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Palladium-catalyzed substitution reactions of 4-allylimidazole derivatives

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Abstract—In the context of synthetic studies toward the oroidin family of pyrrole–imidazole alkaloids, we required an efficient method for conducting substitution reactions of allylic alcohols derived from urocanic acid. While in some cases this could be accomplished quite readily by classical nucleophilic substitution, it was complicated by allylic transposition in others. Application of Pd-catalyzed π–allyl chemistry provided a convenient solution, giving substitution without allylic transposition. Herein we describe the scope of this reaction in imidazole-containing substrates, and the elaboration of one adduct into a homologated histidine derivative, and into a cyclic homohistidine derivative.

1. Introduction

Marine sponges have proven to be remarkable sources of natural products displaying complex and diverse architectures, coupled with important biological activities.[1] Among these is a small family of pyrrole–imidazole natural products, collectively known as the oroidin alkaloids.[2] This family of marine alkaloids, which are thought to be biogenetically derived from oroidin and congeners (**1**–**3**, Fig. 1), presents numerous challenges to organic synthesis due to their often complex architecture and the presence of sensitive functional groups. Among the more complex members of this family of pyrrole–imidazole natural products are the dimeric palau'amine (**4**),[3,4] axinellamine A (**5**),[5,6] and massadine (**6**, Fig. 1),[7] which contain various types of ring fusions, and each possesses a densely functionalized cyclopentane ring. Inspired by these molecules, our lab has been engaged in developing approaches to these targets, and has reported on a Diels–Alder-rearrangement strategy (Fig. 2) involving vinylimidazoles as a means to access the spiro-fused ring system characteristic of **4**–**6**.[8,9]

In the course of implementing this strategy, it was found that the more electron-rich substrates participated in the oxidative rearrangement chemistry more efficiently (**10**→**11**, Fig. 2);[8d] however, the preparation of such substrates was often plagued by difficulties. For example, the DMAS-protected phthalimide **13** could be obtained readily from the corresponding alcohol **12** through either Mitsunobu chemistry or via the in situ preparation of the allyl chloride and reaction with potassium phthalimide (Scheme 1).[8c,10] Whereas, in contrast, the Bn-protected phthalimide **15** derivative could only be obtained in relatively low yield via either pathway (Gabriel route is shown in Scheme 1). The attenuated yield was due to competitive substitution providing the transposed product.[11] The MOM-protected phthalimide **17** can be obtained via the Gabriel pathway in moderate yields, but similar problems with allylic transposition occur during the preparation of *N*-alkoxyphthalimide **18**, where **19** forms in substantial amounts. Access to **18** was required for the

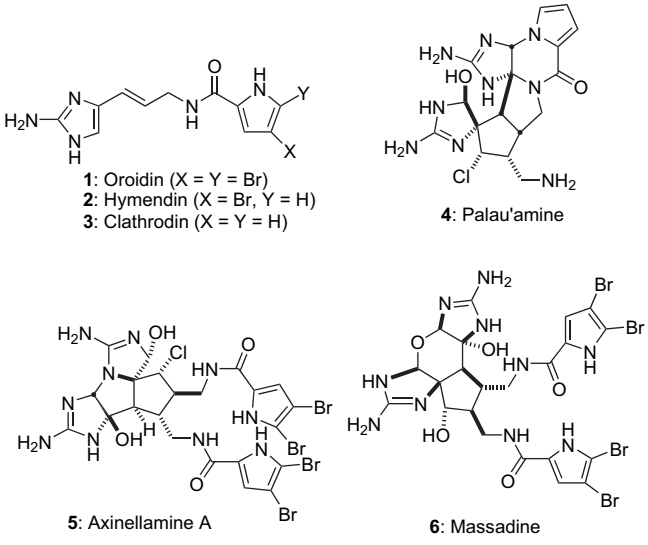

Figure 1. Oroidin and some dimeric congeners.

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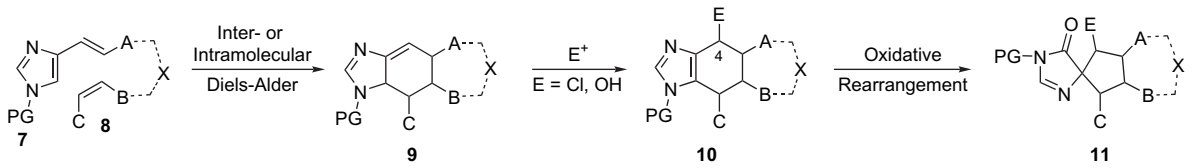
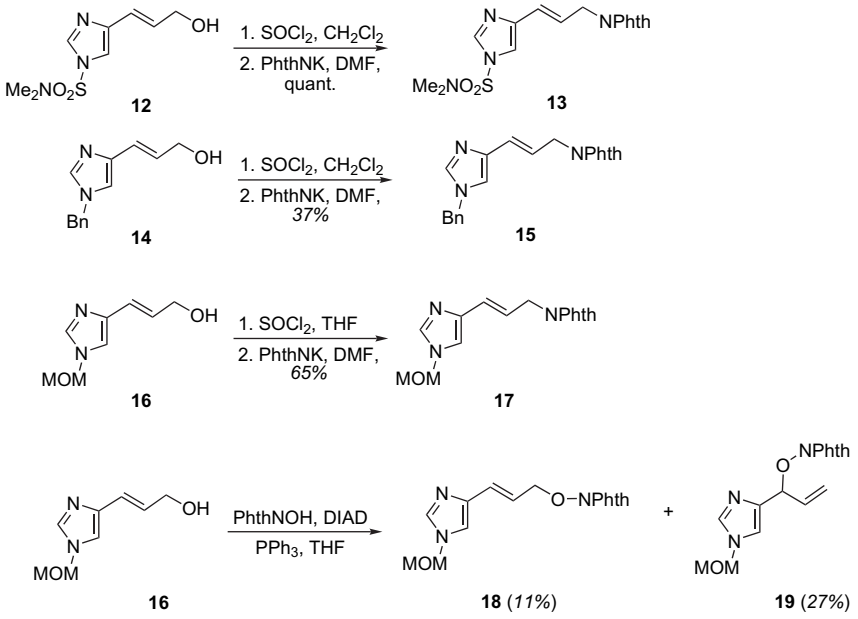


Figure 2. Synthetic strategy toward spiro-fused imidazolylcyclopentane.



Scheme 1.

preparation of some N–O-linked systems for evaluation in intramolecular Diels–Alder reactions.[12] When these results are viewed as a whole, there appears to be a correlation between the electron density of the imidazole moiety and the proportion of allylic transposition, that is the more electron rich the imidazole, the more transposition tends to be observed. We assume that these reactions proceed via SN2/SN2′ pathways but with the development of significant positive charge.[13] Interpretation of these results suggests that the contribution of the resonance form **21** with the positive charge proximal to the imidazole to the overall structure dictates which pathway is followed (Fig. 2). In the case of more electron-rich imidazoles (Bn, MOM) this contribution is more important, and so the SN2′ pathway becomes more competitive, whereas with the more electron poor (dimethylaminosulfonyl = DMAS) this is less important and so SN2 is favored (Fig. 3).

The preparation of the phthalimide derivatives (**13**, **15**, **17**) was driven by our need to access the corresponding amines, while this could be satisfied by using an alternative pathway,

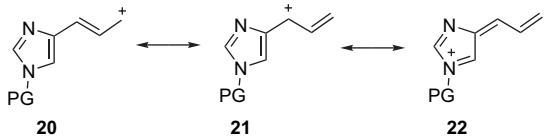
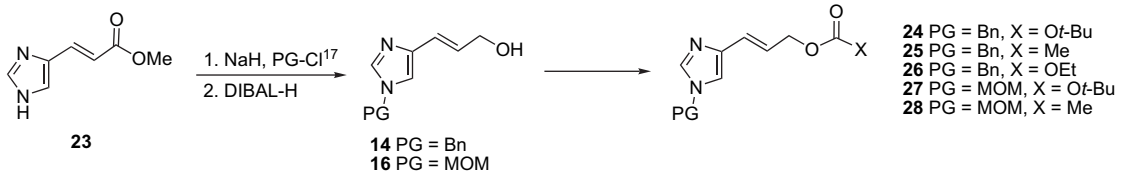


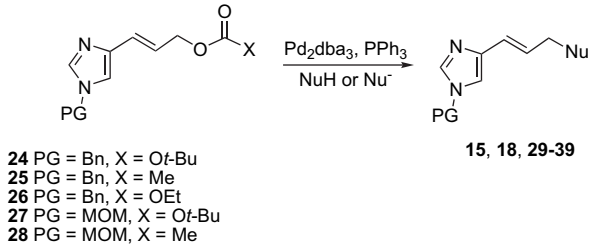
Figure 3. Resonance stabilization of imidazolyl-derived allylic carbocation.

i.e., reductive amination with the corresponding α,β-unsaturated aldehyde.[14] Access to **18** and related congeners however, could not be solved in this way. Furthermore, as our studies progressed, it became increasingly apparent that a solution to the preparation of the more electron-rich Bn- and MOM-protected derivatives had to be found. As indicated above, substrates with these protecting groups engaged in the rearrangement chemistry with greater facility. At this point we became intrigued as to the possibility of using π-allyl chemistry catalyzed by Pd(0).[15] A literature search indicated that no examples involving imidazole substituted allyl systems had been reported,[16] therefore we sought to investigate the viability of this chemistry as it would not only provide a convenient approach to **18**, but may allow access to a variety of other derivatives. The results of this investigation are described below.

The allylic alcohols **14** and **16** are readily available from urocanic acid via the methyl ester (**23**) and chemoselective protection.[17] Acetylation with acetic anhydride, acetyl chloride, ethyl chloroformate or $(BOC)_2O$ occurred uneventfully (Scheme 2), setting the stage for the key substitution reaction. Our initial experiment was conducted with **24** and *N*-hydroxysuccinimide as a nucleophile, using Pd_2dba_3 (3 mol %) and PPh_3 (7 mol %), and we were delighted to discover that the reaction proceeded to provide the terminal substitution product in 86% (Table 1, entry 1) as the sole isolated product. Analysis of the ^1H NMR spectrum of the crude reaction mixture provided evidence that no



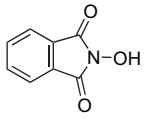
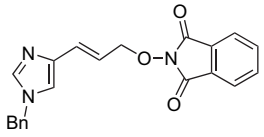
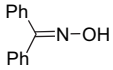
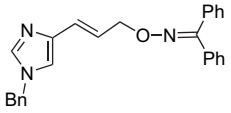
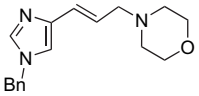
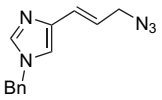
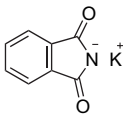
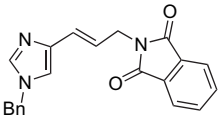
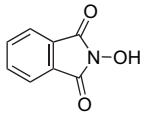
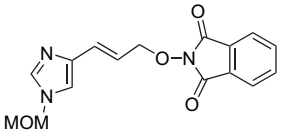
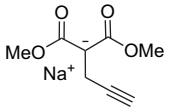
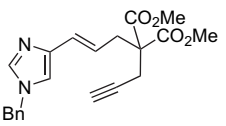
Scheme 2.



Scheme 3.

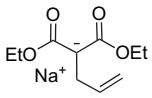
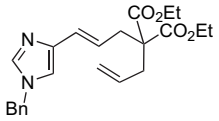
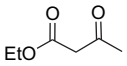
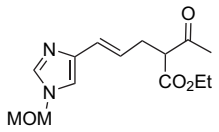
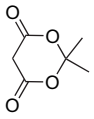
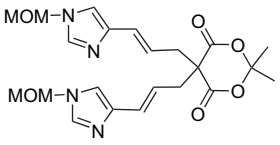
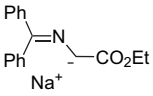
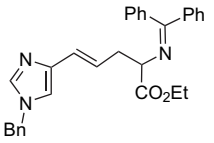
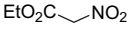
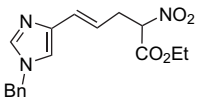
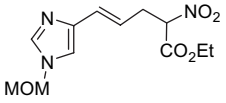
SN2′-susbstitution had occurred. Given the success of this initial reaction, several other nucleophiles were examined, including both heteroatom (Table 1, entries 1–6) and carbon-based (Table 1, entries 7–13). As can be seen from the examples depicted in Table 1, a variety of nucleophiles engage successfully in this reaction. Particularly gratifying was the expedient and selective synthesis of the phthalimide **15** (Table 1, entry 5) and alkoxyphthalimide **18** (Table 1, entry 6). Essentially the same conditions can be employed (3–7 mol % Pd_2dba_3), although some changes in solvent

Table 1. Products and yields from allylic substitution reactions

Entry	Substrate	Nucleophile	Conditions[a]	Product	Yield/%
1	**24**		MeCN, 28 h	 **29**	86
2	**25**		K_2CO_3, CH_2Cl_2, 14 h	 **30**	98
3	**24**		CH_2Cl_2, 16 h	 **31**	83
4	**24**	NaN_3	MeCN, H_2O, 16 h	 **32**	79
5	**26**		DMF, 100 °C, 14 h	 **15**	90
6	**27**		MeCN, 28 h	 **18**	77
7	**24**		THF, 17 h	 **33**	74

(*continued*)

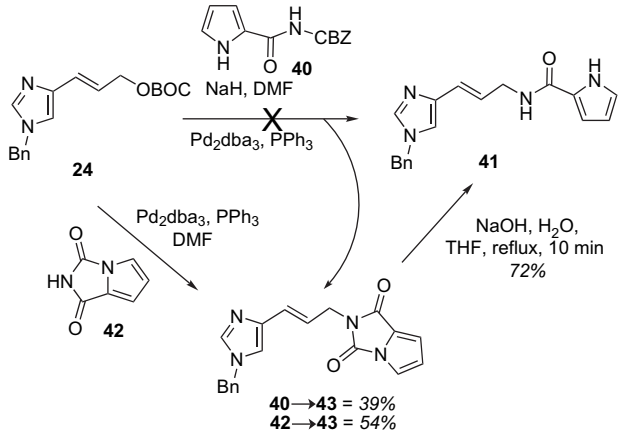
Table 1. (*continued*)

Entry	Substrate	Nucleophile	Conditions[a]	Product	Yield/%
8	**24**		THF, 17 h	 **34**	69
9	**28**		CH_2Cl_2, K_2CO_3, 16 h	 **35**	74
10	**28**		CH_2Cl_2, K_2CO_3, 14 h	 **36**	76
11	**24**		THF, 60 °C, 36 h	 **37**	69
12	**25**		CH_2Cl_2, reflux, 12 h[18]	 **38**	73
13	**28**		CH_2Cl_2, reflux, 12 h	 **39**	62

[a] All reactions were conducted at room temperature unless otherwise noted.

are required to accommodate solubility of some systems, and in some cases heat is required. Of the 13 examples illustrated in Table 1, no evidence of the SN2′ pathway was observed on analysis of the ^{1}H NMR spectra of the crude reaction mixtures (Scheme 3).

Part of the attraction of the successful realization of this chemistry was the possibility of utilizing new types of nucleophiles that might expedite the synthesis of the oroidin alkaloids.[2] In particular, we wanted to examine pyrrole-substituted imides (e.g., **40** in Scheme 4)[19] as a means to incorporate this moiety more directly into targets. Typically, this group is incorporated through acylation of the corresponding amine, which frequently arises through elaboration of an alcohol,[20] and so this strategy would significantly reduce the number of synthetic manipulations. Pyrroles react efficiently with isocyanates to provide the corresponding 2-acyl pyrrole, thus when pyrrole was treated with benzyloxy isocyanate, the corresponding 2-CBZ-imide was obtained. When **40** (after deprotonation with NaH) was used in the Pd-catalyzed substitution chemistry (Scheme 4), it was found that substitution had occurred, but the adduct possessed only one benzyl moiety. Our initial suspicion was that simple reductive debenzylation of the CBZ moiety occurred



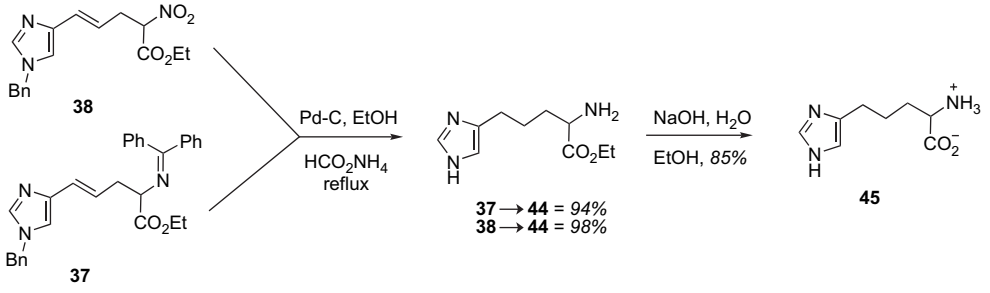
Scheme 4.

after the alkylation through the action of adventitious Pd/H species, providing **41**. However, it quickly became apparent that this analysis was erroneous, as the ^{13}C NMR spectrum revealed the presence of two carbonyl absorptions. It has been shown that imides related to **40** can undergo an intramolecular cyclization reaction between the pyrrole nitrogen and the β-carbonyl to generate a cyclic imide under thermal activation.[19] Based on the two carbonyl absorptions observed in the ^{13}C NMR spectrum, and on mass spectral data, it was thought that the product was in fact **43**. To test this hypothesis, the cyclic imide **42** was prepared according to the method of Papadopoulos and then subjected to the substitution chemistry.[19] Gratifyingly, not only did the imide engage in the substitution reaction, but provided the same adduct as **40**, in 54% yield (Scheme 4). It was found that the pyrrole carboximide in **43** could be revealed simply on treatment with aqueous NaOH, providing **41** in 72% yield, which can be envisioned as a precursor to clathrodin (**3**, Fig. 1).

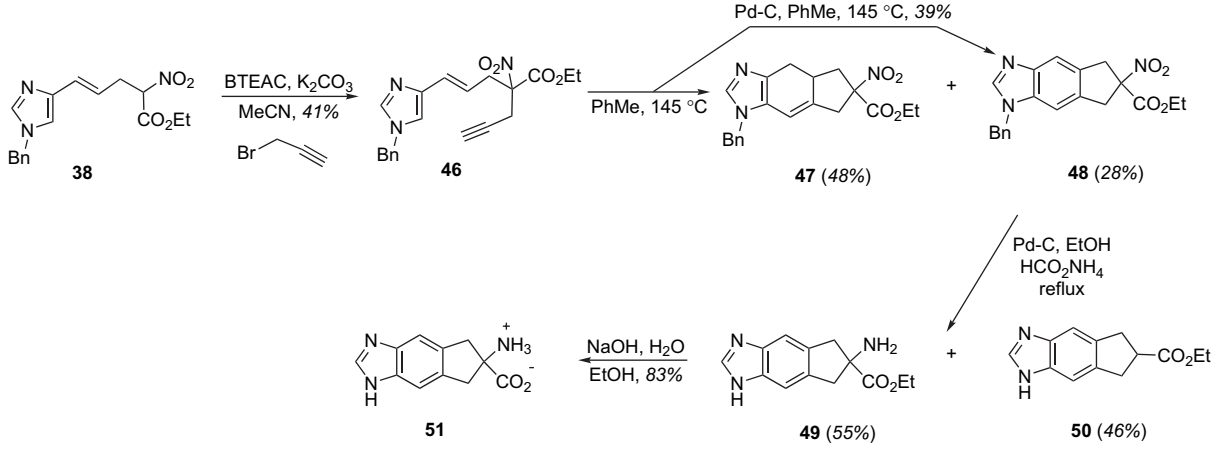
Several active methylene components have been employed in this chemistry with equal facility, including allyl and propargyl malonate systems (Table 1, entries 7 and 8). It was envisioned that these latter derivatives would provide substrates for investigation in the intramolecular Diels–Alder reaction.[21] Meldrum's acid also participates nicely in this substitution chemistry, providing the bis adduct in good yield (Table 1, entry 10). Several glycine synthons were employed in the reaction and found to successfully engage in substitution (Table 1, entries 11–13), potentially providing precursors for the preparation of homologous histidine analogs. Subjection of either **37** or **38** to transfer hydrogenation conditions led to the reduction of the nitro and alkene moieties and cleavage of the benzyl protecting group, providing **44** in excellent yield (Scheme 5).[22,23] Subsequent ester hydrolysis and purification by the ion-exchange chromatography provided the homohistidine analog **45** (Scheme 5).[24]

Additionally, it was found that **38** can serve as a building block for further elaboration, for example, the acidic C–H can be substituted under phase transfer conditions, providing enyne **46** in moderate yield (Scheme 6). This undergoes a Diels–Alder reaction providing the expected cycloadduct **47** in 48% yield, along with the aromatized congener **48** (28%). Treatment of **46** with Pd/C in toluene at 145 °C furnishes the aromatic adduct **48** as the only product in 39% yield. Alternatively the aromatic adduct can be obtained directly from the cycloaddition when it is conducted in the presence of Pd/C (Scheme 6). Subjection of **48** to transfer hydrogenation leads to debenzylation and reduction of the nitro moiety, affording **49**. In addition to the desired compound, and a comparable quantity of the deaminated product **50** was obtained. Ester hydrolysis and purification by ion-exchange chromatography led to the isolation of the constrained homohistidine derivative (Scheme 6).

In summary, we have developed an efficient method for allylic substitution of imidazole derivatives that proceeds without allylic rearrangement. These reactions are tolerant of a variety of nucleophiles, including heteroatom and active methylene compounds. Among the heteroatom nucleophiles, we demonstrate the utility of a pyrrole carboximide (**42**) as a new and more direct means to introduce this moiety



Scheme 5.



Scheme 6.

into the oroidin alkaloids.[25] Two of the adducts were converted to homohistidine adducts, including a novel cyclic derivative. We are currently evaluating other nucleophiles in this chemistry and the utility of asymmetric variants, we will report on these efforts in due course.

2. Experimental

2.1. General

All chemicals were purchased from commercial vendors and were used as received unless stated otherwise. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried glassware. Solvents were dried using a Pure-Solv 400 solvent purification system (Innovative Technologies Inc.), except for DMF, which was dried over CaH_2 and then distilled. ^{1}H NMR spectra were acquired at 300 or 500 MHz in $CDCl_3$, unless indicated otherwise, using residual $CHCl_3$ as a reference. ^{13}C NMR spectra were obtained at 75 or 125 MHz in $CDCl_3$, unless otherwise indicated, using solvent as an internal standard. Low-resolution mass spectra were obtained in-house by electron impact (MS-EI), high-resolution mass spectra were obtained at the University of Florida by electrospray ionization (HRMS-ESI).

2.1.1. (1*E*)-1-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propen-1-ol (16). NaH (60% oil dispersion, 2.10 g, 52.5 mmol) was added portionwise to a cold (0 °C) solution of methyl 3-(1*H*-imidazol-4-yl)acrylate (7.75 g, 50.0 mmol) in dry DMF (100 mL) under N_2 protection. The mixture was allowed to warm to room temperature and stirred for 1.5 h, then cooled to 0 °C again and neat MOMCl (3.99 mL, 52.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred overnight. The DMF was removed in vacuo. The remaining solid was partitioned between water (50 mL) and EtOAc (300 mL), the organic phase was dried (Na_2SO_4) and concentrated to give an off-white solid. ^{1}H NMR analysis indicated that this material was a 10:3 mixture of the 4- and 5-regioisomers. Separation can be accomplished by column chromatography (EtOAc → EtOAc/MeOH 7:1). However, this mixture was transferred to a sealed tube, acetonitrile (20 mL) and MOMCl (0.10 mL, 1.20 mmol) were added. The mixture was heated at 120 °C for 24 h, the 5-isomer was completely converted to 4-isomer. Concentration gave the desired 4-isomer (8.50 g, 91%) as an off-white solid; mp 85–86 °C. IR (KBr, cm^{-1}): 1703, 1641. ^{1}H NMR (500 MHz): δ=3.28 (s, 3H), 3.76 (s, 3H), 5.21 (s, 2H), 6.57 (d, J=15.6 Hz, 1H), 7.20 (s, 1H), 7.54 (d, J=15.6 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (125 MHz): δ=51.7, 56.5, 78.0, 116.6, 121.1, 136.0, 138.8, 139.1, 168.0; MS-EI (*m*/*z*): 196.1 (M$^+$, 100%), 165.1 (M$^+$−31, 37%). Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.17; H, 5.97; N, 14.03.

To a solution of the ester (4.00 g, 20.0 mmol) in CH_2Cl_2 (170 mL) under N_2 was added dropwise DIBAL-H (1 M in hexanes, 3 equiv 60.0 mL, 60.0 mmol) at −78 °C over 100 min, the mixture was allowed to slowly warm up to room temperature (about 80 min) and then cooled to 0 °C. Methanol (10 mL) was added slowly, and then water (70 mL) and NaOH (1 N, 30 mL). The mixture was filtered through Celite and washed with CH_2Cl_2. The organic layer of the filtrate was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 extracts were washed with saturated brine, dried ($MgSO_4$), and concentrated. The residue was subjected to chromatography (EtOAc/methanol 6/1) to afford **16** (2.40 g, 72%) as a light yellow liquid. IR ($CHCl_3$, cm^{-1}): 3237; ^{1}H NMR: δ=3.23 (s, 3H), 4.24 (s, 2H), 5.14 (s, 2H), 6.47–6.48 (m, 2H), 6.92 (s, 1H), 7.51 (s, 1H); ^{13}C NMR: δ=56.2, 63.1, 77.8, 116.3, 121.9, 128.7, 137.7, 140.9; MS-EI (*m*/*z*): 167.9 (M$^+$, 50%), 138.9 (M$^+$−29, 100%).

2.1.2. (1*E*)-1-Benzyl-4-[3-(*N*-phthaloyl)-1-propenyl]imidazole (15). Compound **14** (220 mg, 1.03 mmol) was dissolved in dry THF (30 mL). The mixture was cooled to 0 °C and thionyl chloride (155 mg) was added slowly. The mixture was allowed to warm up to room temperature and stirred for another 2 h. The solution was concentrated in vacuo. The residue was dissolved in DMF (3 mL) and potassium phthalimide (4.7 g, 26 mmol) was added. The mixture was stirred 50 h at rt, and then partitioned between EtOAc (100 mL) and water (20 mL). The organic phase was dried (Na_2SO_4) and concentrated. Purification of the residue by silica gel chromatography (EtOAc/hexane 3:1 → EtOAc/MeOH 6:1) gave 130 mg of **15** (37%) as an off-white solid; mp 177–178 °C. IR (KBr, cm^{-1}): 1758, 1700; ^{1}H NMR (500 MHz): δ=4.39 (d, J=6.4 Hz, 2H), 5.03 (s, 2H), 6.34 (dt, J=15.6, 6.4 Hz, 1H), 6.49 (d, J=15.6 Hz, 1H), 6.79 (s, 1H), 7.10–7.12 (m, 2H), 7.29–7.34 (m, 3H), 7.44 (s, 1H), 7.68–7.69 (m, 2H), 7.80–7.82 (m, 2H); ^{13}C NMR (125 MHz): δ=39.6, 50.9, 117.4, 121.2, 123.3, 125.4, 127.3, 128.4, 129.1, 132.3, 133.9, 136.0, 137.3, 140.0, 168.0; MS-EI (*m*/*z*): 343.5 (M$^+$, 40%), 252.2 (M$^+$−91, 100%). Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.54; H, 5.22; N, 11.86.

2.1.3. (1*E*)-1-Methoxymethyl-4-[3-(*N*-phthaloyl)-1-propenyl]imidazole (17). Allylic alcohol **16** (1.76 g, 10.5 mmol) was dissolved in dry THF (30 mL). The mixture was cooled to 0 °C and thionyl chloride (0.77 mL, 10.5 mmol) was added slowly. The mixture was allowed to warm up to room temperature and stirred for another 2 h. The solution was concentrated in vacuo. The residue was dissolved in 50 mL of DMF and potassium phthalimide (4.70 g, 25.4 mmol) was added. The mixture was stirred 15 h at rt, and then partitioned between EtOAc (100 mL) and water (20 mL). The organic phase was dried with Na_2SO_4 and concentrated. Purification of the residue by silica gel chromatography gave 1.65 g (53%) of **16** as an off-white solid; mp 149–150 °C. IR (KBr, cm^{-1}): 1768, 1701; ^{1}H NMR (500 MHz): δ=3.23 (s, 3H), 4.42 (d, J=6.4 Hz, 2H), 5.15 (s, 2H), 6.39 (dd, J=15.7, 6.4 Hz, 1H), 6.52 (d, J=15.7 Hz, 1H), 6.94 (s, 1H), 7.50 (s, 1H), 7.68–7.71 (m, 2H), 7.81–7.84 (m, 2H); ^{13}C NMR (125 MHz): δ=39.5, 56.2, 77.8, 116.8, 121.9, 123.3, 125.1, 132.3, 134.0, 137.8, 140.4, 168.0; MS-EI (*m*/*z*): 297.2 (M$^+$, 65%), 252.2 (M$^+$−45, 100%), 225.2 (M$^+$−72, 100%). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.62; H, 4.92; N, 14.01.

2.1.4. 2-[(2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (18) and 2-[1-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (19). Diisopropyl azodicarboxylate (337 mg,

1.67 mmol) was added neat to a premixed solution of alcohol **16** (200 mg, 1.19 mmol), PPh_3 (437 mg, 1.67 mmol), and *N*-hydroxyphthalimide (252 mg, 1.55 mmol) in dry THF (10 mL) at 0 °C. The resulting mixture was stirred at room temperature overnight. The reaction mixture was then concentrated under reduced pressure. The oily residue was purified by chromatography (hexane/EtOAc; 1:4) providing **18** and **19**. Further purification by preparative TLC afforded pure **18** and **19**. Compound **18** (100 mg, 27%); mp: 133–135 °C. IR (neat, cm^{-1}): 1786, 1730; ^1H NMR (500 MHz): δ=3.26 (s, 3H), 4.81 (d, *J*=6.9 Hz, 2H), 5.15 (s, 2H), 6.50 (dt, *J*=15.6, 6.9 Hz, 1H), 6.58 (d, *J*=15.6 Hz, 1H), 7.52 (s, 1H), 7.69 (dd, *J*=5.5, 3.0 Hz, 2H), 7.78 (dd, *J*=5.5, 3.0 Hz, 2H); ^{13}C NMR (125 MHz): δ=56.3, 77.8, 78.6, 117.3, 120.9, 123.5, 129.0, 129.1, 134.4, 137.8, 140.0, 163.8; HRMS-ESI: calcd for $C_{16}H_{16}N_3O_4$ $(M+H)^+$ 314.1135, found 314.1129. Compound **19** (40 mg; 11%); mp: 92–94 °C. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): δ=3.56 (s, 3H), 5.49 (ABq, *J*=10.8 Hz, 2H), 5.67 (d, *J*=10.8 Hz, 1H), 5.74 (d, *J*=17.1 Hz, 1H), 6.06 (d, *J*=8.4 Hz, 1H), 6.66 (ddd, *J*=18.9, 10.5, 8.7 Hz, 1H), 7.54 (d, *J*=0.9 Hz, 1H), 7.84 (d, *J*=1.2 Hz, 1H), 7.98–8.01 (m, 2H), 8.05–8.08 (m, 2H); ^{13}C NMR (75 MHz): δ=56.3, 77.9, 84.5, 118.7, 121.8, 123.5, 128.9, 133.7, 134.3, 137.5, 139.2, 163.8; HRMS-ESI: calcd for $C_{16}H_{16}N_3O_4$ $(M+H)^+$ 314.1135, found 314.1133.

2.1.5. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl *tert*-butyl carbonate (24). The allyl alcohol **14** (2.00 g, 9.33 mmol), di-*tert*-butyl dicarbonate (2.50 g, 11.2 mmol), tetra-*n*-butylammonium hydrogen sulfate (158 mg, 0.47 mmol), and 30% w/w aqueous NaOH (4 mL) were mixed together in CH_2Cl_2 (25 mL) at 0 °C and stirred at rt for 6–8 h. The reaction mixture was diluted with water (10 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (EtOAc/hexane; 65:35), affording **26** (2.00 g, 68%) as a pale yellow solid; mp: 73–75 °C. IR (neat, cm^{-1}): 2979, 1738; ^1H NMR (300 MHz): δ=1.47 (s, 3H), 4.67 (d, *J*=6.3 Hz, 2H), 5.05 (s, 2H), 5.06 (s, 2H), 6.37 (dt, *J*=15.6 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.83 (d, *J*=1.2 Hz, 1H), 7.14 (m, 2H), 7.31–7.37 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (75 MHz): δ=27.8, 50.9, 67.5, 82.0, 117.6, 121.3, 126.2, 127.3, 128.4, 129.1, 135.9, 137.8, 140.0, 153.5; HRMS-ESI: calcd for $C_{18}H_{23}N_2O_3$ $(M+H)^+$ 315.1703, found 315.1699.

2.1.6. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl acetate (25). Acetyl chloride (0.37 mL, 5.3 mmol) was added dropwise to a mixture of **14** (750 mg, 3.50 mmol) and K_2CO_3 (966 mg, 7.00 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred at room temperature for 8 h, after which water (3 mL) was added and the organic solution was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic solutions were dried (Na_2SO_4), filtered, and concentrated. The resulting crude product was purified by column chromatography (hexane/EtOAc; 4:1) to furnish the pure acetate **25** (440 mg, 73%) as a thick colorless oil. IR (neat, cm^{-1}): 1733; ^1H NMR (300 MHz): δ=2.06 (s, 3H), 4.65 (d, *J*=6.0 Hz, 2H), 5.03 (s, 2H), 6.34 (dt, *J*=15.9, 6.0 Hz, 1H), 6.48 (d, *J*=15.9 Hz, 1H), 6.82 (s, 1H), 7.11–7.13 (m, 2H), 7.29–7.33 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=21.1, 50.9, 65.1, 117.6, 121.6, 125.9, 127.3, 128.4, 129.1, 135.9, 137.8, 139.8, 171.0; HRMS-ESI: calcd for $C_{15}H_{17}N_2O_2$ $(M+H)^+$ 257.1285, found 257.1280.

2.1.7. (2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl ethyl carbonate (26). Ethyl chloroformate (0.81 mL, 8.4 mmol) was added dropwise to a solution of **14** (1.5 g, 7.0 mmol) and triethylamine (1.95 mL, 14.0 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C. After stirring the reaction mixture at rt for 6 h, water (3 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (hexane/EtOAc; 65:35) to furnish the carbonate **26** (1.56 g, 78%) as a thick colorless oil. IR (neat, cm^{-1}): 2926, 1742; ^1H NMR (300 MHz): δ=1.28 (t, *J*=7.2 Hz, 3H), 4.17 (q, *J*=7.2 Hz, 2H), 4.73 (dd, *J*=6.3, 0.9 Hz, 2H), 5.05 (s, 2H), 6.40 (dt, *J*=15.6, 6.3 Hz, 1H), 6.53 (d, *J*=15.6 Hz, 1H), 6.83 (d, *J*=0.9 Hz, 1H), 7.14 (m, 2H), 7.33 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=14.3, 50.9, 64.0, 68.3, 117.8, 120.9, 126.5, 127.3, 128.4, 129.1, 135.9, 137.8, 139.9, 155.1; HRMS-ESI: calcd for $C_{16}H_{19}N_2O_3$ $(M+H)^+$ 287.1396, found 287.1385.

2.1.8. *tert*-Butyl (2*E*)-3-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-propenyl carbonate (27). A mixture **16** (500 mg, 2.98 mmol), di-*tert*-butyl dicarbonate (844 mg, 3.87 mmol), tetra-*n*-butylammonium hydrogen sulfate (50 mg, 0.15 mmol), and 2 mL of 30% w/w aqueous NaOH were mixed together CH_2Cl_2 (25 mL) at 0 °C and stirred at rt for 6–8 h. Water (10 mL) was added to the reaction mixture and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography on a silica gel column (hexane/EtOAc; 30:70), affording the product as a thick oil (495 mg, 62%). IR (neat, cm^{-1}): 2980, 2936, 1738, 1498; ^1H NMR (300 MHz): δ=1.47 (s, 9H), 3.25 (s, 3H), 4.68 (d, *J*=6.0 Hz, 2H), 5.17 (s, 2H), 6.41 (dt, *J*=15.9, 6.0 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.97 (s, 1H), 7.52 (s, 1H); ^{13}C NMR (75 MHz): δ=27.8, 56.2, 67.4, 77.8, 82.1, 117.0, 122.0, 125.8, 137.8, 140.2, 153.4; HRMS-ESI: calcd for $C_{13}H_{21}N_2O_4$ $(M+H)^+$ 269.1496, found 269.1492.

2.1.9. (2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenyl acetate (28). Acetic anhydride (1.01 mL, 10.7 mmol) was added dropwise to a solution of **16** (1.2 g, 7.14 mmol), pyridine (1.13 g, 14.3 mmol), and DMAP (50 mg) in dry CH_2Cl_2 (50 mL) at 0 °C. The resulting mixture was stirred at room temperature for 6 h, after which water (3 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish the pure acetate **28** (950 mg, 64%) as a thick colorless oil. IR (neat, cm^{-1}): 2935, 1735; ^1H NMR (300 MHz): δ=2.06 (s, 3H), 3.07 (s, 3H), 4.67 (d, *J*=6.0 Hz, 2H), 5.17 (s, 2H), 6.39 (dt, *J*=15.9, 6.0 Hz, 1H), 6.53 (d, *J*=15.9 Hz, 1H), 6.97 (s, 1H), 7.52 (s, 1H); ^{13}C NMR (75 MHz): δ=21.1, 56.2, 65.0, 116.9, 122.2, 125.6, 137.8, 140.3, 170.9; HRMS-ESI: calcd for $C_{10}H_{15}N_2O_3$ $(M+H)^+$ 211.1077, found 211.1074.

2.1.10. 2-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (29). To a degassed reaction mixture containing allylic carbonate **24** (150 mg, 0.47 mmol), PPh_3 (8 mg, 0.032 mmol), and *N*-hydroxyphthalimide (65 mg, 0.40 mmol) in 5 mL of CH_3CN was added $Pd_2(dba)_3$ (15 mg, 0.016 mmol) and stirred at rt for 28 h. The reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish **29** (123 mg, 86%) as a pale yellow solid; mp: 121–123 °C. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): 4.81 (d, J=6.3 Hz, 2H), 5.06 (s, 2H), 6.47 (dt, J=15.9, 6.6 Hz, 1H), 6.58 (d, J=15.9 Hz, 1H), 6.90 (s, 1H), 7.15 (m, 2H), 7.34–7.38 (m, 3H), 7.46–7.51 (m, 2H), 7.69–7.72 (dd, J=3.0, 5.1 Hz, 2H), 7.79 (dd, J=5.4, 3.0 Hz, 2H); ^{13}C NMR (75 MHz): δ=51.1, 78.7, 117.9, 120.4, 123.5, 127.5, 128.5, 128.6, 129.0, 129.1, 129.3, 134.4, 135.6, 137.6, 139.5, 163.8; HRMS-ESI: calcd for $C_{21}H_{18}N_3O_3$ $(M+H)^+$ 360.1343, found 360.1335.

2.1.11. *O*-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl]benzophenone oxime (30). To the degassed reaction mixture containing allylic acetate **25** (100 mg, 0.39 mmol), PPh_3 (13 mg, 0.048 mmol), K_2CO_3 (54 mg, 0.39 mmol), and benzophenone oxime (64 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (0.021 g, 0.023 mmol) followed by stirring at rt for 14 h. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (hexane/EtOAc; 21:3) to furnish **30** as a thick oil (0.096 g, 98%). IR (neat): cm^{-1}=1660, 1494, 1444; ^1H NMR (300 MHz): δ=5.07 (d, J=4.8 Hz, 2H), 5.31 (s, 2H), 6.75 (m, 2H), 7.08 (d, J=1.2 Hz, 1H), 7.39–7.42 (m, 2H), 7.51–7.65 (m, 10H), 7.72–7.75 (m, 4H); ^{13}C NMR (75 MHz): δ=51.2, 75.2, 117.5, 124.5, 124.9, 127.6, 128.3, 128.4, 128.4, 128.6, 129.0, 129.3, 129.4, 129.7, 133.7, 136.1, 137.0, 137.9, 140.8, 156.9; HRMS-ESI: calcd for $C_{26}H_{24}N_3O$ $(M+H)^+$ 394.1914, found 394.1905.

2.1.12. 4-[(2*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-2-propenyl]morpholine (31). To the degassed reaction mixture containing allylic carbonate **24** (200 mg, 0.64 mmol), PPh_3 (13 mg, 0.05 mmol), and morpholine (0.056 mL, 0.65 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated and purified by column chromatography (MeOH/EtOAc; 7:13) to furnish **31** (150 mg, 83%) as thick oil. IR (neat, cm^{-1}): 2856, 2806, 1538, 1495; ^1H NMR (300 MHz): δ=2.47 (dd, J=4.5 Hz, 4H), 3.09 (d, J=6.9 Hz, 2H), 3.69 (dd, J=3.6 Hz, 4H), 5.04 (s, 2H), 6.28 (dt, J=15.3, 7.2 Hz, 1H), 6.39 (d, J=15.3 Hz, 1H), 6.81 (s, 1H), 7.14 (m, 2H), 7.29–7.36 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (75 MHz): δ=50.9, 53.6, 61.3, 67.1, 116.6, 124.3, 125.3, 127.3 (2C), 128.4, 129.1 (2C), 136.0, 137.6, 140.6; HRMS-ESI: calcd for $C_{17}H_{22}N_3O$ $(M+H)^+$ 284.1757, found 284.1751.

2.1.13. (2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl azide (32). To the degassed reaction mixture containing **24** (200 mg, 0.64 mmol), PPh_3 (13 mg, 0.05 mmol), and NaN_3 (50 mg, 0.76 mmol) in 4:1 CH_3CN/H_2O (5 mL) was added $Pd_2(dba)_3$ (23 mg, 0.025 mmol) and stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using hexane/ethyl acetate 3:7 to furnish **32** (120 mg, 79%) as a thick oil. IR (neat, cm^{-1}): 3109, 2112, 1661; ^1H NMR (500 MHz): δ=3.88 (d, J=6.4 Hz, 2H), 5.07 (s, 2H), 6.35 (dt, J=15.6, 6.4 Hz, 1H), 6.49 (d, J=15.6 Hz, 1H), 7.15 (m, 2H), 7.32–7.37 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (125 MHz): δ=51.0, 53.0, 117.7, 120.8, 126.2, 127.4, 128.4, 129.1, 135.9, 137.8, 139.8. HRMS-ESI: calcd for $C_{13}H_{14}N_5$ $(M+H)^+$ 240.1244, found 240.1239.

2.1.14. (1*E*)-1-Benzyl-4-[3-(*N*-phthaloyl)-1-propenyl]-imidazole (15). To the degassed reaction mixture containing **26** (100 mg, 0.35 mmol), PPh_3 (11 mg, 0.041 mmol), and potassium phthalimide (78 mg, 0.42 mmol) in DMF (5 mL) was added $Pd_2(dba)_3$ (20 mg, 0.020 mmol) and stirred at 100 °C for 14 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 3:17) to furnish **15** (108 mg, 90%) as a colorless solid.

2.1.15. 2-[(2*E*)-3-(1-Methoxymethyl-1*H*-imidazol-4-yl)-2-propenoxy]isoindole-1,3(2*H*)-dione (18). To the degassed reaction mixture containing **27** (145 mg, 0.54 mmol), PPh_3 (17 mg, 0.064 mmol), and *N*-hydroxyphthalimide (132 mg, 0.81 mmol) in acetonitrile (10 mL) was added $Pd_2(dba)_3$ (29 mg, 0.032 mmol) and stirred at room temperature for 38 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 1:4) to furnish **18** (130 mg, 77%) as a colorless solid.

2.1.16. Dimethyl 2-[(2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl]-2-(2-propynyl)malonate (33). To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (10 mg, 0.038 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (18 mg, 0.019 mmol). After stirring at rt for 5 min, freshly generated sodium salt generated from dimethyl propargyl malonate [(132 mg, 0.67 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (26 mg, 1.08 mmol) and then stirred at room temperature for 30 min] was added and stirred at room temperature for 17 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:13) to furnish **33** (130 mg, 74%) as a thick colorless oil. IR (neat, cm^{-1}): 3289, 2935, 1735; ^1H NMR (300 MHz): δ=2.11 (t, J=2.7 Hz, 1H), 2.93 (d, J=2.4 Hz, 2H), 3.03 (d, J=8.1 Hz, 2H), 3.83 (s, 6H), 5.14 (s, 2H), 6.15 (dt, J=15.3, 8.1 Hz, 1H), 6.50 (d, J=15.3 Hz, 1H), 6.87 (s, 1H), 7.27–7.36 (m, 2H), 7.43–7.46 (m, 3H), 7.46 (s, 1H); ^{13}C NMR (75 MHz): δ=22.8, 35.8, 51.0, 53.0, 57.3, 71.6, 79.2, 116.8, 121.2, 126.7, 127.5, 128.5, 129.2, 136.1, 137.6, 140.7, 170.3; HRMS-ESI: calcd for $C_{21}H_{23}N_2O_4$ $(M+H)^+$ 367.1638, found 367.1652.

2.1.17. Diethyl 2-(2-propenyl)-2-[(2*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)-2-propenyl]malonate (34). To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (10 mg, 0.038 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (19 mg, 0.019 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt generated

from diethyl allylmalonate [(130 mg, 0.65 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (23 mg, 0.95 mmol and stirred at room temperature for 30 min] was added and stirred at room temperature for 17 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). Organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:13) to furnish **34** (125 mg, 66%) yield as thick colorless oil. IR (neat, cm^{-1}): 1729; ^1H NMR (300 MHz): δ=1.20 (t, J=6.9 Hz, 6H), 2.65 (d, J=7.2 Hz, 2H), 2.73 (d, J=7.5 Hz, 2H), 4.13 (q, J=6.9 Hz, 4H), 5.01–5.08 (m, 4H), 5.68 (m, 1H), 6.07 (dt, J=15.6, 7.5 Hz, 1H), 6.27 (d, J=15.6 Hz, 1H), 6.73 (s, 1H), 7.12 (m, 2H), 7.29–7.35 (m, 3H), 7.42 (s, 1H); ^{13}C NMR (75 MHz): δ=14.2, 35.9, 36.7, 50.9, 57.7, 61.2, 116.3, 119.1, 122.0, 126.0, 127.3, 128.3, 129.0, 132.6, 136.1, 137.5, 140.7, 170.8; HRMS-ESI: calcd for $C_{23}H_{29}N_2O_4$ $(M+H)^+$ 397.2122, found 397.2112.

2.1.18. Ethyl (4*E*)-2-acetyl-5-(1-methoxymethyl-1*H*-imidazol-4-yl)pent-4-enoate (35). To the degassed reaction mixture containing **28** (150 mg, 0.714 mmol), PPh_3 (15 mg, 0.057 mmol), K_2CO_3 (197 mg, 1.43 mmol), and ethyl acetoacetate (115 mg, 0.88 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (26 mg, 0.026 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and residue obtained was purified by column chromatography (hexane/EtOAc; 3:17) to furnish **35** (148 mg, 74%) as a thick colorless oil. IR (neat, cm^{-1}): 1733, 1714; ^1H NMR (300 MHz): δ=1.24 (t, J=6.9 Hz, 6H), 2.24 (s, 3H), 2.71 (t, J=6.6 Hz, 2H), 3.25 (s, 3H), 3.58 (t, J=7.2 Hz, 1H), 4.19 (q, J=6.9 Hz, 2H), 5.15 (s, 2H), 6.22 (dt, J=15.3, 6.6 Hz, 1H), 6.34 (d, J=15.3 Hz, 1H), 6.88 (s, 1H), 7.50 (s, 1H); ^{13}C NMR (75 MHz): δ=14.1, 29.4, 31.4, 56.2, 59.5, 61.5, 77.8, 115.9, 124.1, 124.8, 137.6, 140.9, 169.3, 202.7; HRMS-ESI: calcd for $C_{14}H_{21}N_2O_4$ $(M+H)^+$ 281.1496, found 281.1492.

2.1.19. 5,5-Bis-[(1*E*)-3-(1-methoxymethyl-1*H*-imidazol-4-yl)-1-propenyl]-2,2-dimethyl-[1,3]dioxane-4,6-dione (36). To the degassed reaction mixture containing **28** (150 mg, 0.71 mmol), PPh_3 (15 mg, 0.057 mmol), K_2CO_3 (197 mg, 1.43 mmol), and Meldrum's acid (124 mg, 0.86 mmol) in CH_2Cl_2 (10 mL) was added $Pd_2(dba)_3$ (26 mg, 0.026 mmol) and stirred at room temperature for 14 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (MeOH/EtOAc; 1:9) to furnish **36** (120 mg, 76%) as a pale orange solid; mp: 134–136 °C. IR (neat, cm^{-1}): 2936, 1736; ^1H NMR (300 MHz): δ=1.55 (s, 6H), 2.88 (d, J=7.5 Hz, 4H), 3.23 (s, 6H), 5.14 (s, 4H), 6.22 (dt, J=15.6, 7.5 Hz, 2H), 6.37 (d, J=15.6 Hz, 2H), 6.88 (s, 2H), 7.46 (s, 2H); ^{13}C NMR (75 MHz): δ=29.2, 42.1, 56.2, 56.5, 77.7, 106.1, 116.7, 120.9, 127.17, 137.8, 140.4, 168.7; HRMS-ESI: calcd for $C_{22}H_{29}N_4O_6$ $(M+H)^+$ 445.2082, found 445.2073.

2.1.20. Ethyl (4*E*)-2-(benzhydrylideneamino)-5-(1-benzyl-1*H*-imidazol-4-yl)pent-4-enoate (37). To the degassed reaction mixture containing **24** (500 mg, 1.59 mmol), PPh_3 (50 mg, 0.19 mmol) in dry THF (3 mL), was added $Pd_2(dba)_3$ (87 mg, 0.09 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt prepared from *N*-(diphenylmethylene)glycine ethyl ester [(0.680 g, 2.5 mmol) in dry THF (5 mL) at 0 °C was added 60% NaH (96 mg, 2.40 mmol) and stirred at room temperature for 15 min] was added and stirred at 60 °C for 36 h. The THF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 7:15) to furnish **37** (508 mg, 84%) as a thick colorless oil. IR (neat, cm^{-1}): 1733, 1621; ^1H NMR (300 MHz): δ=1.22 (t, J=7.5 Hz, 3H), 2.65–2.84 (m, 2H), 4.15 (m, 3H), 4.99 (s, 2H), 6.11 (dt, J=15.9, 6.9 Hz, 1H), 6.24–6.29 (d, J=15.9 Hz, 1H), 6.70 (d, J=1.2 Hz, 1H), 7.09–7.16 (m, 4H), 7.25–7.36 (m, 5H), 7.37–7.41 (m, 4H), 7.61–7.64 (m, 2H); ^{13}C NMR (75 MHz): δ=14.3, 37.3, 50.8, 60.9, 65.8, 116.1, 124.3, 124.7, 127.3, 128.01, 128.07, 128.3, 128.5, 128.6, 128.9, 129.0, 130.3, 136.2, 136.5, 137.4, 139.7, 141.1, 170.6, 171.9; HRMS-ESI: calcd for $C_{30}H_{30}N_3O_2$ $(M+H)^+$ 464.2317, found 464.2333.

2.1.21. Ethyl (4*E*)-5-(1-benzyl-1*H*-imidazol-4-yl)-2-nitropent-4-enoate (38). To the degassed reaction mixture containing **25** (1.00 g, 3.91 mmol), PPh_3 (122 mg, 0.47 mmol), and ethyl nitroacetate (623 mg, 4.68 mmol) in CH_2Cl_2 (10 mL), was added $Pd_2(dba)_3$ (214 mg, 0.23 mmol) and stirred at reflux for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 3:17) to furnish **38** (0.94 g, 73%) as a thick colorless oil. IR (neat, cm^{-1}): 1747, 1559; ^1H NMR (300 MHz): δ=1.25 (t, J=7.2 Hz, 3H), 3.04 (m, 2H), 4.25 (q, J=7.2 Hz, 2H), 5.00 (s, 2H), 5.15 (dd, J=9.3, 6.0 Hz, 1H), 6.16 (dt, J=15.6, 6.9 Hz, 1H), 6.36 (d, J=15.6 Hz, 1H) 6.75 (s, 1H), 7.11 (m, 2H), 7.29 (m, 3H), 7.43 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 33.7, 50.9, 63.1, 87.8, 117.3, 119.4, 126.9, 127.4, 128.4, 129.1 (2C), 135.9, 137.7, 139.8, 164.2; HRMS-ESI: calcd for $C_{17}H_{20}N_3O_4$ $(M+H)^+$ 330.1448, found 330.1439.

2.1.22. Ethyl (4*E*)-5-(1-methoxymethyl-1*H*-imidazol-4-yl)-2-nitropent-4-enoate (39). To the degassed reaction mixture containing **28** (152 mg, 0.72 mmol), PPh_3 (15 mg, 0.057 mmol), and ethyl nitroacetate (115 mg, 0.86 mmol) in CH_2Cl_2 (10 mL), was added $Pd_2(dba)_3$ (26 mg, 0.029 mmol) and stirred at reflux for 12 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 1:9) to furnish **39** (125 mg, 62%) as a thick colorless oil. IR (neat, cm^{-1}): 2933, 1747, 1560; ^1H NMR (300 MHz): δ=1.27 (t, J=7.2 Hz, 3H), 3.02–3.10 (m, 2H), 3.23 (s, 3H), 4.27 (q, J=7.2 Hz, 2H), 5.14 (s, 2H), 5.18 (dd, J=6.0, 9.3 Hz, 1H), 6.21 (dt, J=15.3, 6.6 Hz, 1H), 6.39 (d, J=15.3 Hz, 1H), 6.90 (s, 1H), 7.49 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 33.7, 56.2, 63.1, 77.8, 87.7, 116.7, 120.2, 126.6, 137.8, 140.2, 164.1; HRMS-ESI: calcd for $C_{12}H_{18}N_3O_5$ $(M+H)^+$ 284.1241, found 284.1237.

2.1.23. Benzyl (1*H*-pyrrole-2-carbonyl)carbamate (40). Benzyloxycarbonyl isocyanate (22.2 g, 0.125 mol) in

toluene (50 mL) was added dropwise to a stirred solution of pyrrole (8.38 g, 0.125 mol) in toluene (50 mL), over the course of 1 h. The reaction mixture was kept under nitrogen and its temperature was held at 30–40 °C by intermittent cooling. After completion of the addition, the solution was stirred at room temperature for a further 22 h, then it was filtered and the gray precipitate was washed with five 25-mL portions of ether. The precipitate was dissolved in dichloromethane and passed through a bed of silica gel to remove the colored impurities. The product (26.8 g, 88%) obtained after concentration was sufficiently pure enough for further use. Mp: 154–156 °C. IR (neat, cm^{-1}): 3274, 1751, 1664, 1508, 1408; ^1H NMR (500 MHz, CD_3OD): δ=5.21 (s, 2H), 6.19 (dd, J=3.7, 2.8 Hz, 1H), 7.02–7.04 (m, H), 7.31–7.37 (m, 3H), 7.42 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD): δ=66.8, 109.5, 113.8, 124.5, 128.0, 128.1, 128.2, 135.9, 152.2, 159.4; HRMS-ESI: calcd for $C_{13}H_{12}N_2O_3Na$ $(M+Na)^+$ 267.0740, found 267.0737.

2.1.24. 2-[(1*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)-1-propenyl]pyrrolo[1,2-*c*]imidazole-1,3-dione (43). From **40**: To the degassed reaction mixture containing **24** (150 mg, 0.48 mmol), PPh_3 (15 mg, 0.057 mmol) in dry DMF (2 mL), was added $Pd_2(dba)_3$ (26 mg, 0.029 mmol). After stirring at room temperature for 5 min, freshly generated sodium salt prepared from **40** [(142 mg, 0.58 mmol) in dry DMF (5 mL) at 0 °C was added 60% NaH (22 mg, 0.95 mmol and stirred for 30 min at room temperature) and stirred at 100 °C for 22 h. The DMF was removed under reduced pressure and the residue was partitioned between water (2 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography (hexane/EtOAc; 3:7) to furnish **43** (62 mg, 39%) as a colorless solid.

From **42**: To the degassed reaction mixture containing **24** (200 mg, 0.64 mmol), PPh_3 (20 mg, 0.076 mmol), and imide **42** (108 mg, 0.82 mmol) in DMF (4 mL) was added $Pd_2(dba)_3$ (35 mg, 0.038 mmol) and stirred at 70 °C for 32 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexane/EtOAc; 3:7) to furnish **43** (115 mg, 54%) as colorless solid; mp: 105–107 °C. IR (neat, cm^{-1}): 3129, 1790, 1726; ^1H NMR (300 MHz): δ=4.31 (d, J=6.4 Hz, 2H), 5.06 (s, 2H), 6.44 (dt, J=15.6, 6.4 Hz, 1H), 6.43 (t, J=3.2 Hz, 1H), 6.77 (d, J=15.6 Hz, 1H), 6.83 (s, 1H), 7.15 (m, 2H), 7.24 (d, J=2.7 Hz, 1H), 7.32–7.37 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=40.7, 51.3, 113.8, 117.6, 117.9, 119.3, 120.8, 126.3, 127.6, 128.7, 129.4, 136.2, 138.1, 140.1, 149.5, 158.6; HRMS-ESI: calcd for $C_{19}H_{17}N_4O_2$ $(M+H)^+$ 333.1346, found 333.1336.

2.1.25. *N*-[(*E*)-3-(1-Benzyl-1*H*-imidazol-4-yl)prop-1-enyl] 1*H*-pyrrole-2-carboxamide (41). To **43** (50 mg, 0.15 mmol) in THF (3 mL) was added 10% aqueous sodium hydroxide (0.2 mL) and heated at 70 °C for about 15 min. The reaction mixture was cooled and diluted with CH_2Cl_2. The organic solution was washed with water, dried (Na_2SO_4), filtered, and concentrated. The residue obtained was purified by column chromatography (MeOH/EtOAc; 5:95) to furnish the pure **41** (33 mg, 72%) as a colorless solid; mp: 137–139 °C. IR (neat, cm^{-1}): 3229, 1625, 1560, 1522; ^1H NMR (500 MHz, CD_3OD): δ=3.92 (dd, J=1.4, 6.0 Hz, 2H), 5.02 (s, 2H), 6.03 (dd, J=4.2, 2.8 Hz, 1H), 6.11 (dt, J=15.6, 6.0 Hz, 1H), 6.28 (d, J=15.6 Hz, 1H), 6.67 (dd, J=3.7, 1.4 Hz, 1H), 6.77 (dd, J=2.4, 1.4 Hz, 1H), 6.92 (s, 1H), 7.11 (d, J=7.3 Hz, 2H), 7.16–7.24 (m, 4H), 7.53 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD): δ=40.8, 50.5, 109.0, 110.6, 117.3, 121.7, 122.7, 124.5, 125.7, 127.5, 128.1, 128.8, 137.0, 137.8, 139.8, 162.5; HRMS-ESI: calcd for $C_{18}H_{18}N_4O$ $(M+H)^+$ 307.1553, found 307.1547.

2.1.26. Ethyl 5-(1*H*-imidazol-4(5)-yl)-2-aminopentanoate (44). From **37**: To a stirred solution of the diphenylamine Schiff's base **37** (140 mg, 0.30 mmol) in dry ethanol, was added 10% Pd/C (100 mg), followed by anhydrous ammonium formate (285 mg, 4.53 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 14 h under nitrogen. The reaction mixture was filtered over Celite and the filter cake was washed repeatedly with hot ethanol. The filtrate was evaporated under reduced pressure followed by purification of the residue by chromatography on silica gel (MeOH/EtOAc; 1:4) furnished **44** (60 mg, 94%) as viscous oil.

From **38**: To a stirred solution of the nitroester **38** (300 mg, 0.91 mmol) in dry ethanol (5 mL), was added 10% Pd/C (120 mg), followed by anhydrous ammonium formate (0.6 g, 9.5 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 3 h under argon. After cooling to room temperature, the reaction mixture was filtered through Celite and the filter cake was washed repeatedly with hot ethanol. The filtrate was evaporated under reduced pressure to give the pure amino ester **44** in quantitative yield (192 mg). IR (neat, cm^{-1}): 2937, 1731; ^1H NMR (300 MHz): δ=1.23 (t, J=7.2 Hz, 3H), 1.55–1.9 (m, 4H), 2.61 (m, 2H), 3.43 (m, 1H), 4.13 (q, J=7.2 Hz, 2H), 6.73 (s, 1H), 7.51 (s, 1H); ^{13}C NMR (75 MHz): δ=14.2, 25.4, 26.3, 34.2, 54.2, 61.0, 117.1, 134.5, 136.5, 175.8. HRMS-ESI: calcd for $C_{10}H_{18}N_3O_2$ $(M+H)^+$ 212.1394, found 212.1390.

2.1.27. 5-(1*H*-Imidazol-4(5)-yl)-2-aminopentanoic acid (45). The amino ester **44** (50 mg, 0.24 mmol) was treated with NaOH (18 mg, 0.45 mmol) in 3:2 ethanol/water (5 mL) and was allowed to stir at room temperature. The solvent was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 mL). The aqueous layer was rendered acidic with concd HCl solution and loaded on to a prewashed (resin was washed with 100 mL of methanol followed by 100 mL of water) Dowex 50x2, 200 (H^+ form) ion-exchange resin. The column was eluted first with distilled water (100 mL) until the pH was neutral and then with 100 mL of 15% ammonia solution. The eluate was concentrated under reduced pressure to furnish the colorless crystals of the amino acid **45** (85% yield, 37 mg). ^1H NMR (300 MHz, D_2O): δ=1.75 (m, 2H), 1.83 (m, 2H), 2.60 (t, J=6.6 Hz, 2H), 3.66 (t, J=5.1 Hz, 1H), 6.83 (s, 1H), 7.64 (s, 1H).

2.1.28. Ethyl 5-[(4*E*)-3-(1-benzyl-1*H*-imidazol-4-yl)]-2-nitro-2-(2-propynyl)pent-4-enoate acid (46). Propargyl bromide (80 wt % toluene solution, stabilized by MgO,

0.451 mL, 4.01 mmol) was added to a mixture containing the nitroacetate **38** (1.1 g, 3.3 mmol), K_2CO_3 (600 mg, 4.35 mmol), and benzyl triethylammonium chloride (75 mg, 0.33 mmol) in dry CH_3CN (10 mL) and stirred at room temperature overnight. After removing the acetonitrile at rt, the residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography using (hexane/EtOAc, 2:3) to furnish pure **46** as thick oil in 41% (500 mg) yield. IR (neat, cm^{-1}): 3293, 1750, 1555; ^1H NMR (300 MHz): δ=1.27 (t, J=7.2 Hz, 3H), 2.11 (t, J=2.7 Hz, 1H), 3.07–3.26 (m, 4H), 4.27 (q, J=7.2 Hz, 2H), 5.00 (s, 2H), 6.05 (dt, J=15.6, 7.8 Hz, 1H), 6.42 (d, J=15.6 Hz, 1H), 6.79 (s, 1H), 7.15 (m, 2H), 7.34–7.36 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 24.4, 36.7, 51.0, 63.3, 73.3, 76.0, 93.5, 117.3, 117.8, 127.4, 128.2, 128.5, 129.1, 135.8, 137.7, 140.0, 165.1; HRMS-ESI: calcd for $C_{20}H_{22}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1588.

2.1.29. Ethyl 1-benzyl-6-nitro-1,4,4a,5,6,7-hexahydroindeno[5,6-*d*]imidazole-6-carboxylate (47). The substrate **46** (115 mg, 0.31 mmol) was dissolved in toluene (20 mL) in a resealable pressure tube. The solution was degassed by bubbling N_2 through the mixture for a few minutes and then the tube was sealed and heated at 145 °C for 48 h. Finally, the solvent was removed by rotary evaporation, followed by purification of the residue by chromatography (hexane/EtOAc; 16:3) furnished the cycloadducts **47** (55 mg, 48%, viscous oil) and **48** (32 mg, 28%, viscous oil). IR (neat, cm^{-1}):=1747, 1552; ^1H NMR (300 MHz): δ=1.277, 1.271 (t, J=7.2 Hz, 3H), 2.26 (m, 1H), 2.46–2.64 (m, 1H), 2.86–3.34 (m, 4H), 3.52–3.59 (m, 1H), 4.26, 4.27 (q, J=7.2 Hz, 2H), 5.02 (ABq, J=15.7 Hz, 2H), 6.02 (d, J=2.1 Hz, 1H), 7.09 (m, 2H), 7.31–7.36 (m, 4H); ^{13}C NMR (75 MHz): δ=13.9, 28.6, 29.1, 39.7, 40.0, 40.3, 40.4, 40.7, 41.7, 48.8, 63.3, 97.3, 98.7, 108.8, 109.0, 126.8, 127.6, 128.2, 129.1, 135.8, 135.9, 136.1, 137.1, 137.4, 137.6, 166.6, 166.8 (mixture of diastereomers); HRMS-ESI: calcd for $C_{20}H_{22}N_3O_4$ $(M+H)^+$ 368.1605, found 368.1588.

2.1.30. Ethyl 1-benzyl-6-nitro-1,5,6,7-tetrahydroindeno[5,6-*d*]imidazole-6-carboxylate (48). The substrate **46** (130 mg, 0.35 mmol) was dissolved in toluene (30 mL) in a resealable pressure tube. The solution was bubbled with N_2 for a few minutes and 10% Pd/C (0.270 g) was added. The tube was sealed and heated at 145 °C for 48 h. Finally, the solvent was removed by rotary evaporation followed by purification of the residue by chromatography (hexane/EtOAc; 4:1) furnished the cycloadduct **48** as thick oil in yield (50 mg, 39%). IR (neat, cm^{-1}): 2924, 1747, 1553; ^1H NMR (300 MHz): δ=1.29 (t, J=7.3 Hz, 3H), 3.87 (dd, J=17.1, 2.7 Hz, 2H), 4.03 (d, J=17.4 Hz, 1H), 4.13 (d, J=17.4 Hz, 1H), 5.00 (s, 2H), 4.31 (q, J=7.3 Hz, 2H), 7.10 (s, 1H), 7.21 (m, 2H), 7.33 (m, 3H), 7.64 (s, 1H), 7.91 (s, 1H); ^{13}C NMR (75 MHz): δ=13.9, 41.7, 42.0, 49.0, 63.3, 99.4, 106.0, 116.0, 127.0, 128.4, 129.2, 132.2, 133.1, 135.3, 166.7; HRMS-ESI: calcd for $C_{20}H_{20}N_3O_4$ $(M+H)^+$ 366.1448, found 366.1439.

2.1.31. Ethyl 6-amino-1,5,6,7-tetrahydro-indeno[5,6-*d*]imidazole-6-carboxylate (49). To a stirred solution of the nitroester **48** (60 mg, 0.164 mmol) in dry ethanol, was added 10% Pd/C (30 mg), followed by anhydrous ammonium formate (0.103 g, 1.64 mmol) in one portion. The resulting heterogeneous reaction mixture was stirred at reflux for 18 h under argon. The reaction mixture was filtered through Celite and was repeatedly washed with hot ethanol. The filtrate was concentrated by rotary evaporation followed by purification of the residue by chromatography (hexane/EtOAc; 1:19) provided the pure amino ester **49** (22 mg, 55%) as a colorless oil. In addition, the deaminated derivative **50** (17 mg, 45%) was isolated as a white solid. IR (neat, cm^{-1}): 2980, 1725; ^1H NMR (500 MHz): δ=1.26 (t, J=7.3 Hz, 3H), 2.90 (d, J=15.8 Hz, 2H), 3.61 (d, J=15.8 Hz, 2H), 4.19 (q, J=7.3 Hz, 2H), 7.34 (s, 2H), 7.66 (m, 1H); ^{13}C NMR (75 MHz): δ=14.3, 45.6, 61.5, 65.8, 111.4, 135.6, 137.4, 140.5, 176.4. HRMS-ESI: calcd for $C_{13}H_{16}N_3O_2$ $(M+H)^+$ 246.1237, found 246.1233.

2.1.32. Ethyl 1,5,6,7-tetrahydro-indeno[5,6-*d*]imidazole-6-carboxylate (50). Mp: 121–123 °C. IR (neat, cm^{-1}): 2956, 1729; ^1H NMR (300 MHz): δ=1.28 (t, J=7.2 Hz, 3H), 3.31 (m, 5H), 4.17 (q, J=7.2 Hz, 2H), 7.44 (s, 2H), 7.99 (s, 1H); ^{13}C NMR (75 MHz): δ=14.3, 36.0, 44.7, 60.7, 110.8, 137.2, 140.3, 175.4; HRMS-ESI: calcd for $C_{13}H_{15}N_2O_2$ $(M+H)^+$ 231.1128, found 231.1123.

2.1.33. 6-Amino-1,5,6,7-tetrahydroindeno[5,6-*d*]imidazole-6-carboxylic acid (49). The amino ester **49** (15 mg, 0.061 mmol) was treated with NaOH (4 mg, 0.12 mmol) in 3:2 methanol/water (5 mL) and was allowed to stir at room temperature for 6 h. The solvent was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 mL). The aqueous layer was rendered acidic with concd HCl solution and loaded on to prewashed (resin was washed with 100 mL of methanol followed by 100 mL of water) Dowex 50x2, 200 (H^+ form) ion-exchange resin. The column was eluted first with distilled water (100 mL) until neutral pH was achieved and then with 15% ammonia solution (100 mL). The eluate was concentrated under reduced pressure to furnish the colorless crystals of amino acid **51** (11 mg, 83%). Mp: >260 °C. IR (neat, cm^{-1}): 3105, 2123, 1579; ^1H NMR (300 MHz, CD_3OD): δ=3.21 (d, J=16.9 Hz, 2H), 3.82 (d, J=16.9 Hz, 2H), 7.47 (s, 2H), 8.08 (s, 1H); HRMS-ESI: calcd for $C_{11}H_{12}N_3O_2$ $(M+H)^+$ 218.0924, found 218.0920.

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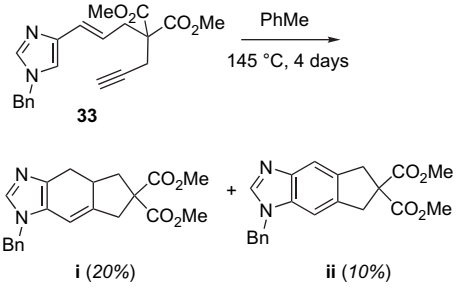

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