck as shown in Fig. 5E. To improve dosing reliability, stock solutions were stirred vigorously on a tumble stirrer to generate well-behaved slurries (Fig. 5C), which were subsequently dosed with wide-bored pipette tips. The source plate of 96 acids was filled with solvent to generate 0.30 M solutions (Fig. 5D), with the OT2 adjusting solvent volume ''on-the-fly''. Of the 96 acids tested, most delivered the ester product (Fig. 5B) as observed by UPLC-MS. Select reactions from this microscale library were repeated on a larger scale, with the ester products isolated by column chromatography (see **46–49**, Fig. 5F and ESI†). The yields were good to excellent.

In summary, an esterification reaction between carboxylic acids and amine-derived Katritzky salts was developed. The protocol serves as an alternative to the amide coupling. The generality of the method was explored and demonstrated to tolerate natural product and drug molecules and was run in a one-pot protocol directly from the free amine. An automation platform was developed to generate a library of 96 amlodipine derivatives.

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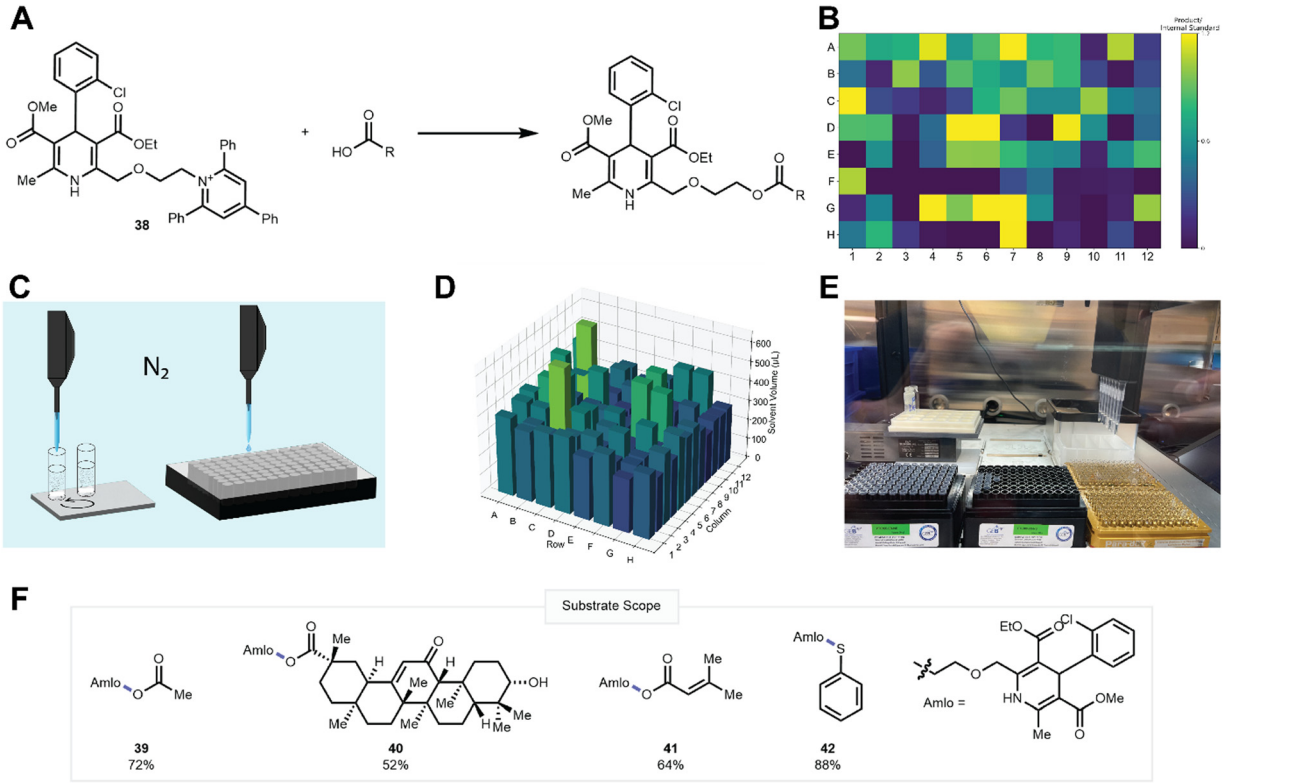

Fig. 5 (A) General reaction scheme. (B) Heatmap of products. Yields are represented as product UV area over internal standard. Acids are aligned such that rows A and B contain mono- and poly-substituted (hetero)aryl acids, row C contains acetic acids, row D contains aliphatic acids with varying functionality, row E contains amino acids with various protecting groups, row F contains non-carboxylic acidic molecules, row G contains drugs with carboxylic acid moieties, and row H contains carboxylate salts with varying counterions. (C) A cartoon depicting slurry loading taking place inside an inert atmosphere glovebox. (D) A heatmap depicting the volume of solvent added to each of the 96 acids. Rather than try to weigh a specific amount, the amount is simply recorded, and the correct amount of solvent added. (E) A photograph of the Opentrons transferring 8 acids using its multichannel pipette head. (F) Scale up of wells D2, G1, D5, and F8.

Conflicts of interest

T. C. is a co-founder and equity holder of Entos, Inc. and equity holder of Scorpion therapeutics. The Cernak Lab receives research funding from MilliporeSigma, Janssen Therapeutics and Relay Therapeutics, and Entos, Inc. as well as gifts from Merck Sharp & Dohme and SPT Labtech. Other authors declare no competing financial interest.

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