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On the reactivity of imidazole carbamates and ureas and their use as esterification and amidation reagents

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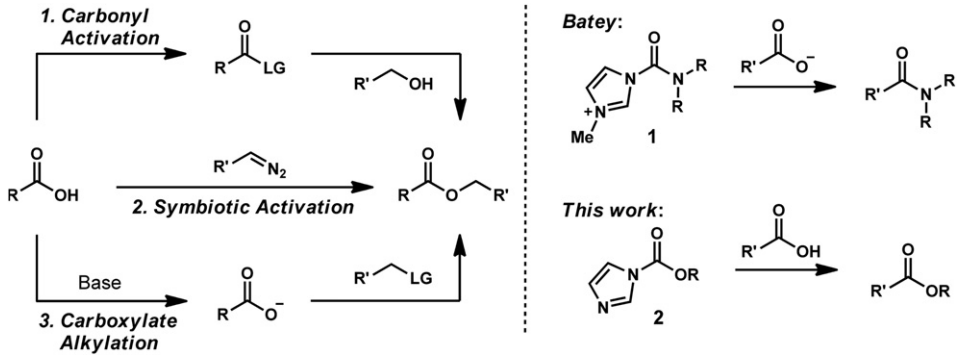
ABSTRACT

The optimization, substrate scope, and mechanism of esterification and amidation of carboxylic acids mediated by imidazole-based reagents are discussed. The innate reactivity of carbonylimidazole reagents with a range of nucleophiles is also explored. New reagents developed for the synthesis of α,β-unsaturated esters are described, as are reagents for the preparation of tertiary amides directly from carboxylic acids.

1. Introduction

Esterification is a critically important process for organic synthesis, and as such, significant effort has been devoted to developing robust and mild esterification methods.[1] The plethora of approaches to the ester group can be distilled into three paradigms (Scheme 1); (1) carbonyl activation, (2) generation of a reactive ion pair that can collapse to an ester product, and (3) conversion of an acid substrate to a carboxylate anion that can be alkylated. Although in situ activation of acids[2] and carboxylate alkylation[3] have been thoroughly explored, reactions that proceed through symbiotic activation of both the acid and esterification agent, as in the case of this second paradigm, lie relatively fallow.



Scheme 1. Major paradigms for esterification.

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One of the best-known examples of symbiotic activation is the reaction of diazomethane with carboxylic acids, which proceeds through a tight ion pair.[4] *O*-Alkylisoureas react with carboxylic acids by a similar pathway to yield the desired ester and a urea byproduct.[5] The advantages of this symbiotic activation are manifold, the most important of which is the inherent chemoselectivity imbued to the esterification process by the requirement that the reagent and substrate *activate each other* in order for the reaction to proceed. The ideal embodiment of this paradigm will use reagents that are inert unless activated, after which they will react rapidly. Diazomethane comes close to this ideal; however, the strict limitations on reagent scope and the challenge of safe handling remain significant practical barriers. Therefore, new methods that utilize this mode of activation are desirable.

The parameters required for mutual activation in esterification through an ion-pair process are typically that the esterification reagent be basic enough to deprotonate a carboxylic acid, and that the resulting conjugate acid be electrophilic enough to react with the conjugate base (i.e., carboxylate), which acts as a nucleophile. A survey of the literature revealed that, in the case of carbonylimidazole-based reagents, these modes have been explored both in tandem and as discrete processes. Batey has demonstrated that quaternized imidazole-based ureas (**1**), in which alkylation is a surrogate for protonation, react smoothly with carboxylate anions to afford amide products (Scheme 1).[6] Moreover, Staab has shown that carbonyldiimidazole (CDI) rapidly reacts with carboxylic acids to afford acylimidazoles, thereby demonstrating that for activated imidazole ureas, the initial proton-transfer step from a carboxyl group, as well as collapse of the resultant conjugate pair, are facile.[7]

We sought to use the existing precedent to develop a new esterification method exploiting reagents that reacted in a similar fashion to CDI or Batey's *N*-methylimidazolium salts, but also carried the alkoxy constituent of the desired ester—much as diazomethane contains both a basic functional group and an alkyl fragment that is incorporated in the ester product. As such, we turned our attention to imidazole carbamates (**2**). Indeed, our previous work has demonstrated that these compounds are highly efficacious esterification reagents.[8] Herein, we disclose experiments delineating the mechanism and substrate scope of this transformation, the fundamental reactivity of **2**, and several new imidazole-based reagents for esterification and amidation.

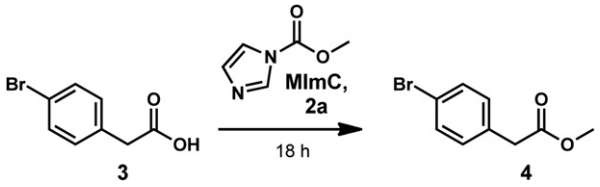
2. Results and discussion

As an initial foray into the applicability of imidazole carbamates as esterification reagents, we monitored the reaction of methylimidazole carbamate (MImC, **2a**, Table 1)[9] with 4-bromophenylacetic acid (**3**) by ^{1}H NMR. No reaction was observed at room temperature, but simply warming the mixture to 60 °C led to partial conversion to the desired methyl ester **4**. This provided proof of concept that the conjugate pair derived from **3** and MImC could collapse to an activated intermediate, which could then be trapped by the liberated alkoxy group.

Our general mechanistic hypothesis—protonation of the imidazole carbamate followed by ion pair collapse through attack of the carboxylate anion on the now activated carbamate carbonyl—also hinted at an initial direction for reaction optimization. Specifically, the polarity of the reaction medium needed to be increased. Indeed, we found that the yield of **4** correlated with solvent polarity, although the variance in yields was modest (Table 1, entries 1–5).[8]

Analysis of crude reaction mixtures demonstrated that 1-methylimidazole was generated during the course of the esterification reaction. Since imidazole is also generated as a byproduct, we reasoned that an intermolecular methyl group transfer between

Table 1
Optimization of esterification with imidazole carbamates



3 4

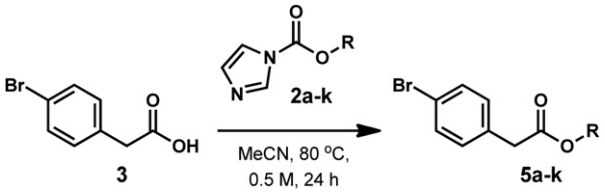
Entry	Solvent	Temp (°C)	MImC (equiv)	[Acid] (M)	Yield (%)
1	Toluene	80	1.2	0.2	58
2	1,2-DCE	80	1.2	0.2	63
3	EtOAc	80	1.2	0.2	66
4	MeCN	80	1.2	0.2	72
5	DMF	80	1.2	0.2	73
6	MeCN	60	1.2	0.2	47
7	MeCN	60	1.2	0.5	70
8	MeCN	60	1.2	1.0	74
9	MeCN	60	1.2	2.0	69
10	MeCN	60	2.0	0.5	72
11	MeCN	60	3.0	0.5	80
12	MeCN	60	4.0	0.5	83
13	MeCN	80	1.2	0.5	85
14	MeCN	80	2.0	0.5	93

MImC and imidazole may be occurring (vide infra). Therefore, further optimization was aimed at suppressing this side reaction. Reaction concentration was investigated first, and a significant increase in yield (entry 7, Table 1) was obtained at higher concentrations. However, at very high concentrations (entries 8 and 9), the decomposition of MImC by imidazole became more pronounced. To offset this side reaction, additional equivalents of MImC were employed, but this modification had only a limited impact on the isolated yield of **4** as 1-methylimidazole formation was accelerated as well (entries 10–12). We hypothesized that esterification must slow appreciably once a significant amount of imidazole has been generated because this byproduct is more basic than MImC, leading to sequestration of the remaining carboxylic acid. As such, further optimization was aimed at accelerating the esterification rather than suppressing or compensating for imidazole alkylation. Eventually, success was achieved through modification of concentration and stoichiometry, along with an increase in the reaction temperature from 60 °C to 80 °C.[10]

With optimized reaction conditions in hand, we began our investigation into the scope of the methylation reaction. As previously reported, a wide variety of carboxylic acids could be successfully esterified in good to excellent yields in acetonitrile.[8] Acid substrates that exhibited limited solubility in acetonitrile under the reaction conditions could be successfully esterified in high yield using DMF as the solvent. This was especially true for benzoic acids where the yield increased by 10–15% when the reaction was run in DMF as compared with acetonitrile. However, acetonitrile proved to be sufficient as a solvent for the majority of substrates that were examined and was therefore employed due to its ease of removal.[11]

Many types of ester derivatives could be prepared using imidazole carbamates[12] under the optimized reaction conditions (Table 2).[8] For instance, allyl imidazole carbamate reacted with **3** to provide the corresponding allyl ester **5d** (entry 4). Significantly, secondary allylic imidazole carbamates mediated regiospecific esterification (entries 7 and 8). Secondary imidazole carbamates reacted more slowly with carboxylic acids (entries 3 and 8) and a tertiary carbamate (entry 10) did not provide the ester product, but instead underwent carbamate cleavage and decarboxylation.

Table 2
Reagent scope

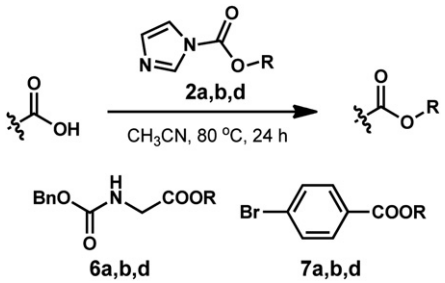


Entry	R	Yield (%)
1	Methyl (**2a**)	93
2	Ethyl (**2b**)	89
3	Isopropyl (**2c**)	70[a]
4	Allyl (**2d**)	91
5	Benzyl (**2e**)	81[b]
6	Propargyl (**2f**)	87
7	*trans*-3-Methylallyl (**2g**)	84
8	1-Methylallyl (**2h**)	85
9	Cyclopropylmethyl (**2i**)	83
10	*tert*-Butyl (**2j**)	Trace
11	Phenyl (**2k**)	>95[c]

Entries 3, 8, and 10 were run for 48 h.
[a] The reaction did not reach completion.
[b] Chromatography was required to remove benzyl carbonate.
[c] Conversion by ^{1}H NMR due to diphenyl carbonate contamination.

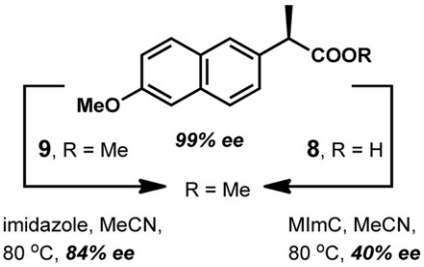
Further investigation of the substrate scope of the imidazole carbamate-mediated esterification demonstrated that other variants of the esterification reagents typically perform similarly to MImC (Table 3). However, a limitation of this esterification was discovered when the protected amino acid Boc-Phe-OH was subjected to MImC-mediated esterification and was found to undergo partial racemization. This result compelled us to probe whether epimerization was specific to carbamate protected amino acids through the well-known oxazolone pathway[13] or whether α-chiral carboxylic acids in general were inappropriate substrates for imidazole carbamate-mediated esterification (Scheme 2). Converting enantioenriched naproxen (**8**) to its methyl ester (**9**) using our conditions resulted in significant epimerization. The enantiopurity of naproxen methyl ester (**9**) was also eroded (to a lesser extent) when heated in the presence of imidazole, suggesting that most of the observed epimerization resulted from an intermediate with enhanced acidity reacting with the basic imidazole byproduct.

Table 3
Substrate scope for additional imidazole carbamates



R	Yield **6** (%)	Yield **7**[a] (%)
Me (**2a**)	93	94
Et (**2b**)	89	86
Allyl (**2c**)	91	95

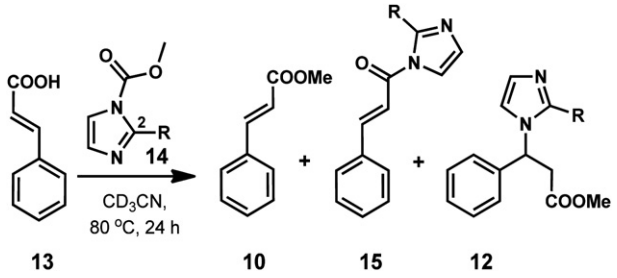
Yields are for isolated product.
[a] DMF was used as the solvent.



Scheme 2. Epimerization of naproxen.

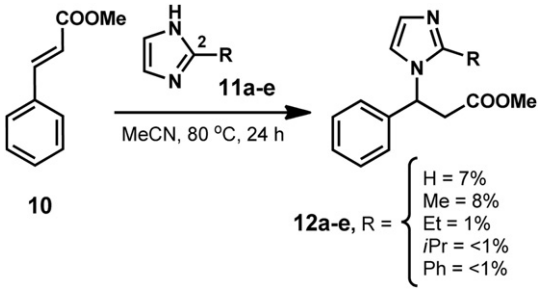
The nucleophilicity of imidazole also led to side reactions in some cases. Although enoic acids (e.g., **13**, Table 4) could be converted to the corresponding esters using our carbamate reagents, a minor amount of product arising from competing conjugate addition of imidazole was also recovered (**12**). In some cases, this side reaction consumed an appreciable amount of the substrate, necessitating the development of new reagents (Scheme 3) or reoptimization of the esterification reaction for α,β-unsaturated acid substrates.

Table 4
Esterification of cinnamic acid



Entry	R	**13** (%)	**10** (%)	**15** (%)	**12** (%)
1	H (**2a**)	2	73	0	25
2	Me (**14b**)	4	81	5	11
3	Et (**14c**)	4	69	22	5
4	*i*-Pr (**14d**)	3	62	32	3

Conversions based on integration of resonances in the ^{1}H NMR spectra.



Scheme 3. Conjugate addition of substituted imidazoles.

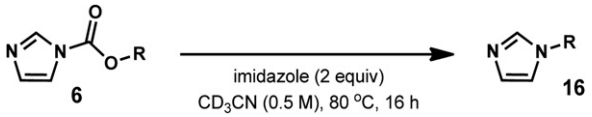
Initial investigation with methyl cinnamate (**10**) showed that only small amounts of conjugate addition product (**12a**) could be formed from the product ester, so it seemed likely that a putative activated ester intermediate was the competent Michael acceptor in the reaction mixture. Increasing the steric bulk of the C-2 substituent on the free imidazole (**11a**–**e**) decreased the levels of conjugate addition product (**12a**–**e**, Scheme 3). On the basis of this result, imidazole carbamate reagents with substitution at the C-2 position (**14a**–**c**) were prepared and found to disfavor conjugate

addition when reacted with cinnamic acid (**13**, Table 4). However, the concomitant decrease of the electrophilicity of the putative acylimidazole intermediate led to an appreciable amount of unreacted activated ester (**15**) after 24 h.

2.1. Alternative reaction pathways of imidazole carbamates

Our observation that MImC (**2a**) reacts with imidazole to provide 1-methylimidazole led us to investigate the general stability and reactivity of imidazole carbamates. Although MImC and allyl imidazole carbamate (**2d**) rapidly and completely react with imidazole (Table 5, entries 1 and 3), higher alkane homologs, such as **2b** are not competent electrophiles.[14] Curiously, 1-methylallyl imidazole carbamate (**2h**, entry 6) resisted attack by imidazole, whereas 3-methylallyl imidazole carbamate (**2g**, entry 5) was completely consumed to provide **16g**. This latter result suggests that an S_N2' pathway is not operative under the relevant conditions. Further experimentation demonstrated that the imidazole alkylation was highly concentration dependent, with little alkylation occurring when the concentration of imidazole was kept at or below 0.2 M. As a control experiment to probe the possibility of an intramolecular alkyl group transfer, **2d** was heated to 80 °C in dry CD_3CN, but only starting material was observed by ^1H NMR.

Table 5
N-Alkylation of imidazole by **6**



Entry	R	Conversion (%)
1	Me (**2a**)	>95
2	Et (**2b**)	Trace
3	Allyl (**2d**)	>95
4	Benzyl (**2e**)	>95
5	*trans*-3-Methylallyl (**2g**)	>95
6	1-Methylallyl (**2h**)	9

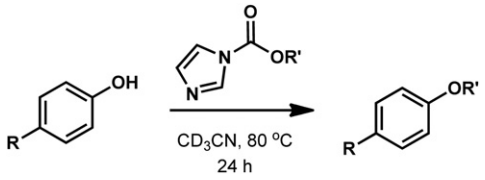
Conversions based on integration of resonances in the ^1H NMR spectra.

Further investigation of the reactivity of imidazole carbamates focused on understanding the nature and scope of the proton-transfer activation step that the esterification reaction appears to exploit. Specifically, we wondered whether other acidic functional groups could be alkylated under the esterification conditions. To test this hypothesis, a series of imidazole carbamates were reacted with phenols of varying acidity under the standard esterification conditions. In most cases, phenol alkylation was negligible (Table 6), but imidazole alkylation proceeded as usual.

Increasing the acidity of the phenolic hydroxyl group retarded the rates of phenol alkylation (entries 4–6) as well as the *N*-alkylation of imidazole. The use of ethylimidazole carbamate (**2b**, entry 7) led to significant quantities of the phenoxycarbonate, suggesting that formation of a carbonate could be occurring as an initial step in the reaction of MImC with phenols.

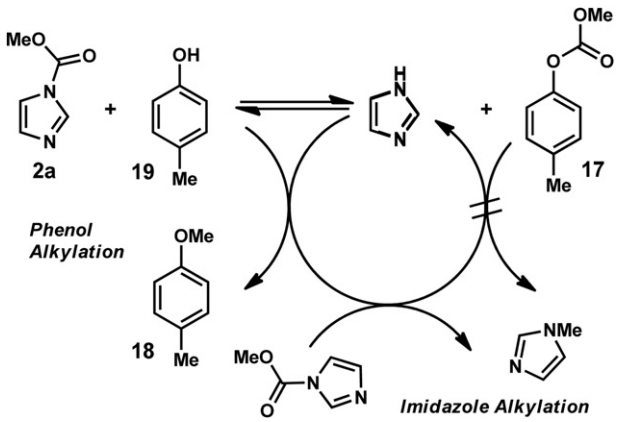
The possible intermediary role of a phenoxycarbonate was investigated by reacting 4-methylphenyl methyl carbonate (**17**, Scheme 4) with imidazole under the relevant conditions. After 2 h, 23% of the imidazole had been converted to methylimidazole carbamate (**2a**), while only a trace amount of *N*-methylimidazole and no 4-methylanisole (**18**) was observed—suggesting that the aryl carbonate is not the active methylating reagent in situ. After an additional 14 h of heating, the mixture consisted primarily of *p*-cresol (**19**) and *N*-methylimidazole, along with trace amounts of **2a**, **18**, and **17**. This result closely parallels that obtained from the reaction of MImC with *p*-cresol.

Table 6
Reaction of phenols with imidazole carbamates



Entry	R	R′	Conversion[a] (%)
1	OMe	Me (**3**)	8
2	Me	Me (**3**)	18
3	F	Me (**3**)	11
4	Cl	Me (**3**)	8
5	CN	Me (**3**)	2
6	NO_2	Me (**3**)	2
7	Me	Et (**6a**)	0[b]
8	Me	Allyl (**6b**)	5[c]

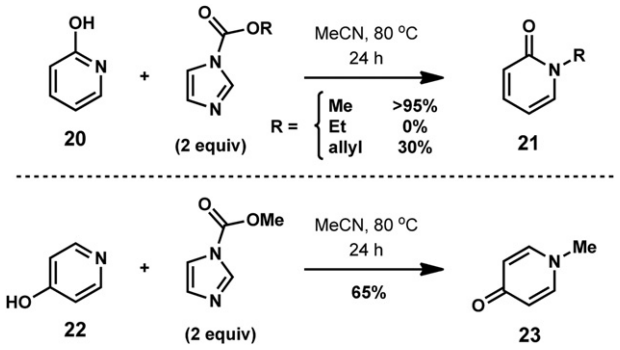
[a] Conversions based on integration of resonances in the ^1H NMR spectra.
[b] 60% conversion to 4-methylphenyl ethyl carbonate.
[c] 22% conversion to 4-methylphenyl allyl carbonate.



Scheme 4. Intermedacy of phenoxycarbonates in phenol methylation.

Thus, it seems likely that under the reaction conditions some amount of imidazole and phenoxycarbonate (**17**) is formed from the phenol (**19**) and imidazole carbamate (**2a**). The imidazole can then react with additional imidazole carbamate to generate an alkylimidazole and another molecule of imidazole. The relevant alkyl electrophile is therefore most likely the imidazole carbamate in both phenol and imidazole alkylation. This mechanistic hypothesis also explains the inverse correlation of gross methylation with phenol pK_a. More acidic—and therefore less nucleophilic—phenols should disfavor the formation of the phenoxycarbonate, leading to lower overall concentrations of imidazole and slower rates of methylation.

On the other hand, hydroxypyridines were efficiently *N*-alkylated by MImC (Scheme 5). Given the correlation between pK_a and extent of methylation observed in the case of phenols, it seemed unlikely that the increased acidity of hydroxypyridine isomers was leading to alkylation. Instead, an S_N2 mechanism could be envisioned, which would be analogous to the reactivity observed between imidazole and MImC (Table 4). This hypothesis explains the near complete regioselectivity for *N*-alkylation in both 2- and 4-hydroxypyridine (**20** and **22**)[15] to yield *N*-methylpyridinones **21** and **23**, as well as the fact that an ethyl group was not transferred from ethylimidazole carbamate (**2b**).[16]

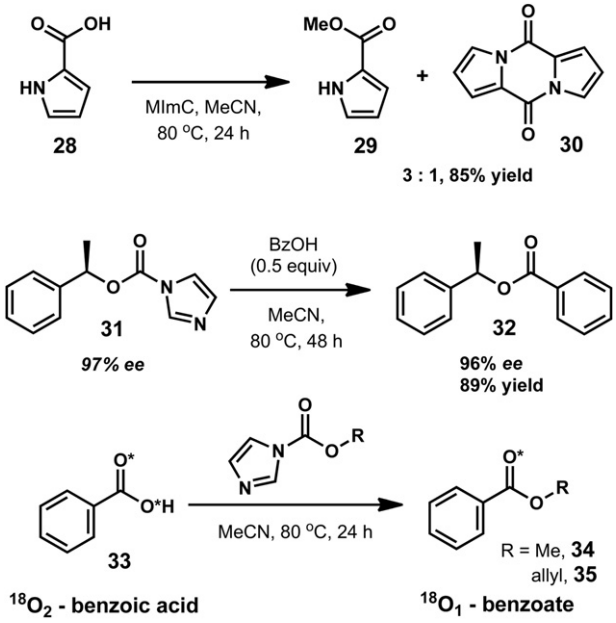


Scheme 5. *N*-Alkylation of hydroxypyridines with imidazole carbamates.

2.2. Mechanism of esterification

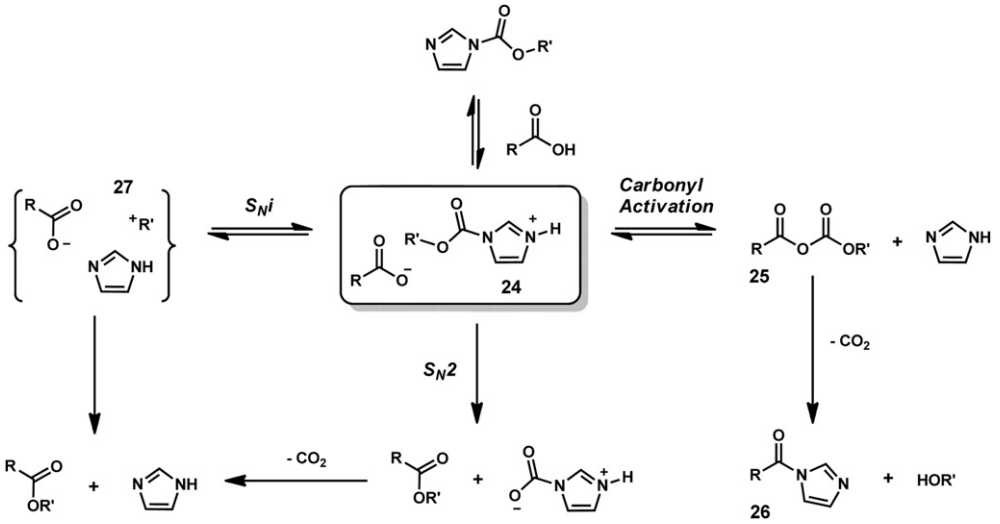
At the outset of our investigation of imidazole carbamates as esterification reagents we considered three mechanistic possibilities (Scheme 6). Cognizant of the early work of Staab and coworkers,[5,17] we reasoned that the imidazole carbamate could first be protonated to generate an ion pair (**24**), which could decompose through attack of the carboxylate ion on the R group, expelling CO_2 and imidazole through a formal S_N2 mechanism. Alternatively, we could not rule out the possibility that the postulated imidazolium carbamate intermediate (**24**) could ionize to a carbocation (**27**) that could then be trapped by the tightly bound carboxylate anion, a mechanistic possibility borne out in the studies on the S_Ni mechanism by Cowdrey,[18] Lewis,[19] and Cram.[20] Finally, this intermediate ion pair could collapse through carboxylate attack on the carbonyl of the imidazolium carbamate (see **24**). The resulting acylcarbonate **25** could then be re-engaged by liberated imidazole to generate an acylimidazole **26** along with a carbonic ester. The latter could undergo decarboxylation to unmask an alcohol that could then react with **26** to provide an ester.

The observation that imidazole is readily methylated by MImC under standard esterification reaction conditions seemed to indicate that an S_N2 pathway with imidazole carbamates acting as electrophiles was possible. However, small amounts of acylimidazole were often detected when the reaction was monitored by ^1H NMR.[21] Similarly, when 2-pyrrolecarboxylic acid (**28**) was treated with MImC (Scheme 7), it was converted to a mixture of the desired methyl ester (**29**) along with significant quantities of cyclic dimer **30**, which presumably arises through condensation of the pyrrole nitrogen with an activated ester intermediate.[22]



Scheme 7. Observations leading to the proposal of an activated ester intermediate.

Because substrate and reagent specific observations lent varying levels of support to all three hypotheses, we undertook a systematic mechanistic study. To that end, enantioenriched imidazole carbamate **31** (Scheme 7) was reacted with benzoic acid to afford **32** with essentially complete retention of stereochemical information.[23] Furthermore, MImC, the imidazole carbamate most likely to undergo an S_N2 displacement, methylated $^{18}O_2$-benzoic acid (**33**) to provide ^{18}O-methyl benzoate (**34**), where one oxygen label had been lost. These two results were inconsistent with an S_N2 mechanism.[24] Similarly, allylation of **33** with allyl imidazole carbamate (**6b**), a reagent expected to generate a relatively stabilized carbocation, yielded ^{18}O-allyl benzoate (**35**), contradicting the operation of an S_Ni mechanism. Rather, the outcome of these isotopic labeling experiments lends strong support to a mechanism involving an activated ester intermediate.

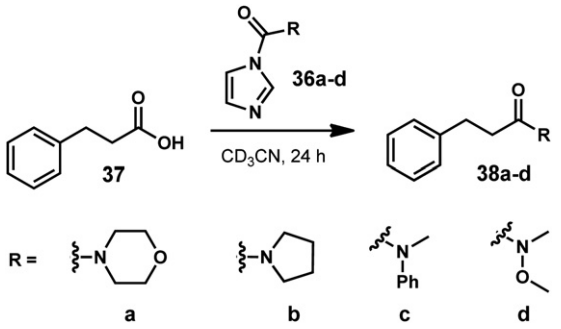


Scheme 6. Possible mechanisms for imidazole carbamate-mediated esterification.

2.3. Amidation

A synthetically useful consequence of this mechanistic investigation was the insight that if a mechanism proceeding through an activated intermediate (e.g., **25**, Scheme 6) was indeed operative, the group lost during formation of an acylimidazole (**26**) could undergo decarboxylation and the resulting species, if nucleophilic, could engage **26**. Therefore, an immediate extension was to change the heteroatom of the nucleophile from an oxygen to a nitrogen, which would result in an amide. To test this potential outcome, a series of unsymmetrical ureas (**36a**–**d**, Table 7) were prepared according to the method reported by Batey.[4] These reagents were then treated with hydrocinnamic acid (**37**) and the reactions were monitored by ^{1}H NMR. Surprisingly, only *N*-methoxy urea **36d** efficiently mediated amidation under typical conditions used in the esterification reaction. Increased temperature led to somewhat higher conversions for recalcitrant imidazole ureas, such as **36a** or **36b** (entries 1–4).

Table 7
Amidation of hydrocinnamic acid with imidazole ureas



Entry	R	Temp (°C)	Conversion (%)
1	**a**	80	19
2	**a**	100	45
3	**b**	80	0
4	**b**	100	17
5	**c**	80	0
6	**d**	80	>95 (93)[a]

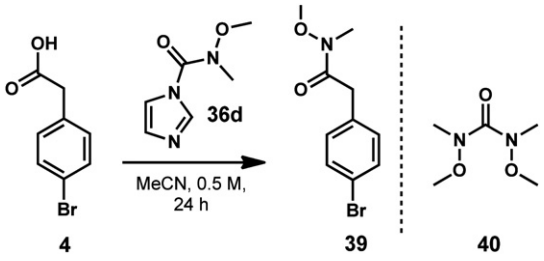
Conversions based on integration of resonances in the ^{1}H NMR spectra.
[a] Isolated yield in parentheses.

In all cases, only the expected hydrocinnamic amide product (**38a**–**d**), the unsymmetrical urea (**36a**–**d**), and imidazole were observed during the course of the reaction. This result suggests that collapse of the initial ion pair may slow as the carbonyl of the imidazole reagent becomes less electrophilic. In this regard, a parallel can be drawn between the known reactivity differences between the Weinreb amide and tertiary amides without α-heteroatoms and the observed difference between carbonyl-1-(*N*,*O*-dimethylhydroxylamino)-1-imidazole (WImC, **36d**) and **36a**–**c**.[25]

Given the utility of Weinreb amides, we moved forward and optimized the amidation of carboxylic acids with WImC. As before, we found the reaction to be highly temperature dependent, with no observable reaction occurring at room temperature (Table 8, entries 1–4). Reducing the number of equivalents of amidation reagent **36d** led to the finding that a slight excess was sufficient for synthetically useful transformations (entry 7).[26] The mass balance of the WImC-mediated Weinreb amide synthesis was good, and the only observable products were imidazole, the desired product **39**, and a trace amount of symmetrical urea **40** arising from addition of liberated *N*,*O*-dimethylhydroxylamine to WImC.[27]

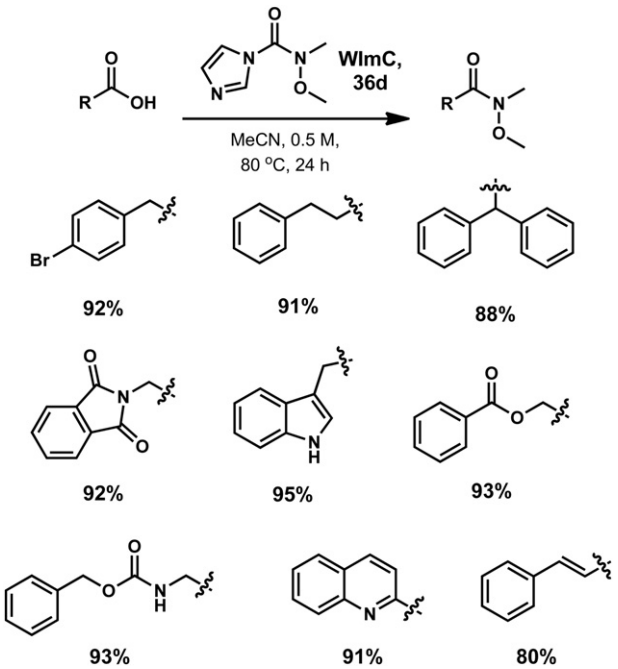
The substrate scope for amidation with WImC was broad, and a number of previously challenging substrates were converted to their Weinreb amide analogues in excellent yields;[28] however, highly sterically encumbered acids, such as 1-methyl-1-cyclohexanecarboxylic acid, did not undergo efficient amidation. In general, the amidation reaction appears to be chemoselective as esters, unprotected indoles, carbamate protected amines, and even electrophilic carbonyls, such as those in phthalimide, are well tolerated (Scheme 8).[8]

Table 8
Optimization of the synthesis of Weinreb amides using WImC



Entry	Temp (°C)	WImC (equiv)	Conversion (%)
1	22	2.0	0
2	40	2.0	52
3	60	2.0	82
4	80	2.0	>95
5	80	1.0	80
6	80	1.1	86
7	80	1.2	93
8	80	1.3	>95
9	22	2.0	11[a]

Conversions based on integration of resonances in the ^{1}H NMR spectra.
[a] DMAP (20 mol %) added.



Scheme 8. Scope of the Weinreb amide synthesis using WImC.

Even though we have not carried out a detailed mechanistic investigation on the amidation reaction, it likely proceeds through a pathway similar to that postulated for imidazole carbamate-mediated esterification. Unlike the esterification reaction, we

found that amidation is slowed by higher pressures of CO_2. This may be due to a shift in the equilibrium of the decarboxylation of a carbamic acid intermediate.[29]

3. Conclusion

We have demonstrated that imidazole-based reagents can mediate efficient esterification of carboxylic acids. The reaction is typically high yielding and generates minimal waste. New reagents have also been introduced for the esterification of α,β-unsaturated acids. Limitations of this method include the epimerization of α-chiral acid substrates and the use of tertiary imidazole carbamates. Amidation reagents have also been reported, but only relatively activated imidazole ureas afford amide products in synthetically useful yields. The mechanism of the esterification reaction was studied using stereochemical and isotopic labeling techniques, which support the intermediacy of an activated ester, such as an acylimidazole.

4. Experimental section

4.1. General experimental

Unless stated otherwise, reactions were performed in oven-dried glassware sealed with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stir bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF), toluene, acetonitrile (MeCN), and dimethylformamide (DMF) were dried by passage over a column of activated alumina; dichloromethane was distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Thin layer chromatography was performed using silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation and anisaldehyde or potassium permanganate stain. Sorbent silica gel (particle size 40–63 μm) was used for flash chromatography. Enantiomeric ratios were measured by an HPLC instrument equipped with SPD-M10A microdiode array detector using a Chiral PAK AD-H column. NMR experiments were performed on spectrometers operating at 300, 400 or 500 MHz for ^{1}H and 75, 100, or 125 MHz for ^{13}C experiments. ^{1}H and ^{13}C chemical shifts (δ) are reported relative to the residual solvent signal. Data are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet), br s (broad singlet). Compounds not listed below have been reported previously.[8]

4.2. General esterification procedure

Carboxylic acid (0.5 mmol) and MImC (**2a**, 1.0 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread. A magnetic stirbar was added, followed by dry MeCN (1.0 mL), and the vial was quickly sealed with a plastic cap (*gas is evolved during the course of the reaction! All experiments should be performed behind a blast shield if a sealed container is used*!). The reaction mixture was then stirred at 23 °C for 15 min and then heated to 80 °C using a heating block for 24 h. The mixture was cooled to room temperature and then the vial was carefully opened (*CAUTION*: *vial under pressure*!). The volatiles were removed in vacuo, the resulting residue was dissolved in diethyl ether (20 mL), and then washed with 1 M HCl (10 mL). The aqueous layer was back-extracted with diethyl ether (20 mL) and the organic fractions were combined, washed with a saturated solution of $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated in vacuo to afford the desired ester.

4.3. General amidation procedure

Carboxylic acid (0.5 mmol) and WImC (**36d**, 0.75 mmol) were placed in a dry 20 mL vial with a Teflon tape-coated thread. A magnetic stirbar was added, and then MeCN (1.0 mL) was added, and the vial was quickly sealed with a plastic cap (*gas is evolved during the course of the reaction! All experiments should be performed behind a blast shield if a sealed container is used*!). The reaction mixture was then heated with stirring to 80 °C and held at this temperature in a heating block for 24 h. The mixture was cooled to room temperature and then the vial was carefully opened (*CAUTION*: *vial under pressure*!). The volatiles were removed in vacuo, the resulting residue was dissolved in diethyl ether (20 mL), and then washed with 1 M HCl (10 mL). The aqueous layer was back-extracted with diethyl ether (20 mL) and the organic fractions were combined, washed with a saturated solution of $NaHCO_3$ and then brine, dried over $MgSO_4$, and concentrated in vacuo to afford the desired ester. Minor amounts of 1,3-dimethoxy-1,3-dimethylurea were removed by heating the crude product mixture at 50 °C under high vacuum for several hours. (*NOTE*: 1,3-*dimethoxy*-1,3-*dimethylurea* can *also be removed by column chromatography if the product amide is also volatile*.)

4.4. Reaction of imidazole carbamates with imidazole

Imidazole carbamate (1 equiv) and imidazole (2 equiv) were dissolved in CD_3CN to make a 0.5 M solution with respect to imidazole carbamate in a 4 mL screwcap vial. The vial was then sealed and the mixture was heated to 80 °C for 16 h. The reaction mixture was cooled and an aliquot was removed and analyzed by ^{1}H NMR.

4.5. Reaction of imidazole carbamates with phenols

Imidazole carbamate (2 equiv) and phenol (1 equiv) were dissolved in CD_3CN to make a 0.5 M solution with respect to phenol in a 4 mL screwcap vial. The vial was then sealed and the mixture was heated to 80 °C for 24 h. The reaction mixture was cooled and an aliquot was removed and analyzed by ^{1}H NMR.

*4.5.1. Cyclopropylmethyl 1-imidazolecarboxylate (**2i**).* 1,1′-Carbonyldiimidazole (2.20 g, 13.6 mmol) was dissolved in DCM (40 mL) and the resulting solution was stirred with cooling to 0 °C. A solution of cyclopropanemethanol (0.81 g, 11.2 mmol) in DCM (10 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 16 h. The homogeneous mixture was then diluted with DCM (100 mL), washed with water (2×20 mL), dried over $MgSO_4$, and concentrated in vacuo to afford a colorless oil (1.78 g, 96%), contaminated with a small amount of imidazole. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.44 (s, 1H), 7.06 (s, 1H), 4.23 (d, J=7.5 Hz, 2H), 1.35–1.19 (m, 1H), 0.73–0.60 (m, 2H), 0.49–0.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 137.1, 130.5, 117.1, 73.3, 9.6, 3.5. HRMS-EI (70 eV) m/z: M^+ calcd for $C_8H_{10}N_2O_2$, 166.0743; found 166.0742.

*4.5.2. Cyclopropylmethyl 4-bromophenylacetate (**5i**).* Prepared using the general esterification procedure using 4-bromophenylacetic acid (0.108 g, 0.5 mmol) to yield a pale yellow oil (0.112 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=8.3 Hz, 2H), 7.17 (d, J=8.3 Hz, 2H), 3.92 (d, J=7.3 Hz, 2H), 3.59 (s, 2H), 1.21–1.02 (m, 1H), 0.66–0.45 (m, 2H), 0.30–0.20 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.2, 133.1, 131.6, 131.0, 121.0, 69.8, 40.7, 9.7, 3.2. HRMS-EI (70 eV) m/z: M^+ calcd for $C_{12}H_{13}O_2Br$, 268.0099; found 268.0098.

*4.5.3. Methyl 2-methyl-1-imidazolecarboxylate (**14b**).* 2-Methylimidazole (10.6 g, 129 mmol) was dissolved in 120 mL dry THF and the mixture was stirred at 0 °C. Methyl chloroformate (5.0 mL,

65 mmol) was added dropwise and the resulting mixture was stirred and allowed to warm to room temperature over 16 h. The reaction mixture was concentrated to a slurry and 200 mL hexanes was added. The heterogeneous mixture was filtered through Celite, the filtrate was dried with Na_2SO_4, filtered, and concentrated in vacuo to afford a pale yellow oil (8.21 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=1.8 Hz, 1H), 6.84 (d, J=1.8 Hz, 1H), 3.97 (s, 3H), 2.63 (s, 3H). Spectra were consistent with those reported previously.[30]

*4.5.4. Methyl 2-ethyl-1-imidazolecarboxylate (**14c**).* Prepared by analogy to methyl 2-methyl-1-imidazolecarboxylate using 2-ethylimidazole to yield a pale yellow oil (3.50 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H), 3.02 (q, J=7.4 Hz, 2H), 1.31 (t, J=7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.8, 149.9, 127.8, 118.0, 54.3, 23.2, 11.5. HRMS-EI (70 eV) m/z: M^+ calcd for $C_7H_{10}N_2O_2$, 154.0742; found 154.0742.

*4.5.5. Methyl 2-isopropyl-1-imidazolecarboxylate (**14d**).* Prepared by analogy to methyl 2-methyl-1-imidazolecarboxylate using 2-isopropylimidazole to yield a pale yellow oil (3.73 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J=1.8 Hz, 1H), 6.87 (d, J=1.7 Hz, 1H), 3.97 (s, 3H), 3.67 (hept, J=6.8 Hz, 1H), 1.31 (d, J=6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.7, 149.8, 127.6, 118.0, 54.3, 28.1, 21.2. HRMS-EI (70 eV) m/z: M^+ calcd for $C_8H_{12}N_2O_2$, 168.0899; found 166.0900.

*4.5.6. Z-Gly-OEt (**6b**).* Prepared using the general amidation procedure with *Z*-Gly-OH (0.105 g, 0.5 mmol) to obtain a colorless syrup (0.106 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 5.26 (br s, 1H), 5.13 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 4.06–3.89 (m, 2H), 1.28 (t, J=7.2 Hz, 3H). Spectra were consistent with those reported previously.[31]

*4.5.7. Z-Gly-OAllyl (**6d**).* Prepared using the general amidation procedure with *Z*-Gly-OH (0.105 g, 0.5 mmol) to obtain a colorless syrup (0.113 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.27 (m, 6H), 5.91 (ddt, J=19.2, 10.8, 5.8 Hz, 1H), 5.43–5.20 (m, 3H), 5.13 (s, 3H), 4.70–4.59 (m, 2H), 4.02 (d, J=5.6 Hz, 2H). Spectra were consistent with those reported previously.[32]

*4.5.8. Ethyl 4-bromobenzoate (**7b**).* Prepared using the general esterification procedure using 4-bromobenzoic acid (0.100 g, 0.5 mmol) in DMF (1 mL) to yield a colorless syrup (0.099 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J=8.5 Hz, 2H), 7.57 (d, J=8.5 Hz, 2H), 4.37 (q, J=7.1 Hz, 2H), 1.39 (t, J=7.1 Hz, 3H). Spectra were consistent with those reported previously.[33]

*4.5.9. Allyl 4-bromobenzoate (**7d**).* Prepared using the general esterification procedure using 4-bromobenzoic acid (0.100 g, 0.5 mmol) in DMF (1 mL) to yield a pale yellow syrup (0.115 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J=8.5 Hz, 2H), 7.58 (d, J=8.5 Hz, 2H), 6.02 (ddt, J=16.6, 10.9, 5.7 Hz, 1H), 5.48–5.18 (m, 2H), 4.81 (d, J=5.6, 2H). Spectra were consistent with those reported previously.[34]

*4.5.10. (R)-Naproxen methyl ester (**9**).* (*R*)-Naproxen (0.349 g, 1.52 mmol) was dissolved in MeOH (10 mL) and then concentrated sulfuric acid (0.1 mL) was added dropwise. The resulting solution was heated to 60 °C for 12 h and then cooled to room temperature. K_2CO_3 (0.50 g) was added and the heterogeneous mixture was stirred for 5 min and then diluted with Et_2O (50 mL). The mixture was filtered and the filtrate was concentrated in vacuo to afford the title compound as a white solid (0.330 g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.71 (m, 2H), 7.69 (s, 1H), 7.43 (dd, J=8.5, 2.1 Hz, 1H), 7.17 (dd, J=8.5, 2.1 Hz, 1H), 7.13 (s, 1H), 3.97–3.85 (m, 4H), 3.69 (s, 3H), 1.61 (d, J=7.1 Hz, 2H). Spectra were consistent with those reported previously.[35] HPLC (99:1 hexanes/2-propanol), 1.0 mL/min, t_R 8.29 min (major), 9.05 min (minor), 99% ee. This chromatographic method was used to determine the enantiomeric excess of naproxen methyl ester produced using MImC as well as that from the treatment of enantiopure ester with imidazole.

*4.5.11. N-Methoxy-N-methylindole-3-acetamide (**41**).* Prepared using the general amidation procedure with 3-indoleacetic acid (0.088 g, 0.5 mmol) to obtain a white solid (0.104 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.65 (dd, J=7.7, 1.0 Hz, 1H), 7.34 (dd, J=8.1, 1.0 Hz, 1H), 7.22–7.08 (m, 3H), 3.92 (s, 2H), 3.67 (s, 3H), 3.22 (s, 3H). Spectra were consistent with those reported previously[36]

*4.5.12. Z-Gly-N(Me)OMe (**42**).* Prepared using the general amidation procedure with *Z*-Gly-OH (0.105 g, 0.5 mmol) to obtain a colorless syrup (0.118 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.28 (m, 5H), 5.56 (br s, 1H), 5.13 (s, 2H), 4.15 (d, J=4.5 Hz, 2H), 3.72 (s, 3H), 3.20 (s, 3H). Spectra were consistent with those reported previously.[37]

*4.5.13. N-Methoxy-N-methylquinoline-2-carboxamide (**43**).* Prepared using the general amidation procedure with quinaldic acid (0.087 g, 0.5 mmol) to obtain a tan solid (0.098 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, J=8.4 Hz, 1H), 8.14 (d, J=8.5 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.76 (ddd, J=8.3, 7.0, 1.5 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 3.79 (s, 4H), 3.46 (s, 3H). Spectra were consistent with those reported previously.[38]

*4.5.14. N-Methoxy-N-methylcinnamamide (**44**).* Prepared using the general amidation procedure with cinnamic acid (0.074 g, 0.5 mmol) to obtain a colorless oil (0.076 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J=15.6 Hz, 1H), 7.60–7.56 (m, 2H), 7.40–7.34 (m, 3H), 7.07 (d, J=15.6 Hz, 1H), 3.75 (s, 3H), 3.30 (s, 3H). Spectra were consistent with those reported previously.[39]

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Supplementary data

Copies of ^{1}H spectra for **2i**, **5i**, **6b**, **6d**, **7b**, **7d**, **9**, **14b**–**d**, **41**–**44**, and copies of ^{13}C NMR for **2i**, **5i**, **14c**–**d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.057.

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