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RESEARCH ARTICLE

Practical Chemoselective Acylation: Organocatalytic Chemodivergent Esterification and Amidation of Amino Alcohols with *N*-Carbonylimidazoles

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Abstract: Chemoselective transformations are a cornerstone of efficient organic synthesis; however, achieving this goal for even simple transformations like acylations is often a challenge. We report that *N*-carbonylimidazoles undergo catalytic chemodivergent acylations of anilines or alcohols in the presence of pyridinium ions or DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), respectively. Both of these acylations display simultaneously high and broad chemoselectivity for the target group. Unprecedented levels of chemoselectivity were achieved in the DBU-catalyzed esterification: a single esterification product was obtained from a molecule containing primary aniline, alcohol, phenol, secondary amide, and *N*-H indole groups. These acylations are highly practical as they involve only readily available, inexpensive, and relatively safe reagents; can be performed at the multigram scale; and can be used on carboxylic acids directly via *in situ* formation of the acylimidazole electrophile. Reaction discovery, scope, assessment of practicality, and preliminary mechanistic investigations are discussed.

Introduction

It is sometimes said that organic synthesis can now deliver almost any complex molecule, given enough time and resources;[1] however, the caveat in that statement is arguably necessary because we still lack comprehensive and inexpensive strategies for achieving chemoselectivity within complex structures. Indeed, it has been estimated that "lack of chemoselectivity frequently accounts for as many as 40% of the steps of a complex synthesis."[2] This limitation derives in large part from the fact that even foundational reactions such as acylations—especially esterifications and amidations—are often controlled by the innate reactivities of competing groups. Of course, the use of protecting groups remains a popular way to sidestep these seemingly intrinsic limitations; however, the excess of steps they introduce is problematic from both traditional and green chemistry efficiency metrics.[3] More desirable would be catalytic chemoselective methods that allow chemists to override the innate reactivity preferences of a polyfunctional substrate without resorting to blocking group tactics.[2, 4]

Numerous catalytic methods for chemoselective acylations (typically esterifications) have appeared, some of which allow for even the most challenging modes of selectivity such as esterification in the presence of amines. Most of these methods involve bespoke—and not readily available—metal clusters or complexes in conjunction with esters[5],[6],[7],[8],[9],[10],[11] or vinyl esters[12] as electrophiles (transesterification). Selective esterification of amino alcohols may also be achieved with *N*-heterocyclic carbene (NHC) catalysis of oxidative esterification[13] or transesterification.[14] Enzyme-catalyzed esterifications of amino alcohols have been reported, for instance of a Phe-Ser dipeptide with a lipase,[15] as have several niche methods. For instance, alcohols may be esterified in the presence of anilines via a modified haloform reaction[16] and sufficiently electron-poor anilines can act as spectators in carbodiimide-mediated esterifications[17] and Mitsunobu reactions.[18]

However, in order to achieve these more challenging chemoselectivities, practical considerations such as scope, cost, or reagent availability are often sacrificed—a fundamental tension in the development of new synthetic methods. Moreover, almost none of these reported methods were tested on substrates with more than two competing groups (e.g., an amine and an alcohol) so the true extent of chemoselectivity remains at best unknown.

With these limitations in mind, we propose that a truly practical chemoselective acylation would not only be selective for one group out of *many* (as opposed to two), but also be catalytically chemodivergent: the desired selectivity would arise from choice of catalyst, not the class of electrophiles employed. Moreover, these materials should be simple enough and benign enough that the method will be adopted by those charged with making complex molecules. Here we report an advance toward this ideal: the organocatalytic chemodivergent acylation of complex polyfunctional molecules containing alcohols, anilines, and some amines, among other groups using readily available, inexpensive, and relatively safe reagents. To the best of our knowledge, the

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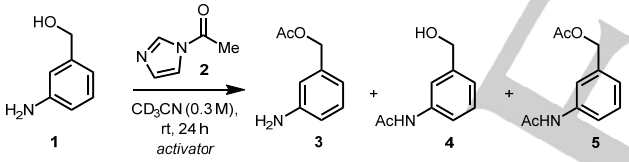
breadth of selectivity displayed in some of these reactions is not generally achievable by other means.

Results and Discussion

Screening for Catalytic Chemodivergence

Initial catalyst and electrophile screening revealed the unique ability of *N*-acylimidazole electrophiles (e.g., **2**) to undergo catalytic chemodivergent acylations. DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) catalyzed the highly chemoselective esterification of model anilino-alcohol **1**, while pyridine hydrochloride promoted the corresponding amidation reaction (Table 1). We were surprised by these results given earlier reports that DBU is capable of promoting *both* amidation of anilines[19] and esterification[20] with *N*-acylimidazoles, as well as our own discovery that the pyridinium cation strongly accelerates alcohol esterification with *N*-acylimidazoles.[21] There was no clear correlation between selectivity for *O*-acylation and the basicity of the catalyst: DMAP (4-(dimethylamino)pyridine) has nearly the same basicity as triethylamine[22] but promotes the opposite acylation chemoselectivity. The solvent-dependency of both acylations was also evaluated but found to be limited. Polar aprotic solvents such as DMF and acetonitrile were most effective. The DBU-catalyzed esterification slowed as the polarity of the solvent decreased (e.g., in THF or toluene) but the observed chemoselectivity was not noticeably affected. The pyridinium ion promoted amidation was plagued by solubility problems in these less polar solvents. In both cases, use of DMSO led to the formation of small amounts of several unidentified side products.

Table 1. Impact of Activator on Acylation Chemoselectivity

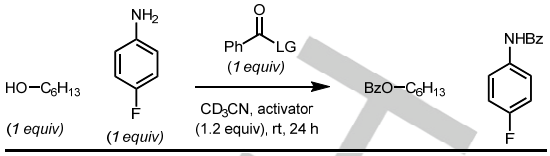


Entry	Activator	mol(%)	%**1**	%**3**	%**4**	%**5**
1	—	—	100	0	0	0
2	DABCO	20	42	35	14	9
3	DMAP	20	28	6	56	10
4	NEt_3	100	43	51	3	3
5	DBU[a]	5	<1	>98	<1	0
6	pyridine•HCl[b]	100	<1	<1	<96	4

Product distribution determined by integration of methylene resonances in ^{1}H NMR spectrum; [a] >98% conversion after 30 min; [b] 89% conversion after 2 h. DABCO = 1,4-diazabicyclo[2.2.2]octane.

Of several popular and readily available—widely commercially available or easily prepared from carboxylic acids—acyl donors, only *N*-acylimidazoles underwent chemoselective esterification (Table 2). The presence of DBU tempered the inherent selectivity for *N*-acylation to some degree regardless of electrophile structure but this effect appears to become more significant as the reactivity of the electrophile decreases.

Table 2. Impact of Electrophile on Acylation Chemoselectivity



Entry	LG	Activator	amide:ester	% conversion[a]
1	Cl	DIPEA	>99 : 1	>98
2	Cl	DBU	10.1 : 1	>98
3	OBz	DIPEA	9.4 : 1	73
4	OBz	DBU	3.8 : 1	>98
5	OSu	DIPEA	NR	<1
6	OSu	DBU	ND[b]	ND[b]
7	imidazole	DBU	1 : >98	>98

Product distribution determined by integration of resonances in ^{1}H NMR and ^{19}F NMR spectra; [a] Percentage of electrophile consumed; [b] Not Determined; complex mixture of products was observed. DIPEA = *N*,*N*-diisopropylethylamine, OBz = benzoyl, OSu = *N*-Hydroxysuccinimidyl.

Impact of Carbonylazole Electrophile Structure on Chemoselectivity

A wide variety of *N*-carbonylimidazoles were found to react exclusively with the hydroxyl group of 3-aminobenzyl alcohol in the presence of DBU (Figure 1A)—selectivity for *O*-acylation was at or above the limits of detection by ^{1}H NMR in all cases (>20:1).[23] Neither steric (**9**, **14**) nor electronic effects (**12**, **13**) from the acyl group significantly affected selectivity or yield. Similarly, imidazole carbamates could be employed in a chemoselective synthesis of carbonates (**16**, **17**). Imidazole ureas (**18**) could also be used to produce carbamate products, albeit with noticeably reduced reaction rates relative to other carbonylimidazole electrophiles.

On the other hand, use of superstoichiometric[24] amounts of pyridine hydrochloride led to highly selective *N*-carbonylation of 3-aminobenzyl alcohol with a variety of *N*-carbonylimidazoles (Figure 1B), with the exception of imidazole ureas (**23**), which did not react even after 72 hours at 80 °C.

Scope of the Chemoselective Esterification

Having established that most types of *N*-carbonylimidazoles are capable of this chemodivergent acylation, we then sought to probe the scope—both respect to the nature of the alcohol group and the breadth of the chemoselectivity profile—of the DBU-catalyzed esterification.

The DBU-catalyzed esterification using *N*-acylimidazoles was essentially limited to primary and secondary alcohols (Figure 2A), as acylimidazoles react much more slowly with tertiary alcohols than anilines in the presence of DBU (**30**).[25] Only the most severe β-branching noticeably impacted the extent of chemoselectivity

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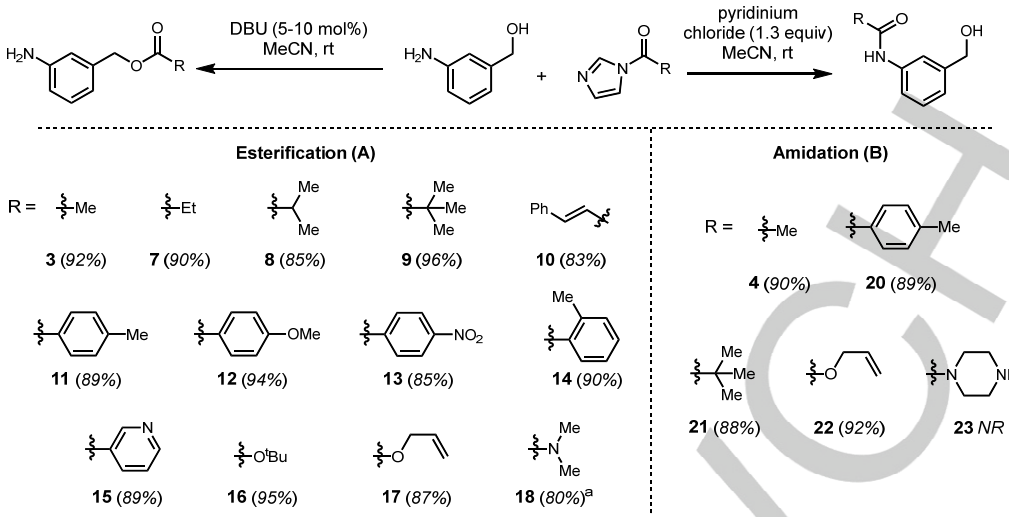

Figure 1. Chemoselectivity of Carbonyl Transfer Is Not Affected by *N*-Carbonylimidazole Structure. All yields are for isolated products. All reactions performed on a 2 mmol scale. [a] 100 mol% DBU used. Boc = *tert*-Butyloxycarbonyl.

(**28** vs **29**); however, *O*-acylation was still the major pathway in these cases. The functional group tolerance of this transformation was remarkably broad, encompassing the use of anilines, alkylbromides (Figure 2B, **34**), alkynes (**35**), and carbamates (**32**). Selectivity to the limit of detection in the esterification of *o*-(hydroxymethyl)aniline to yield **36** illustrated that post-esterification *O*→*N* intramolecular acyl transfer can be avoided under these conditions. Functional groups acidic enough to react with DBU such as sulfonamides (**31**), carboxylic acids (**37**), and phenols (Figure 2C, **38**-**40**) did not interfere with the desired esterification so long as

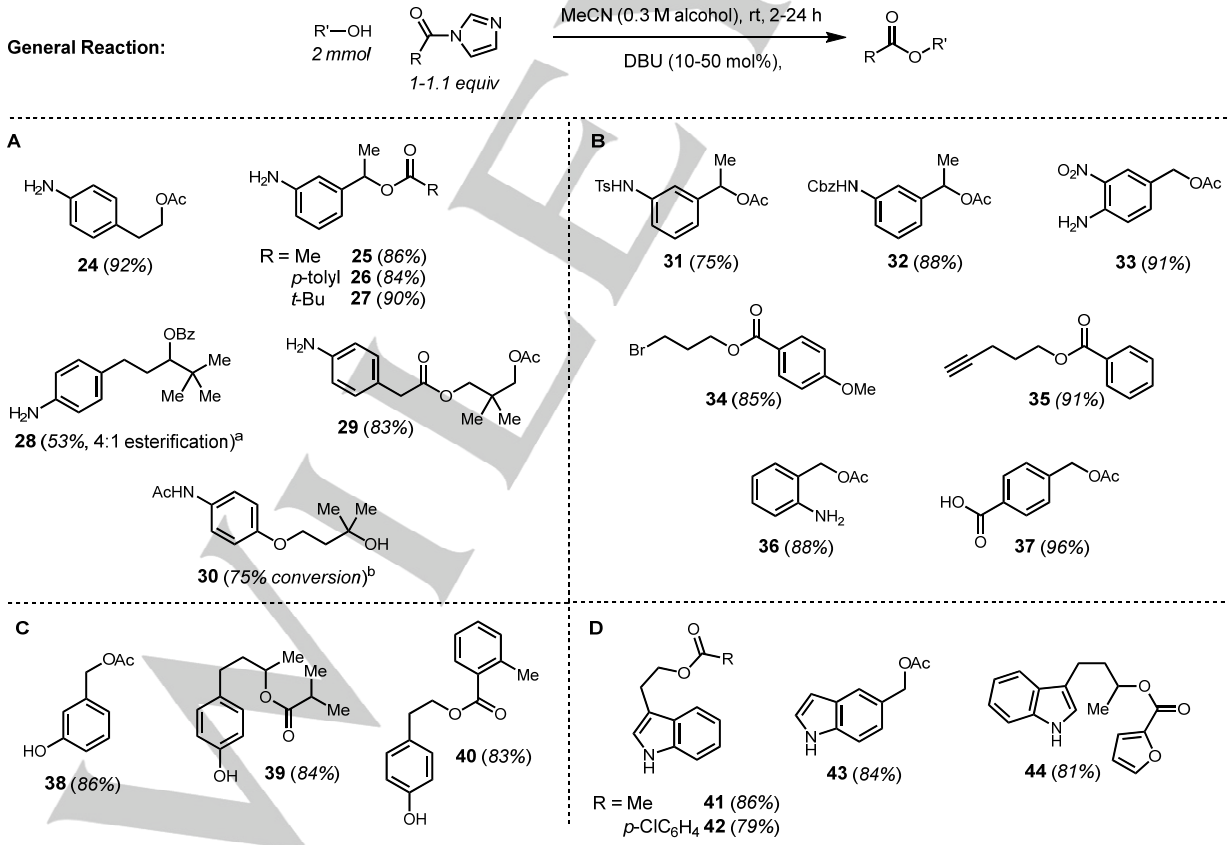

Figure 2. A) Steric Profile of Alcohol Influences Chemoselectivity. [a] Isolated yield in italics. A 4:1 ratio of mono-*O*- to all *N*-acylated products (mono- and bis-acylation) was observed in the ^{1}H NMR spectrum of the crude product. [b] Conversion determined by ^{1}H NMR after 24 h. B) Functional Group Tolerance in the Chemoselective Esterification. C) Chemoselective Esterification in the Presence of Phenols. D) Chemoselective Esterification in the Presence of *N*-H Indoles.

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an increased amount of DBU was used (40-50 mol%). Similarly, *N*-H indoles (Figure 2D, **41-44**), which can undergo facile DBU-catalyzed *N*-acylation with *N*-carbonylimidazoles,[26] did not appear to interfere with the esterification process. In most cases, reactions were performed on a two millimole scale without optimization for individual substrates.[27] In many cases, a simple extractive workup was sufficient to obtain pure ester products.

The DBU-catalyzed esterification proved to be sufficiently selective that it could be employed on truly *poly*functional substrates (Figure 3). Several permutations of structures containing alcohols, anilines, secondary amides, indoles, phenols—including a compound containing all five of these nucleophilic groups (**49**)—were evaluated. All were esterified at the aliphatic alcohol moiety in good isolated yield and with selectivity at the limit of detection (>20:1) favoring esterification.[28] Chemoselective esterification in the presence of an aliphatic amine could also be affected at the preparative scale (**51**) despite the use of anodyne materials such as DBU and *N*-acylimidazoles rather than complex metal catalysts.

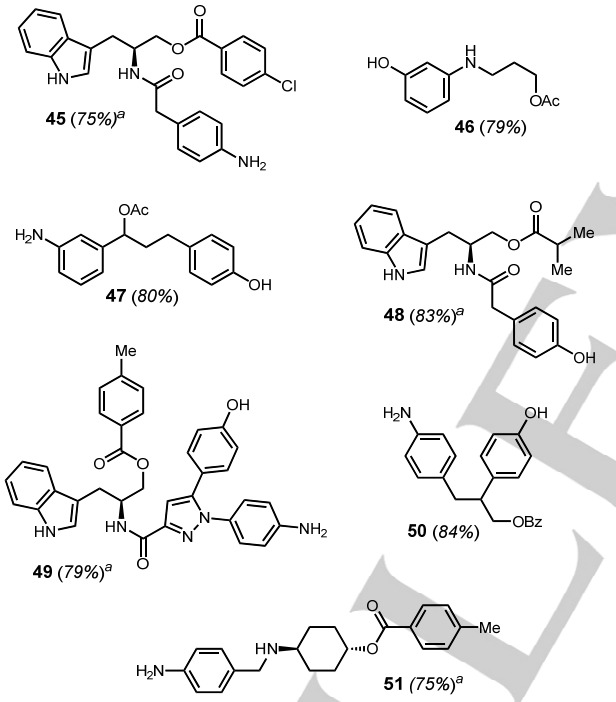
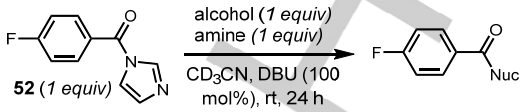


Figure 3. Chemoselective Esterification of Polyfunctional Substrates. [a] Reaction conducted in DMF due to limited solubility of the alcohol substrate in MeCN.

Further evaluation of the chemoselectivity of the DBU-catalyzed esterification in the presence of aliphatic amines was achieved through competition experiments monitored by ^{19}F NMR. In all cases, 1-hexanol was favorably esterified in the presence of a range of aliphatic amines. However, some limitations should be noted: modestly hindered amines were well-tolerated in esterifications of primary alcohols (Table 3, entries 2, 3, and 5) but simple primary or cyclic amines were able to compete for the acylimidazole electrophile to an extent that would be problematic in a synthetic context (entries 1 and 4). Secondary alcohols can be chemoselectively esterified in the presence of relatively sterically hindered aliphatic amines (e.g., **51**, Figure 3) but otherwise react too slowly to achieve synthetically relevant selectivity for esterification (Table 3, entries 6 and 7).

Table 3. Competition Experiments with Aliphatic Amines and Alcohols



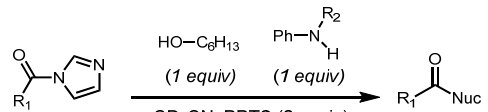
entry	alcohol	Amine	%ester	%amide
1	1-hexanol	benzylamine	65	30
2	1-hexanol	3-aminopentane	94	2
3	1-hexanol	*N*-methylbenzylamine	95	3
4	1-hexanol	piperidine	65	29
5	1-hexanol	2-methylpiperidine	>98	ND
6	3-pentanol	*N*-methylbenzylamine	73	27
7	3-pentanol	benzylamine	1	98

Product distribution determined by integration of resonances in ^{1}H NMR or ^{19}F NMR spectrum using 4-fluorobenzotrifluoride as an internal standard.

Impact of Aniline Structure on Chemoselective Amidation

The pyridinium ion promoted amidation proved to have broad functional group tolerance as well, but also a significant dependence on the steric profile of the aniline nitrogen. Experiments in which 1-hexanol and an aniline were allowed to compete for an acylimidazole electrophile in the presence of PPTS (pyridinium *p*-toluenesulfonate, used for solubility reasons) illustrated that sterically demanding isopropyl groups slowed amidation to such an extent that the pyridinium ion promoted esterification[21] reaction became competitive (entry 2, Table 4). Increasing the steric impact of the acylimidazole exacerbated this effect (entry 4). Electronically deactivating groups had an even more powerful inhibitory effect on amidation (entry 5).

Table 4. Nitrogen Substitution Pattern Mediates Chemoselectivity of the Amidation of Anilines in the Presence of Alcohols



Entry	R_1	R_2	%ester	%amide	%acylimidazole
1	Me	Me	<1	>99	<1
2	Me	*i*-Pr	29	65	6
3	*p*-FC_6H_4	Me	3	97	<1
4	*p*-FC_6H_4	*i*-Pr	52	10	30
5	Me	Ph	53	<1	39

Product distribution determined by integration of resonances in ^{1}H NMR or ^{19}F NMR spectrum

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Similar observations were borne out in preparative scale experiments, where good yields of amide product were obtained for somewhat sterically hindered anilines (**53** and **55**, Figure 4). This amidation protocol was tolerant of phenols and indoles as judged from isolated yields and ^{1}H NMR analysis of crude reaction mixtures (**54** and **56**, Figure 4). In all of these reactions, the pyridinium ion promoted acylation was highly selective for amidation (>20:1) unless an excess of acylimidazole was employed, in which case bis-acylation could be observed. The desired product could typically be isolated in pure form by a simple extraction protocol.

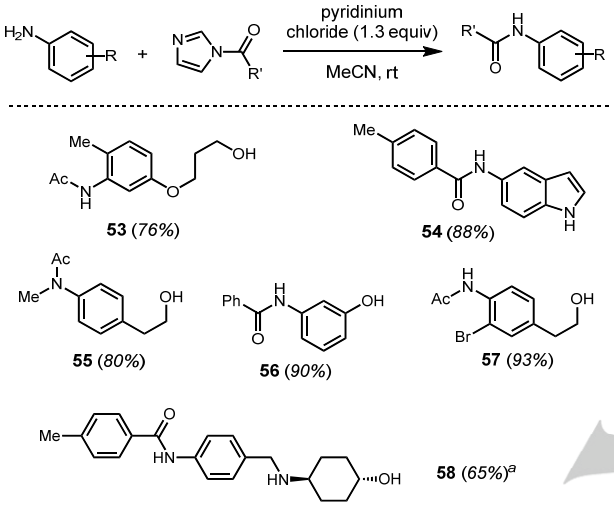


Figure 4. Functional Group and Steric Tolerance of Pyridinium Ion Promoted Amidation. [a] The reaction was performed in DMF and employed 3 equivalents of PPTS.

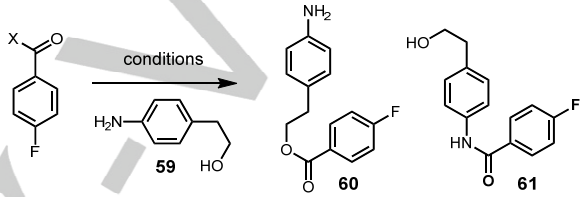
Interestingly, the catalytic chemodivergence of the DBU and pyridinium ion catalyzed acylations extends even to subtrates containing aliphatic amines as *N*-acylation of anilines could be performed using slightly modified reaction conditions without observable amidation of an aliphatic amine (**58**, compare to **51** in Figure 3). Preliminary experiments illustrated that the rate of amidation—but not selectivity—were improved by using a larger excess of pyridinium ion and that significant precipitate was generated upon mixing the anilino-amine substrate with pyridinium hydrochloride. We therefore surmise that the aliphatic amine is at least partially protonated by the pyridinium ion and thus rendered non-nucleophilic. From a practical perspective, reactions in which premature[29] precipitation is observed may be improved simply by performing the reaction in DMF rather than acetonitrile and using PPTS instead of pyridine hydrochloride.

Practical Considerations for Use of the Catalytic Chemodivergent Acylation

As our goal was not simply to develop chemoselective transformations but to create synthetic strategies with minimal barriers to adoption, we evaluated the chemodivergent acylation along two metrics of practicality: ease of access to the requisite *N*-carbonylimidazoles and scalability.

Given that *N*-carbonylimidazoles are crucial to the chemoselectivity of these acylations but are not generally commercially available, their use in a truly practical protocol hinges on the ability to generate them *in situ* from widely available feedstocks. Importantly, we found that the yields and selectivities of both esterification and amidation do not appear to be sensitive to the preparation method of the *N*-acylimidazole. Carboxylic acids may be converted to the requisite acylimidazole *in situ* by short treatment with CDI (1,1'-carbonyldimidazole)[30] prior to addition of the amino alcohol substrate and the catalyst (compare Methods B and E, Table 5).[31] Alternatively, brief treatment of an appropriate acid chloride with imidazole and DBU prior to the introduction of the alcohol substrate provides comparable results to use of the preformed acylimidazole (Method C). It should be noted that Methods B-E were unoptimized and that specific reaction conditions for *in situ* formation of the acylimidazole may depend on the acid chloride or carboxylic acid used.

Table 5. *In Situ* Generation of Acylimidazoles Yields Results Comparable to Use of Preformed Acylimidazoles



Method	X	Conditions	Yield
Esterification			
A	imidazole	DBU (10 mol%), rt	93
B	OH	CDI (1.1 equiv), 40 °C, 1 h; **59**, DBU (10 mol%), rt	84
C	Cl	Imidazole (1.1 equiv), DBU (1.1 equiv), 15 min; **59**	91
Amidation			
D	imidazole	Pyridine•HCl (2 equiv), rt	89
E	OH	CDI (1.1 equiv), 40 °C, 1 h; **59**, pyridine•HCl (3.2 equiv), rt	90

The ability to generate *N*-acylimidazoles from carboxylic acids *in situ* also allowed for additional modes of selectivity by facilitating inclusion of some kinds of reactive groups in the acyl electrophile. In a limited study, we found that carboxylic acids containing phenols (**62**), *N*-H indoles (**63**), and some aniline groups (**64**) could be employed using method B. In many cases, these acylimidazoles could not be readily isolated. Two limitations to this

tactic were noted: CDI reacted with aliphatic amines and primary anilines[32] instead of the carboxylic acid moiety.

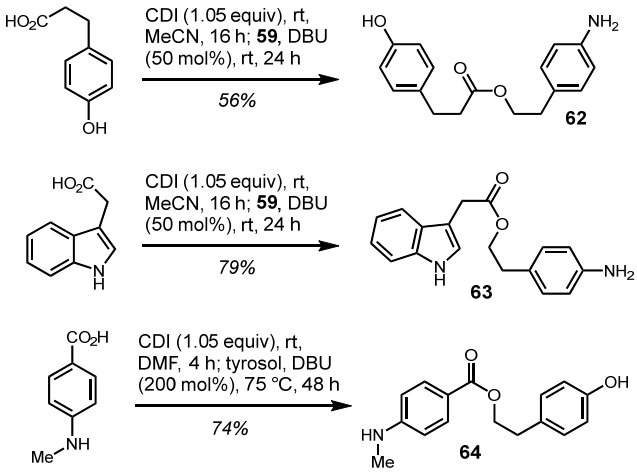


Figure 5. Broad Functional Group Tolerance Afforded By *In Situ* Generation of Acylimidazoles

Practical synthetic methods should also be scalable without appreciable changes in reaction yield or selectivity. Both the DBU-catalyzed esterification and the pyridinium ion promoted amidation could be used to prepare multigram quantities of product without noticeable loss of efficiency (Figure 6). The requisite acylimidazole electrophile was generated *in situ* from 4-toluic acid using Methods B and E, respectively (see Table 5).

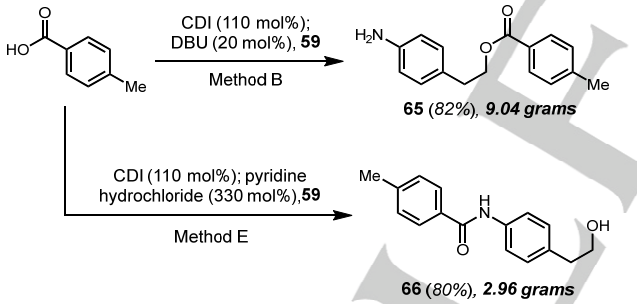


Figure 6. Facile Multigram Scale Chemoselective Esterification and Amidation

Possible Mechanistic Origins of Chemoselectivity

During the course of this work, we became interested in understanding the general mechanistic features through which each catalyst operates. We also sought to guide implementation of this method by establishing a mechanism-based model that could predict the chemoselectivities of acylations of complex structures using widely-available pK_a values (in DMSO).[33]

We have previously reported on the special dual role of the pyridinium ion in activating *N*-acylimidazole electrophiles[21] and believe that mechanistic proposal is likely valid in the aniline amidation reaction as well: through sequential protonation of the imidazole group by the weakly acidic pyridinium ion and subsequent nucleophilic catalysis by its conjugate base, pyridine, to generate an *N*-acylpyridinium species. As the pyridinium ion accelerates acylation by interacting with the electrophile, there is no clear reason for acylation to occur selectively at an intrinsically weaker nucleophilic group (e.g., an alcohol), we therefore expect that the most nucleophilic group available will generally be acylated as demonstrated here.[34]

The remarkable selectivity of the DBU-catalyzed esterification is more complex as the less-nucleophilic alcohol moiety is acylated in preference to more nucleophilic groups such as anilines or some amines while other groups that are even less nucleophilic—but more acidic—than alcohols (e.g., phenols or indoles) are *also* generally isolated unchanged. Taken together, these findings are suggestive of DBU interacting with most or all of the nucleophilic groups (alcohols, anilines, phenols, etc.) present in a molecule, either as a Brønsted base or hydrogen-bond acceptor, and thereby modifying their relative nucleophilicities.[35]

Two observations along with literature precedent[36] initially suggested DBU may function as a hydrogen-bond acceptor toward at least aliphatic alcohols: ^{1}H NMR spectra of 1:1 DBU-alcohol mixtures in CD_3CN reveal strongly concentration-dependent O-H chemical shifts ($\Delta\delta$ = 3.49 ppm),[37] and the available acidity data suggests that DBU (pK_{aH} = 13.9 in DMSO[38]) may not be sufficiently basic to generate appreciable quantities of alkoxide (pK_{aH} ≈ 30 in DMSO[39]) intermediates.

Turning our attention to developing a predictive model of chemoselectivity among multiple functional groups, we sought to explain chemoselectivity in the presence of less nucleophilic groups such as phenols. Among other possibilities, we considered the potential for thermodynamic control from equilibrating acyl transfer between two or more functional groups in the substrate. It has been shown both that 1,2,4-triazole can serve as a nucleophilic catalyst in amidations employing phenyl esters as acyl donors[40] and that imidazole reacts with phenyl esters in the absence of a catalyst to yield *N*-carbonylimidazoles,[41] suggesting that reversible acyl transfer involving acylimidazoles is feasible.

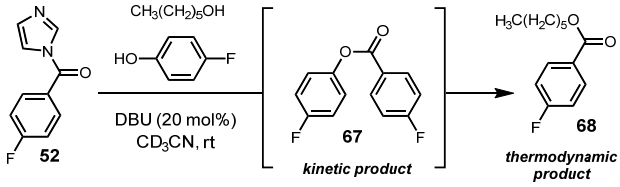


Figure 7. Thermodynamic Control Explains Chemoselectivity in Presence of Acidic Groups

To evaluate this possibility, a DBU-catalyzed competitive acylation of 1-hexanol (pK_a ≈ 30[39]) and the much more acidic 4-fluorophenol (pK_a = 18.0 in DMSO[42]) with a fluorinated *N*-acylimidazole (**52**, Figure 7) was monitored by ^{1}H and ^{19}F NMR over time. In the event, **52** disappeared completely within a minute of mixing, with phenyl benzoate **67** appearing as the predominant product. Over the next four hours, **67** gradually disappeared and a proportional increase in the concentration of hexyl ester **68** was observed, indicating thermodynamically controlled acylation (plot

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of composition over time available in the Supporting Information). The chemoselective acylation of alcohols in the presence of *N*-H indoles was also found to occur under thermodynamic control as *N*-acylindole intermediates[43] could be directly observed by NMR. In these cases, it appears that more acidic functional groups (e.g., phenol or indole) are highly activated by DBU and are therefore kinetically competent, but the resulting products are unfavorable relative to the possible ester product (e.g., **68**) and are therefore thermodynamically incompetent.

On the other hand, the remarkably general selectivity for esterification over aniline amidation in the DBU-catalyzed acylation is not consistent with thermodynamic control as neither *N*-acyl intermediates nor transacylations of ester- or amide-containing substrates (see Figures 2 and 3) were observed during the esterification of alcohols in the presence of anilines. Instead, the observed selectivity likely arises from kinetic control: if DBU serves as a hydrogen-bond acceptor, the alcohol might be expected to associate to the catalyst to a greater extent and therefore represent the most common activated nucleophile.

To evaluate these possibilities more directly, and to further probe whether DBU serves as a hydrogen-bond acceptor, we monitored a competition experiment involving 1-hexanol and a significantly acidified—and therefore significantly enhanced hydrogen-bond donating— aniline, 4-cyanoaniline (Figure 8, pK_a = 25.3 in DMSO[44]), finding that ester **68** was the only detectable product (assuming a limit of detection of 20:1 by ^{19}F NMR). Unlike in the case of phenols, amide **69** was not observed during the course of the reaction, further supporting kinetic rather than thermodynamic control in the aniline-alcohol selectivity scenario. Given the pK_a difference between 4-cyanoaniline and 1-hexanol, this result is also consistent with DBU serving as a hydrogen-bond acceptor.

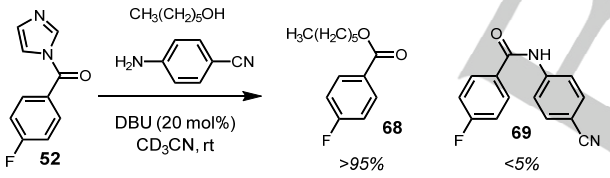

Figure 8. Acidic Anilines Are Acylated More Slowly Than Alcohols

With these general mechanistic features in hand, we propose the following predictive model for the chemoselectivity of the DBU-catalyzed esterification, which accounts for the dual modes of selectivity: groups of *similar or lesser acidity*[45] than aliphatic alcohols are unlikely to be sufficiently activated by DBU and are therefore kinetically incompetent, while groups *substantially more acidic* are thermodynamically incompetent and reversibly acylated. These more acidic groups (e.g., phenols or indoles) will give rise to the kinetic acylation product but may generally be assumed to transfer the acyl group to less acidic—but kinetically competent—groups (e.g., alcohols). Based on the reversible acylation of indole, we propose its pK_a, 21.0, in DMSO,[46] as a rough cutoff for groups that can be reversibly acylated.

Conclusion

The combination of carbonylimidazole electrophiles and judiciously chosen catalysts facilitates catalytic chemodivergent acylations of anilines or alcohols, and in particular gives rise to unprecedented breadths of chemoselectivity in esterifications of truly *poly*functional molecules. To the best of our knowledge, the DBU-catalyzed protocol is the first esterification method demonstrated to *simultaneously* and efficiently select against more acidic nucleophilic groups (e.g., phenols) under thermodynamic control *and* intrinsically more nucleophilic groups (e.g., amines) under kinetic control. The fact that these synthetic dividends are derived from safer, inexpensive organocatalysts and electrophiles generated *in situ* from ubiquitous carboxylic acids should make these methods a useful addition to the synthetic chemists' toolbox.

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