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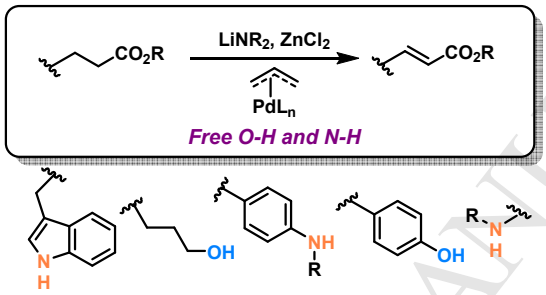

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ABSTRACT

A direct and selective method for the α,β-dehydrogenation of esters using palladium catalysis in the presence of free O-H and N-H functionalities is reported herein. Allyl-palladium catalysis allows for preservation of readily oxidizable functionalities such as amines and alcohols. Furthermore, an economical protocol using LDA was developed for the dehydrogenation of β-amino esters.

1. Introduction

Methodologies with defined chemoselectivity profiles are important for the practical synthesis of complex organic materials. In particular, the ability to oxidize a specific functional group in the presence of another allows for strategic orchestration of sequential synthetic transformations leading to efficient multistep syntheses. The functional group compatibility of methods to dehydrogenate carbonyl compounds has historically been limited to substrates that do not have other oxidation-prone functionalities owing to the strong, electrophilic oxidants employed in such methods.[1]

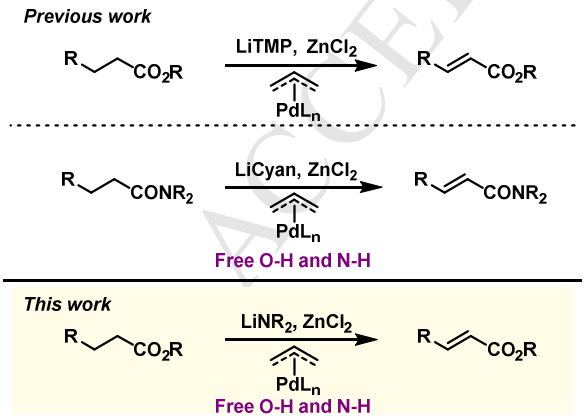

Figure 1. Allyl-palladium catalysis for carbonyl α,β-dehydrogenation

Our group has recently reported that a variety of carbonyl compounds, including esters[2a], can be transformed to their unsaturated counterparts via conversion to the zinc enolates and treatment with catalytic Pd(II) and stoichiometric allyl oxidant (Figure 1). Our initial report[2a] described the use of this approach for the dehydrogenation of nitriles and esters, and subsequently we demonstrated the applicability of this mechanistic paradigm to amides[2b], carboxylic acids[2c], and ketones[2d,2e]. Interestingly, we found in the case of amide dehydrogenation our method could tolerate oxidation-prone functionality such as unprotected alcohols and N-H containing amide substrates, which could readily undergo oxidation to the corresponding C=X systems.[2b] The key to obtaining complete conversion and synthetically useful yields was forming the dianion with lithium cyclohexyl(2,6-diisopropylphenyl)amide (LiCyan) used as a hindered amide base.

In this report, we extend our earlier findings to the dehydrogenation of O-H- and N-H-containing esters and additionally disclose a more cost-effective protocol using inexpensive LDA for the specific case of β-amino ester dehydrogenation. The success of allyl-palladium catalysis for these selective oxidation reactions is remarkable considering the known propensity for Pd(II) to coordinate to and even oxidize oxygen[3]- and nitrogen[4]-based nucleophiles.

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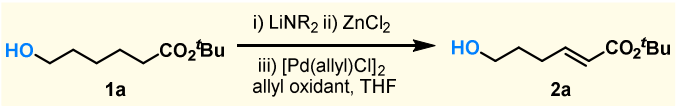
2. Results and Discussion

In our initial attempts to dehydrogenate ester **1a** in the presence of a free alcohol, reaction conditions previously reported by our group were examined (Table 1). The reaction proceeds via formation of a zinc enolate, transmetalation to Pd and subsequent β-hydride elimination. To our delight, the conditions reported for dehydrogenation of amides (Entry 1) in the presence of free O-H and N-H functionalities were successful and provided slightly improved conversion as compared to our original conditions for ester and nitrile dehydrogenation (Entries 2-3). $Zn(TMP)_2$ (Entries 4-5), which was utilized for the dehydrogenation of carboxylic acids and ketones, proved to be minimally effective for this transformation.

Table 1. Application of previously reported conditions



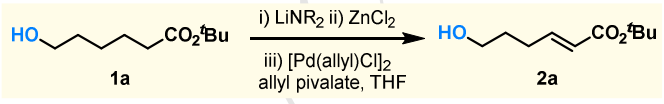
Entry	Conditions	Base	Allyl Oxidant	Yield (%)[a]
1	amides[2b]	LiCyan	-OAc	90%
2	esters[2a]	LiTMP	-OPiv	87%
3	nitriles[2a]	LiTMP	-OAc	80%
4	ketones[2d]	$Zn(TMP)_2$	$-OP(O)(OEt)_2$	21%
5	acids[2c]	$Zn(TMP)_2 \bullet 2LiCl$	-OAc	3%

[a]Yields were determined by ^{1}H-NMR analysis using dibromomethane as internal standard.

2.1 Optimization

Table 2 shows a further examination of reaction conditions for the dehydrogenation of **1a**. The combination of allyl pivalate and LDA (Entry 1) led to slightly higher conversion than allyl acetate and LDA (Entry 2). Additionally, LDA outperformed other commercial bases such as LHMDS (Entry 3), and $LiNCy_2$ (Entry 4). Nonetheless, the optimal conditions for this transformation utilize LiCyan as the lithium anilide base (Entry 5). Examination of the equivalents of base and $ZnCl_2$ additive (Entries 6-7) demonstrated that formation of the dianion with an excess of $ZnCl_2$ was critical to achieving high conversion.

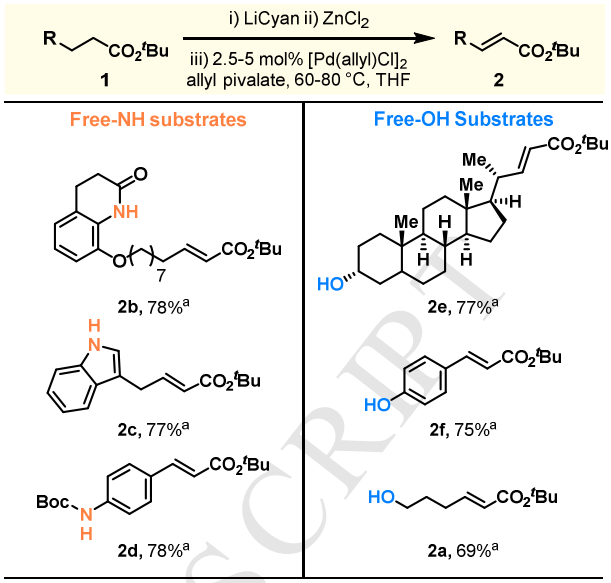
Table 2. Optimization of ester dehydrogenation



Entry	Base	Equiv Base	Equiv $ZnCl_2$	Yield (%)[a]
1	LDA	2.5	4.0	79
2	LDA[b]	2.5	4.0	72
3	LHMDS	2.5	4.0	51
4	$LiNCy_2$	2.5	4.0	43
5	LiCyan	2.5	4.0	89
6	LiCyan	2.5	2.0	62
7	LiCyan	1.2	4.0	0 (21)

[a]Yields were determined by ^{1}H-NMR analysis using dibromomethane as internal standard. Conversion is shown in parentheses. [b]Allyl acetate was used instead of allyl pivalate.

Figure 2. Scope of *tert*-butyl ester dehydrogenation



[a]Isolated yields.

With these conditions in hand, we evaluated a variety of *tert*-butyl esters with free O-H and N-H functionalities (Figure 2). A lactam (**2b**), indole (**2c**), and aniline (**2d**) were all tolerated and led to the generation of the dehydrogenated compound in high yields. Both secondary (**2e**) and primary alcohols (**2a**) remained intact as did a free phenol (**2f**).

More challenging methyl esters such as methyl 4-hydroxycyclohexane carboxylate proceeded with lower yields. This is partially due to lower solubility of the resultant dianion, as compared to the *tert*-butyl esters.

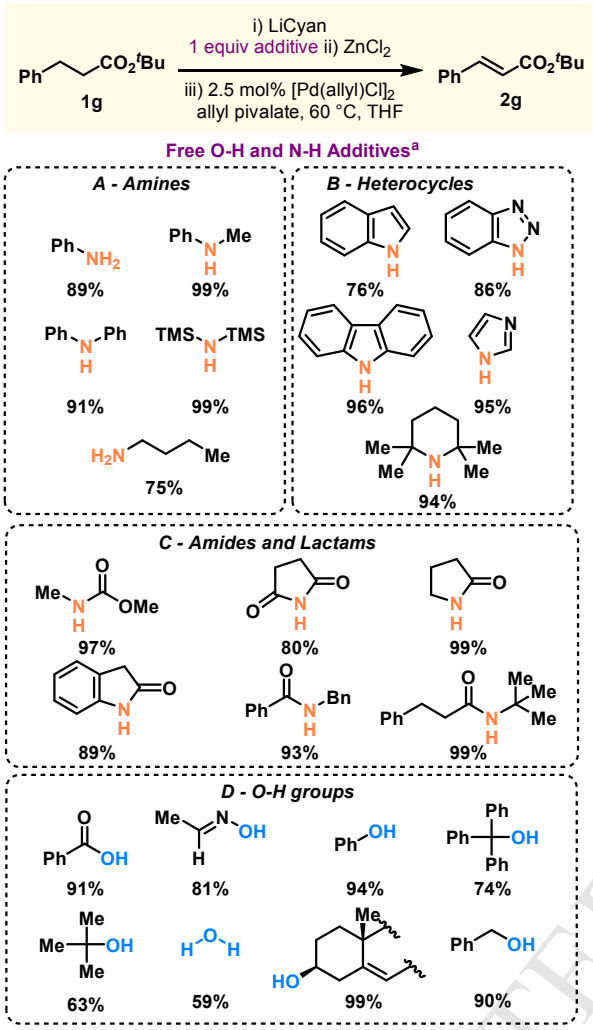
2.3 Intermolecular experiments

In order to further probe the scope of this reaction and demonstrate its robustness, a variety of commercial compounds with free O-H and N-H functionalities were introduced as additives to the standard reaction conditions for the dehydrogenation of ester **1g** with LiCyan (Figure 3).[5] The change in yield of the dehydrogenated product (**2g**) relative to the control experiment without an additive was evaluated by ^{1}H-NMR analysis. The yield of **2g** without additives is consistently around 99%. The additive was introduced directly after the starting material (**1g**), and an extra equivalent of the base presumably deprotonated the additive during the enolate formation stage. The reaction proceeded with good to excellent conversion in the presence of a variety of additives. Amines and anilines (Figure 3A) are well tolerated, as are a variety of nitrogen-based heterocycles (Figure 3B). Amides, carbamates, and lactams also did not impact the reaction (Figure 3C). Additives with free O-Hs such as carboxylic acids, oximes, and phenols (Figure 3D) showed minimal inhibition of the reaction. Alcohols such as cholesterol and even oxidation-prone benzyl alcohol remained intact without significantly affecting the dehydrogenation. Neither oxidation nor dehydrogenation of any these additives was observed.

The addition of thiophenol led to a decreased yield of **2g** to 44% however, thioanisole did not significantly inhibit the catalytic cycle providing 74% of **2g**. Water (Figure 3D) notably decreased the yield of **2g** to 59% suggesting that hydroxide affects the reaction beyond quenching the available base. These

intermolecular studies suggest a wider scope for the selective dehydrogenation of esters than what is demonstrated in Figure 2.

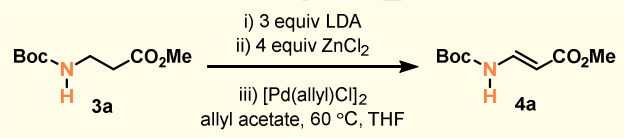
Figure 3. Intermolecular dehydrogenation in the presence of free O-H and N-H compounds



[a]Yields of **2g** were determined by ^{1}H-NMR analysis using dibromomethane as internal standard.

2.4 β-Amino ester optimization

Table 3. Optimization of β-amino ester dehydrogenation



Entry	Variation from Standard Conditions	Yield (%)[a]
1	none	81[b] (90)
2	6 equiv $ZnCl_2$	59 (88)
3	3 equiv LiCyan	75 (81)
4	3 equiv LiTMP	52 (60)
5	3 equiv $Zn(TMP)_2$, no $ZnCl_2$	0 (32)
6	3 equiv $Zn(TMP)_2$, 3 equiv $ZnCl_2$	0 (13)

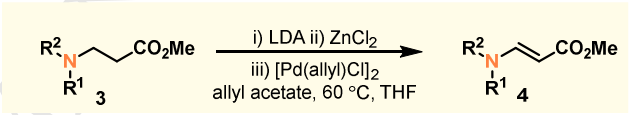
[a]Yields were determined by ^{1}H-NMR analysis using dibromomethane as internal standard. Conversions are in parentheses. [b]Isolated yield.

β-Amino acid derivatives are commonly occurring in unnatural peptides, natural products, and heterocyclic compounds. Incorporating β-amino acids into the peptide backbone of pharmaceutically active compounds has been shown to increase drug potency.[6] Dehydrogenation of these compounds is therefore a desirable transformation to aid in the synthesis of β-amino acid derivatives.[7] In the dehydrogenation of methyl ester **3a**, LDA outperformed LiCyan, LiTMP, and $Zn(TMP)_2$ (Table 3). With 4 equivalents of $ZnCl_2$, up to 90% conversion could be obtained. Moreover, LDA is an economical and process-friendly base for this transformation.

2.5 β-Amino ester dehydrogenation

In order to evaluate the scope of this transformation, a variety of β-amino methyl esters with common protecting groups were synthesized (Table 4). It was determined that mono-protected amino esters were more efficiently dehydrogenated than their diprotected analogues. For example, *N*,*N*-dibenzylated **3b** provided a significantly lower yield than substrate **3a**. In addition, β-amino esters protected with Cbz (**3c**), Piv (**3d**), and Bz (**3e**) groups underwent dehydrogenation in good to excellent yields. Substitution at the α- or β-positions led to decomposition of the starting materials under the reaction conditions.

Table 4. Scope of β-amino ester dehydrogenation



Substrate	R^1	R^2	Yield (%)[a]
3a	H	Boc	81
3b	Bn	Bn	55
3c	H	Cbz	90
3d	H	Piv	82
3e	H	Bz	75

[a]Isolated yields.

3. Conclusion

In conclusion, we have demonstrated the scope of ester dehydrogenation in the presence of free O-H and N-H functionalities. In addition, we have identified a highly practical and inexpensive protocol for the dehydrogenation of β-amino acid derivatives that may find utility in the synthesis of unnatural amino acids and peptides. The robustness and reliability of this reaction in the presence of a variety of coordinating groups provokes questions about the role and identity of the active palladium catalyst in these transformations. This study has also highlighted the unique interplay between the selection of amide base and allyl oxidant for efficient dehydrogenation of different substrates. These topics, along with further mechanistic studies, are currently under investigation in our laboratory.

4. Experimental

4.1 General experimental procedure

All reactions were carried out under an inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Reactions were capped with a rubber septum or Teflon–coated silicon microwave cap unless otherwise stated.

Stainless steel cannulas or syringes were used to transfer solvent and air-/moisture-sensitive reagents. Reactions were monitored by thin-layer chromatography (TLC) and carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as the visualizing agent. Potassium permanganate and an acidic solution of *p*-anisaldehyde were used as developing agents. Flash column chromatography employed SiliaFlash® P60 (40-60 μm, 230-400 mesh) silica gel purchased from SiliCycle Inc.

4.2 Materials

All reaction solvents were purified using a Seca solvent purification system by Glass Contour. The molarity of *n*-butyllithium solutions were determined by titration with *N*-benzylbenzamide. All other reagents were used as received without further purification, unless otherwise stated.

4.3 Instrumentation

All new compounds were characterized by means of R_f, ^1H NMR, ^{13}C NMR, FT-IR (thin film from CH_2Cl_2), and high-resolution mass spectroscopy (HR-MS). Copies of the ^1H and ^{13}C NMR spectra can be found in the Supplementary Material. NMR spectra were recorded using a Varian 400 MHz NMR spectrometer or a Varian 600 MHz NMR spectrometer. All ^1H NMR data are reported in δ units, parts per million (ppm), and were calibrated relative to the signal for residual chloroform (7.26 ppm) in deuterochloroform ($CDCl_3$). All ^{13}C NMR data are reported in ppm relative to $CDCl_3$ (77.16 ppm) and were obtained with ^1H decoupling. The following abbreviations or combinations thereof were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, br = broad, m = multiplet, and a = apparent. All IR spectra were taken on an FT-IR/Raman Thermo Nicolet 6700. HR-MS data was recorded on a Bruker microTOF mass spectrometer using ESI–TOF (electrospray ionization-time of flight).

4.4 Solutions

4.4.1 Zinc chloride stock solution (0.5 M in THF):

Finely powdered anhydrous $ZnCl_2$ (0.68 g, 5.0 mmol) was weighed into a 50-mL flame-dried flask in the glove box under an inert atmosphere. The flask was taken out of a glove box and placed under vacuum. The flask was heated with a heat gun for 2 min under vacuum and then back filled with nitrogen (this process was repeated 3 times). After the flask was cooled to ambient temperature, the flask was back filled with nitrogen, THF (10 mL) was added, and the suspension was vigorously stirred for 1-2 hours before it was used.

Note: Commercial 1.9 M $ZnCl_2$ solution in 2-Me THF and freshly prepared $ZnCl_2$ stock solution in THF can be used interchangeably.

4.4.2 Palladium stock solution:

$[Pd(allyl)Cl]_2$ was weighed into a flame dried vial which was evacuated and backfilled with nitrogen. Allyl oxidant and THF were added sequentially and the solution was stirred for 0.5-1 hour.

4.5 General Procedures

*4.5.1 General dehydrogenation of tert-butyl esters (**1**):*

To a –40 °C solution of *N*-cyclohexyl-2,6-diisopropylaniline (CyanH) (135 mg, 0.52 mmol, 2.6 equiv) in THF (4 mL, 0.05 M) was added *n*-butyllithium (0.20 mL, 0.50 mmol, 2.5 M in hexanes, 2.5 equiv). After 3-5 mins, the reaction mixture became cloudy and was stirred for 1 hour. A stock solution of the desired substrate (0.20 mmol, 1.0 equiv) in THF (0.4 mL, 0.5 M) was added, the reaction quickly became translucent, and was stirred for 1 hour more at the same temperature. A solution of $ZnCl_2$ (1.6 mL, 0.80 mmol, 0.5 M in THF, 4.0 equiv) was added, and the reaction was stirred for 1 hour. The stock solution of $[Pd(allyl)Cl]_2$ (1.8 mg, 0.0050 mmol, 2.5 mol %) and allyl pivalate (38 μL, 0.24 mmol, 1.2 equiv) in THF (0.2 mL, 1.2 M) was added. The reaction mixture was removed from the –40 °C bath, placed into a preheated oil bath, and stirred at least 12 hours until completion (as determined by TLC or ^1H NMR analysis). The reaction was cooled to room temperature and quenched by the addition of sat. aq. NH_4Cl (15 mL). The reaction mixture was diluted with EtOAc (5 mL) and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation.

*4.5.2 General dehydrogenation of β-amino esters (**3b**):*

To a –40 °C solution of diisopropylamine (56 μL, 0.40 mmol, 2.0 equiv) in THF (2.0 mL, 0.2 M) was added *n*-butyllithium (0.16 mL, 0.4 mmol, 2.5 M in hexanes, 2.0 equiv) and the reaction was stirred for 1 hour at the same temperature. A stock solution of desired substrate (0.20 mmol, 1.0 equiv) in THF (0.4 mL, 0.5 M) was slowly added, and the reaction mixture was stirred for 1 hour at –40 °C to form a light-yellow heterogeneous mixture. A solution of $ZnCl_2$ (0.42 mL, 0.80 mmol, 1.9 M in 2-MeTHF, 4.0 equiv) was added, and the reaction was stirred for 1 hour to give a homogeneous solution. The stock solution of $[Pd(allyl)Cl]_2$ (1.8 mg, 0.0050 mmol, 2.5 mol %) and allyl acetate (26.0 μL, 0.24 mmol, 1.2 equiv) in THF (0.2 mL, 1.2 M) was added. The reaction mixture was removed from the –40 °C bath, placed into a 60 °C preheated oil bath and stirred for 12 hours. The reaction was cooled to room temperature and quenched with the addition of sat. aq. NH_4Cl (15 mL). The reaction mixture was diluted with EtOAc (5 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation.

*4.5.3 General dehydrogenation of free N-H: β-amino esters (**3**):*

To a –40 °C solution of diisopropylamine (84 μL, 0.60 mmol, 3.0 equiv) in THF (2.5 mL, 0.24 M) was added *n*–butyllithium (0.24 mL, 0.60 mmol, 2.5 M in hexanes, 3.0 equiv), and the reaction was stirred for 1 hour at the same temperature. A stock solution of desired substrate (0.20 mmol, 1.0 equiv) in THF (0.4 mL, 0.5 M) was slowly added, and the reaction mixture was stirred for 1 hour at –40 °C to form a light-yellow heterogeneous mixture. A solution of $ZnCl_2$ (0.42 mL, 0.80 mmol, 1.9 M in 2-MeTHF, 4.0 equiv) was added and stirred for 1 hour to give a homogeneous solution. Then the stock solution of $[Pd(allyl)Cl]_2$ (1.8 mg, 0.0050 mmol, 2.5 mol %) and allyl acetate (26.0 μL, 0.24 mmol, 1.2 equiv) in THF (0.2 mL, 1.2 M) was added. The reaction mixture was removed from the –40 °C bath, placed into a 60 °C preheated oil bath and stirred for 12 hours. The reaction was cooled to room temperature and quenched with the addition of sat. aq. NH_4Cl (15 mL). The reaction mixture was diluted with EtOAc (5 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (10 mL), dried

over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation.

4.6 Substrate Synthesis

Esters **1a**[8], **1f**[9], **1g**[2a], **3a**[10], and **3b**[11] were synthesized according to previously published procedures.

*4.6.1 Allyl pivalate (**SI-1**)*

3-Bromopropene (50.0 mL, 0.60 mol, 3.0 equiv) was added to a flask containing K_2CO_3 (36.0 g, 0.26 mol, 1.3 equiv) and pivalic acid (20.4 g, 0.20 mol, 1.0 equiv). DMF (500 mL) was added. The mixture was stirred vigorously at ambient temperature for 48 hours. The reaction was diluted with water (1.0 L) and EtOAc (500 mL). The organic layer was separated and the aqueous phase was extracted with EtOAc (3 x 500 mL). The organic layers were combined and washed with water (500 mL) and brine (2 x 500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. The crude oil was distilled by vacuum distillation to yield allyl pivalate as a colorless oil (19.67 g, 69%). This procedure was modified from previous syntheses and spectral data values match those from the literature.[12] $\mathbf{R_f}$ = 0.69 (hexanes/EtOAc = 5:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.96–5.86 (m, 1H), 5.30 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.2 Hz 1H), 4.56 (dt, *J* = 5.6, 1.6 Hz, 2H) 1.22 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 178.3, 132.6, 117.6, 65.0, 38.9, 27.3 **IR** (cm^{-1}): 1730, 1280, 1144, 962, 930 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_8H_{15}O_2^+$: 143.1067; found: 143.1075.

*4.6.2 tert-butyl 11-((2-oxo-1,2,3,4-tetrahydroquinolin-8-yl)oxy)undecanoate (**1b**)*

tert-Butyl 11-bromoundecanoate was prepared according to a previously published procedure.[13] To a solution of *tert*-Butyl 11-bromoundecanoate (321 mg, 1.0 mmol, 1.0 equiv) in DMF (2.0 mL, 0.50 M) was added 7-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (163 mg, 1.0 mmol, 1.0 equiv) and K_2CO_3 (163 mg, 1.2 mmol, 1.2 equiv). The mixture was placed into a preheated 80 °C oil bath and stirred for 26 hours. The resulting mixture was cooled to room temperature and water (50 mL) was added, the mixture was diluted with EtOAc (80 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with water (100 mL), brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 3:1 to 2:1) afforded the title compound (258 mg, 64%) as an off-white solid. $\mathbf{R_f}$ = 0.22 (hexanes/EtOAc = 2:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.91 (ad, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.31 (br s, 1H), 3.91 (t, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 7.4 Hz, 2H), 1.78–1.72 (m, 2H), 1.62–1.55 (m, 2H), 1.44 (s, 9H), 1.44–1.39 (m, 2H), 1.29 (br s, 10H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.5, 171.7, 158.9, 138.2, 128.8, 115.7, 108.8, 102.3, 80.1, 68.3, 35.8, 31.3, 29.6, 29.5, 29.5, 29.4, 29.4, 29.2, 28.3, 26.1, 25.2, 24.7 **IR** (cm^{-1}): 2928, 1682, 1368, 1265, 1190, 1169 **ESI–HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{24}H_{38}NO_3^+$: 388.2846; found: 388.2826.

*4.6.3 tert-Butyl 4-(1H-indol-3-yl)butanoate (**1c**)*

This procedure was modified from a previous literature report.[2a] To a 0 °C solution of 4-(1*H*-indol-3-yl)butanoic acid (0.989 g, 4.9 mmol, 1.0 equiv) in CH_2Cl_2 (20.0 mL, 0.25 M) was added 4-dimethylaminopyridine (DMAP) (61.1 mg, 0.50 mmol, 0.1 equiv), *tert*-butanol (2.4 mL, 25 mmol, 5.0 equiv) and *N*,*N*′-dicyclohexylcarbodiimide (DCC) (1.12 g, 5.4 mmol, 1.1 equiv). After stirring for 5 min at 0 °C, the mixture was stirred for 17 hours at 23 °C. After filtration through Celite, the mixture was concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 6:1) afforded the title compound (0.556 g, 44%) as an off-white solid. $\mathbf{R_f}$ = 0.40 (CH_2Cl_2) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.99 (br s, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.99 (s, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.05–2.01 (m, 2H), 1.46 (s, 9H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.3, 136.5, 127.6, 122.0, 121.6, 119.3, 119.1, 116.0, 111.2, 80.2, 35.4, 28.3, 25.7, 24.6 **IR** (cm^{-1}): 3416, 2976, 1708, 1264, 1151 **ESI-HRMS** (*m/z*): $[M+Na]^+$ calc'd for $C_{16}H_{21}NNaO_2^+$: 282.1465; found: 282.1540.

*4.6.4 tert-Butyl 3-(4-((tert-butoxycarbonyl)amino)phenyl)propanoate (**1d**)*

3-(4-Aminophenyl)propanoic acid (1.0 g, 6.0 mmol, 1.0 equiv) was dissolved in dry THF (15 mL, 0.4 M). Di-*tert*-butyl dicarbonate (1.5 mL, 6.5 mmol, 1.1 equiv) was added and the reaction was stirred at ambient temperature for 12 hours. The solvent was removed by reduced pressure rotary evaporation. The residue was dissolved in CH_2Cl_2 (4.0 mL, 1.5 M) then DMAP (76 mg, 0.62 mmol, 0.10 equiv) and *tert*-butanol (0.72 mL, 7.5 mmol, 1.3 equiv) were added. A solution of DCC (1.57 g, 7.3 mmol, 1.2 equiv) in CH_2Cl_2 (6.0 mL, 1.0 M) was added to the solution of starting material. The reaction quickly became cloudy and was stirred for 2 hours more at ambient temperature. The reaction was filtered through a Celite plug, and concentrated under reduced pressure by rotary evaporation. Purification by flash chromatography on silica gel (hexanes/EtOAc = 10:1 to 8:1) afforded the titled compound as a white solid (1.42 g, 73%). $\mathbf{R_f}$ = 0.65 (hexanes/EtOAc = 2:1) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 7.18 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.53 (t, *J* = 7.8 Hz, 2H), 1.41 (s, 18H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 172.4, 153.0, 136.5, 135.6, 128.9, 80.5, 37.3, 30.6, 28.5, 28.2 **IR** (cm^{-1}): 2977, 1727, 1526, 1367, 1236, 1159 **ESI-HRMS** (*m/z*): $[M+Na]^+$ calc'd for $C_{18}H_{27}NaNO_4^+$: 344.1832; found: 344.1870.

*4.6.5 Lithocholic tert-butyl ester (**1e**)*

This procedure was modified from a previous literature report.[14] To a solution of lithocholic acid (1.01 g, 2.7 mmol, 1.0 equiv) in THF (24 mL, 0.12 M) at 0 °C, was added dropwise trifluoracetic anhydride (3.0 mL, 21 mmol, 7.8 equiv). After stirring for 1.5 hours at 0 °C, the mixture was treated with *tert*-butanol (7.0 mL, 73 mmol, 28 equiv) and let stir at 0 °C for 12 hours. The reaction was neutralized with sat. aq. NH_4OH (5 mL) and let stir at 23°C for 6 hours. The reaction was diluted with Et_2O (20 mL) and washed with aq. 1M NaOH (40 mL), water (40 ml), and brine (40 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Recrystallization from hot water gave lithocholic *tert*-butyl ester (1.03 g, 81%) as a white powder. $\mathbf{R_f}$ = 0.32 (hexanes/EtOAc = 3:1) **^{1}H NMR** (600 MHz, $CDCl_3$): δ 3.63-3.62 (m, 1H), 3.50 (br s, 1H) 2.28–2.23 (m, 1H), 2.15–2.09 (m, 1H), 1.96 (dt, *J* = 12.6, 3.0 Hz, 1H), 1.89–1.72 (m, 5H), 1.67–1.65 (m, 1H), 1.58–1.50 (m, 2H), 1.44 (s, 9H), 1.42–1.36 (m, 6H), 1.36–1.19 (m, 6H), 1.16–1.08 (m, 5H), 1.00–0.94 (m, 1H), 0.92 (s, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.64 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$): δ 173.9, 80.0, 72.0, 56.6, 56.2, 42.9, 42.2, 40.6, 40.3, 36.6, 36.0, 35.5, 35.5, 34.7, 32.7, 31.2, 30.7, 28.4, 28.3, 27.4, 26.6, 24.4, 23.5, 21.0, 18.4, 12.2 **IR** (cm^{-1}):

2928, 1729, 1264, 1150. **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{28}H_{49}O_3^+$: 433.3676; found: 433.3699.

*4.6.6 β-Cbz amino ester (**3c**)*

β-Alanine methyl ester[15] (515 mg, 5.0 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of methanol and water (20 mL, 0.25 M) then cooled to 0 °C. $NaHCO_3$ (1.1 g, 12.5 mmol, 2.5 equiv) was added to the stirred solution, followed by dropwise addition of CbzCl (2.2 mL, 15.0 mmol, 3.0 equiv). After stirring for 10 min at 0 °C, the reaction mixture was removed from the ice bath, warmed to ambient temperature, and stirred for 12 hours. The volatile organics were removed by rotary evaporation, the residue was diluted with EtOAc (30 mL) and sat. aq. NH_4Cl (50 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 3:1) afforded β-amino ester **3c** (749 mg, 64%) as a colorless oil. $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc = 3:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.38–7.29 (m, 5H), 5.29 (br s, 1H), 5.09 (s, 2H), 3.68 (s, 3H), 3.47 (q, *J* = 6.0 Hz, 2H), 2.55 (t, *J* = 6.0 Hz, 2H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.9, 156.4, 136.6, 128.6, 128.2, 128.2, 66.8, 51.9, 36.7, 34.4 **IR** (cm^{-1}): 3337, 2954, 1720, 1526, 1247, 698 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{12}H_{16}NO_4^+$: 238.1074; found: 238.1071.

*4.6.7 β-Piv amino ester (**3d**)*

β-Alanine methyl ester[15] (515 mg, 5.0 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL, 0.25 M) and cooled to 0 °C. Triethylamine (1.1 mL, 7.5 mmol, 1.5 equiv) was added to the stirred solution followed by dropwise addition of PivCl (0.80 mL, 6.5 mmol, 1.3 equiv). After stirring for 10 min at 0 °C, the reaction mixture was removed from the ice bath, warmed to room temperature, and stirred for 12 hours. The reaction was stopped by the addition of sat. aq. NH_4Cl (50 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 1:1) afforded β-amino ester **3d** (673 mg, 72%) as a white solid. $\mathbf{R_f}$ = 0.30 (hexanes/EtOAc = 1:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.30 (br s, 1H), 3.70 (s, 3H), 3.50 (q, *J* = 6.0 Hz, 2H), 2.53 (t, *J* = 6.0 Hz, 2H), 1.18 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 178.6, 173.5, 51.9, 38.8, 35.0, 33.9, 27.6 **IR** (cm^{-1}): 3364, 2956, 1740, 1642, 1528, 1174 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_9H_{18}NO_3^+$: 188.1281; found: 188.1279.

*4.6.8 β-Benzoyl amino ester (**3e**)*

β-Alanine methyl ester[15] (515 mg, 5.0 mmol, 1.0 equiv) was dissolved in THF (20 mL, 0.25 M) and cooled to 0 °C. Triethylamine (1.1 mL, 7.5 mmol, 1.5 equiv) was added to the stirred solution followed by dropwise addition of BzCl (0.76 mL, 6.5 mmol, 1.3 equiv). After stirring for 10 min at 0 °C, the reaction mixture was removed from the ice bath, warmed to room temperature, and stirred for 12 hours. The reaction was stopped by the addition of sat. aq. NH_4Cl (50 mL), diluted with EtOAc (15 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$ (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure by rotary evaporation. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 1:1) afforded β-amino ester **3e** (703 mg, 68%) as a white solid. $\mathbf{R_f}$ = 0.31 (hexanes/EtOAc = 1:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77–7.75 (m, 2H), 7.51–7.47 (m, 1H), 7.44–7.41 (m, 2H), 6.85 (br s, 1H), 3.73 (q, *J* = 6.0 Hz, 2H), 3.72 (s, 3H), 2.66 (t, *J* = 6.0 Hz, 2H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.5, 167.4, 134.5, 131.6, 128.7, 127.1, 52.0, 35.4, 33.9 **IR** (cm^{-1}): 3332, 1735, 1640, 1536, 1264, 702 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{11}H_{14}NO_3^+$: 208.0968; found: 208.0969.

4.7 Product Characterization

*4.7.1 tert-Butyl (E)-6-hydroxyhex-2-enoate (**2a**)*

The reaction was stirred at 60 °C for 16 hours. 5 mol% of $[Pd(allyl)Cl]_2$ was used. Purification by flash column chromatography on silica gel (hexanes/EtOAc = 6:1 to 1:3) afforded **2a** as a yellow oil (25.8 mg, 69%). $\mathbf{R_f}$ = 0.10 (hexanes/EtOAc = 3:1). The spectral data are consistent with those reported in the literature.[16] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90–6.83 (m, 1H), 5.77 (d, *J* = 15.2 Hz, 1H), 3.68 (br s, 2H), 2.31–2.25 (m, 2H), 1.76–1.69 (m, 2H), 1.48 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.1, 147.2, 123.6, 80.3, 62.2, 31.1, 28.5, 28.3 **IR** (cm^{-1}): 1710, 1368, 1264, 1149. **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{10}H_{19}O_3^+$: 187.1329; found: 187.1251.

*4.7.2 tert-Butyl (E)-11-((2-oxo-1,2,3,4-tetrahydroquinolin-8-yl)oxy)undec-2-enoate (**2b**)*

The reaction was stirred at 60 °C for 5 hours. 3.5 equiv LiCyan base were used. Purification by flash column chromatography on silica gel (hexanes/ EtOAc = 10:1 to 2:1) afforded the title product as a white solid (31 mg, 78%). $\mathbf{R_f}$ = 0.22 (hexanes/EtOAc = 2:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.85 (dt, *J* = 15.6, 7.2 Hz, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.73 (d, *J* = 15.6 Hz, 1H), 3.91 (t, *J* = 6.8 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.74 (quin, *J* = 7.6 Hz, 2H), 1.47–1.28 (m, 19H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 172.3, 166.3, 158.9, 148.2, 138.3, 128.7, 123.0, 115.7, 108.8, 102.4, 80.1, 68.2, 32.1, 31.2, 29.4, 29.3, 29.2, 28.3, 28.2, 26.1, 24.7 **IR** (cm^{-1}): 2855, 1681, 1368, 1264, 1162 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{24}H_{36}NO_3^+$: 386.2690; found: 386.2371.

*4.7.3 tert-Butyl (E)-4-(1H-indol-3-yl)but-2-enoate (**2c**)*

The reaction was stirred at 90 °C for 12 hours. 5 mol% of $[Pd(allyl)Cl]_2$ was used. 3.0 equiv of LiCyan were used. Purification by flash column chromatography on silica gel (hexanes/Et_2O = 6:1) afforded the product as a pale-yellow solid (39.8 mg, 77%). $\mathbf{R_f}$ = 0.40 (CH_2Cl_2) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (br s, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.15–7.05 (m, 2H), 7.03 (s, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 3.63 (d, *J* = 6.4 Hz, 2H), 1.46 (s, 9H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 166.3, 146.3, 136.4, 127.3, 122.3, 119.7, 119.0, 112.5, 111.3, 80.3, 28.3, 28.1 **IR** (cm^{-1}): 3410, 1695, 1392, 1264, 1154 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{16}H_{20}NO_2^+$: 258.1489; found: 258.2284.

*4.7.4 tert-Butyl (E)-3-(4-((tert-butoxycarbonyl)amino)phenyl)acrylate (**2d**)*

The reaction was stirred at 80 °C for 16 hours. 5 mol% of $[Pd(allyl)Cl]_2$ was used. Purification by flash column chromatography on silica gel (hexanes/Et_2O = 9:1) afforded the product as an off white solid (50.0 mg, 78%). $\mathbf{R_f}$ = 0.15 (hexanes/Et_2O = 6:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 16.0 Hz, 1H) ,7.44 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.56 (s, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 1.52 (s, 18H) **^{13}C NMR** (151 MHz, $CDCl_3$): δ 166.7, 152.5, 143.1, 140.1, 129.5, 129.1, 118.6, 118.4, 80.5, 28.4, 28.4 **IR** (cm^{-1}): 2977,

1705, 1522, 1319, 1149 **ESI-HRMS** (*m/z*): $[M+Na]^+$ calc'd for $C_{18}H_{25}NNaO_4^+$: 342.1676; found: 342.1649.

*4.7.5 Lithocholic (E)-tert-butylenoate (**2e**)*

The reaction was stirred at 60 °C for 16 hours. Purification by flash column chromatography on silica gel (hexanes/Et_2O 3:1) afforded the product as a white foam (64.8 mg, 77%). $\mathbf{R_f}$ = 0.32 (hexanes/EtOAc = 3:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.72 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.64 (d, *J* = 15.6 Hz, 1H), 3.66–3.59 (m, 1H), 2.27–2.19 (m, 1H), 1.96–1.93 (m, 1H), 1.97–1.65 (m, 6H), 1.48 (s, 9H), 1.44–1.18 (m, 15H), 1.07–1.05 (m, 5H), 0.92 (s, 3H), 0.67 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 166.7, 153.7, 120.7, 80.1, 72.0, 56.5, 55.3, 43.1, 42.2, 40.6, 40.2, 39.7, 36.6, 36.0, 35.5, 34.7, 30.7, 28.4, 28.3, 27.3, 26.5, 24.4, 23.5, 20.9, 19.4, 12.4 **IR** (cm^{-1}): 2928, 1713, 1366, 1151 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{28}H_{47}O_3^+$: 431.3520; found: 431.3531.

*4.7.6 tert-Butyl (E)-3-(4-hydroxyphenyl)acrylate) (**2f**)*

The reaction was stirred at 80 °C for 16 hours. Purification by flash column chromatography on silica gel (hexanes/ Et_2O = 5:1) afforded the product as a pale-yellow oil (33.1 mg, 75%). The spectral data are consistent with those reported in the literature.[17] $\mathbf{R_f}$ = 0.31 (hexanes/EtOAc = 3:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 16.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.23 (d, *J* = 16.0 Hz, 1H), 5.36 (br s, 1H), 1.53 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.3, 143.3, 129.9, 117.9, 115.9, 110.2, 80.5, 31.7, 31.4, 29.9, 28.4, 22.8 , **IR** (cm^{-1}): 2977, 1674, 1604, 1514, 1264, 1146, **ESI-HRMS** (*m/z*): $[M+Na]^+$ calc'd for $C_{13}H_{16}NaNO_3^+$: 243.0992; found: 243.1012.

*4.7.7 Methyl (E)-3-((tert-butoxycarbonyl)amino)acrylate (**4a**)*

Purification by flash column chromatography on silica gel (hexanes/EtOAc = 11:1) afforded the title product as a light-yellow oil (32.6 mg, 81%). The spectral data are consistent with those reported in the literature.[18] $\mathbf{R_f}$ = 0.50 (hexanes/EtOAc = 7:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.58 (br s, 1H), 7.23 (t, *J* = 10.4 Hz, 1H), 5.00 (d, *J* = 8.8 Hz, 1H), 3.70 (s, 3H), 1.48 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.6, 152.3, 140.6, 93.6, 82.1, 51.2, 28.2 **IR** (cm^{-1}): 3342, 2980, 1740, 1689, 1634, 1380, 1211, 1147, 802 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_9H_{16}NO_4^+$: 202.1074; found: 202.1078.

*4.7.8 Methyl (E)-3-(dibenzylamino)acrylate (**4b**)*

Purification by flash column chromatography on silica gel (hexanes/EtOAc = 5:1) afforded the title product as a pale-yellow solid (30.9 mg, 55%). The spectral data are consistent with those reported in the literature.[19] $\mathbf{R_f}$ = 0.22 (hexanes/EtOAc = 5:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 13.2 Hz, 1H), 7.36–7.28 (m, 6H), 7.18–7.16 (m, 4H), 4.80 (d, *J* = 13.2 Hz, 1H), 4.30 (s, 4H), 3.67 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 170.3, 152.9, 136.1, 128.9, 127.9, 127.6, 85.6, 50.7 **IR** (cm^{-1}): 2946, 1688, 1609, 1350, 1142, 791, 698 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{18}H_{20}NO_2^+$: 282.1489; found: 282.1488.

*4.7.9 Methyl (E)-3-(((benzyloxy)carbonyl)amino)acrylate (**4c**)*

Purification by flash column chromatography on silica gel (hexanes/EtOAc = 20:1) afforded the title product as a light-yellow oil (42.3 mg, 90%). $\mathbf{R_f}$ = 0.25 (hexanes/EtOAc = 11:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.81 (br s, 1H), 7.39–7.34 (m, 5H), 7.28 (t, *J* = 10.0 Hz, 1H), 5.22 (s, 2H), 5.07 (d, *J* = 8.4 Hz, 1H), 3.71 (s, 3H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 169.3, 153.4, 140.2, 135.4, 128.7, 128.7, 128.4, 94.9, 68.1, 51.3 **IR** (cm^{-1}): 3326, 2952, 1740, 1686, 1632, 1392, 1174, 697 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{12}H_{14}NO_4^+$: 236.0917; found: 236.0914.

*4.7.10 Methyl (E)-3-pivalamidoacrylate (**4d**)*

Purification by flash column chromatography on silica gel (hexanes/EtOAc = 13:1) afforded the title product as a light-yellow oil (30.4 mg, 82%). $\mathbf{R_f}$ = 0.23 (hexanes/EtOAc = 11:1) **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.83 (br s, 1H), 7.52 (dd, *J* = 10.8, 8.8 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 3.73 (s, 3H), 1.27 (s, 9H) **^{13}C NMR** (101 MHz, $CDCl_3$): δ 177.0, 170.0, 139.2, 96.0, 51.4, 39.4, 27.3 **IR** (cm^{-1}): 3340, 2963, 1683, 1622, 1378, 1201, 1154, 805, 703 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_9H_{16}NO_3^+$: 186.1125; found: 186.1126.

*4.7.11 Methyl (E)-3-benzamidoacrylate (**4e**)*

Purification by flash column chromatography on silica gel (hexanes/EtOAc = 13:1) afforded the title product as a white solid (30.8 mg, 75%). $\mathbf{R_f}$ = 0.20 (hexanes/EtOAc = 11:1). The spectral data are consistent with those reported in the literature.[20] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.47 (br s, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.75 (dd, *J* = 11.0, 8.5 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 5.27 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H) **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.1, 164.6, 139.1, 133.0, 132.3, 129.0, 127.8, 96.8, 51.5 **IR** (cm^{-1}): 3332, 2950, 1682, 1619, 1378, 1180, 805, 694 **ESI-HRMS** (*m/z*): $[M+H]^+$ calc'd for $C_{11}H_{12}NO_3^+$: 206.0812; found: 206.0811.

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Supplementary material

Appendix A: Supplementary data related to this article can be found at DOI…