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FULL PAPER

Multicomponent Synthesis of Structurally Diverse Imidazoles Featuring Azirines, Amines and Aldehydes

Thaís A. Rossa,[a] Mariane Fantinel,[a] Adailton J. Bortoluzzi,[a] Marcus M. Sá*[a]

Abstract: A novel and efficient method for the synthesis of structurally diverse imidazoles through a multicomponent reaction involving an azirine, an amine, and an aldehyde is described. The method is simple and environmentally benign, producing multifunctionalized imidazoles in moderate-to-good yields and in a regioselective manner, which was demonstrated by NMR experiments and X-ray analysis. A mechanism is proposed where the amine participates not only as a reactant, but also as a nucleophilic reaction promoter.

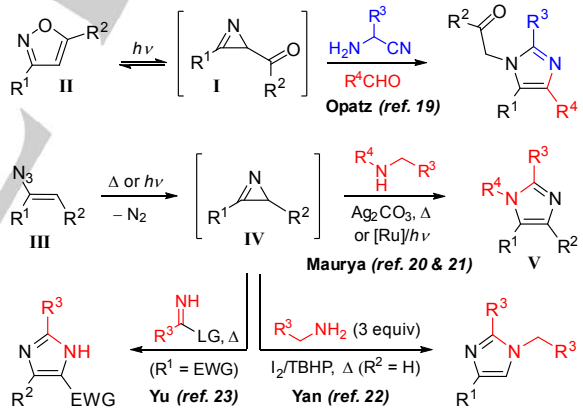
Introduction

The increasing environmental awareness of the chemical community within the past two decades has boosted the development of reliable synthetic strategies to produce useful chemicals in a simple and sustainable way.[1] In this context, azirines have been recognized as versatile building blocks in organic synthesis, being able to undergo ring expansion reactions under mild conditions, mainly due to the ring strain of the unsaturated three-membered ring.[2] Nevertheless, substituted azirines are usually stable and can be stored for long periods. Over the years, significant studies have been reported on the synthesis of N-heterocycles from azirines,[3-8] including, among others, pyrazines, pyrroles, oxazoles, indoles, and imidazoles.[9-11]

Imidazoles are a major class of heterocyclic compounds, being highly relevant in medicinal chemistry and materials science. Imidazoles and analogues are related to a broad spectrum of biological properties, such as anti-inflammatory, antitumor, antifungal, antimicrobial, and antiparasitic activity.[12-14] Due to its unique acid-base character, the imidazole scaffold is also very useful for the creation of advanced materials, including ionic liquids[15] and functionalized catalysts.[16] The substitution pattern of the imidazole ring is frequently associated with the chemical, physical, and biological properties of the resultant compound and can modulate its potential application. Thus, the development of simple and efficient strategies for the selective preparation of structurally diverse imidazoles is highly desirable.

The conventional approach for the synthesis of tetrasubstituted imidazoles usually employs a 1,2-diketone, an aldehyde, an amine and an ammonia source. However, significant limitations, such as competitive formation of trisubstituted imidazoles and lack of structural diversity, motivates the development of green and efficient methods.[17,18]

In recent years, the synthesis of imidazoles employing azirines or their precursors as starting materials has been actively pursued. Pusch & Opatz proposed the intermediacy of acyl azirine **I** in the synthesis of tetrasubstituted imidazoles through a photochemical one-pot reaction between isoxazole **II**, an α-aminonitrile, and an aldehyde (Scheme 1).[19] The synthesis of tri- and tetrasubstituted imidazoles from vinyl azides **III** and amines under oxidative conditions was independently reported by the research groups of Maurya[20,21] and Yan.[22] Both authors proposed the *in situ* generation of azirines **IV** through thermolysis or photolysis of the corresponding vinyl azides **III**. Similarly, Yu and co-workers developed a method for the synthesis of trisubstituted imidazoles from activated imidates and α-azido enoates or enones (**III**, R^1 = electron-withdrawing group, EWG), possibly involving the intermediacy of azirine **IV**.[23]



Scheme 1. Previous synthesis of imidazoles from isoxazoles **II** or vinyl azides **III** through the possible intermediacy of azirines **I** or **IV**.

The direct synthesis of imidazoles from azirines can be achieved by treating **IV** with imines in the presence of stoichiometric amounts of Lewis acids, as demonstrated by Auricchio[24] and later by Pinho e Melo[25] (Scheme 2). Although the expected imidazole **V** has been obtained as a sole product in a number of cases, the regioselectivity is strongly dependent on the substitution pattern at the azirine ring[25] as well as on the reaction conditions.[24] Therefore, further progress in the selective synthesis of imidazoles from azirines is needed in order for this to be considered a simple and reliable process.

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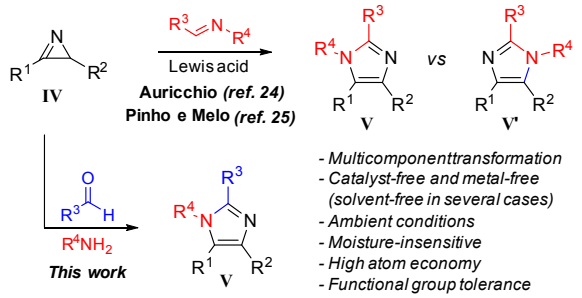


Scheme 2. Synthesis of imidazoles from azirines **IV**.

The development of a simple, yet efficient, protocol for the synthesis of imidazoles from azirines requires readily available starting materials. In addition, the procedure should involve mild and environmentally friendly conditions, offer high atom economy and excellent tolerance to functional groups, and possibly generate structurally diverse imidazoles in a single synthetic operation.

While the participation of small-ring heterocycles in domino and multicomponent transformations has been recently reviewed,[26] only one report on the multicomponent reaction involving azirines could be found in the literature.[7] Herein, we report a novel and straightforward procedure for the synthesis of type **V** tetrasubstituted imidazoles through a three-component reaction involving azirines **IV**, aldehydes and amines at room temperature (Scheme 2). The conditions employed here are extremely simple, without any addition of Lewis acid, additive or oxidant agent, and is solvent-free in several cases.

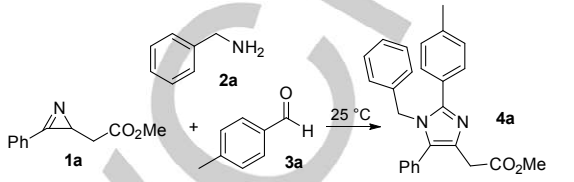
Results and Discussion

Azirine **1a**, benzylamine (**2a**) and tolualdehyde (**3a**) were used as model substrates for the initial experiments. Several environmentally benign solvents[27,28] were evaluated (Table 1, entries 1-6), with the most effective being ^{i}PrOH, which gave imidazole **4a** in 74% isolated yield (entry 6). The reaction under neat conditions also showed encouraging results, furnishing imidazole **4a** in fair isolated yield (entry 7).

Remarkably, the reaction is strongly dependent on the amine/aldehyde ratio (Table 1, entries 6, 8-10), with the optimal results being observed when amine **2a** is in slight excess relative to the aldehyde **3a** (entries 6 and 10). Conversely, the use of equal amounts of **2**:**3** (entry 8) or an incremental excess of aldehyde **3a** (entry 9) was detrimental to the reaction rate. Several additives were also tested, but, as a rule, they exerted little or no influence on the outcome of the reaction (results not shown). The only notable result was that the use of anhydrous Na_2SO_4, which possibly acts as a desiccant agent, provided the expected imidazole **4a** in slightly better yield, but at the expense of a prolonged reaction time (entry 11).

After defining the best conditions (Table 1, entries 6, 7, 11), the scope of the multicomponent transformation was investigated in detail. The reactions were carried out using representative aromatic as well as aliphatic aldehydes and primary amines containing several functionalities, evidencing the broad scope of this method (Scheme 3).

Table 1. Optimization of reaction conditions[a]



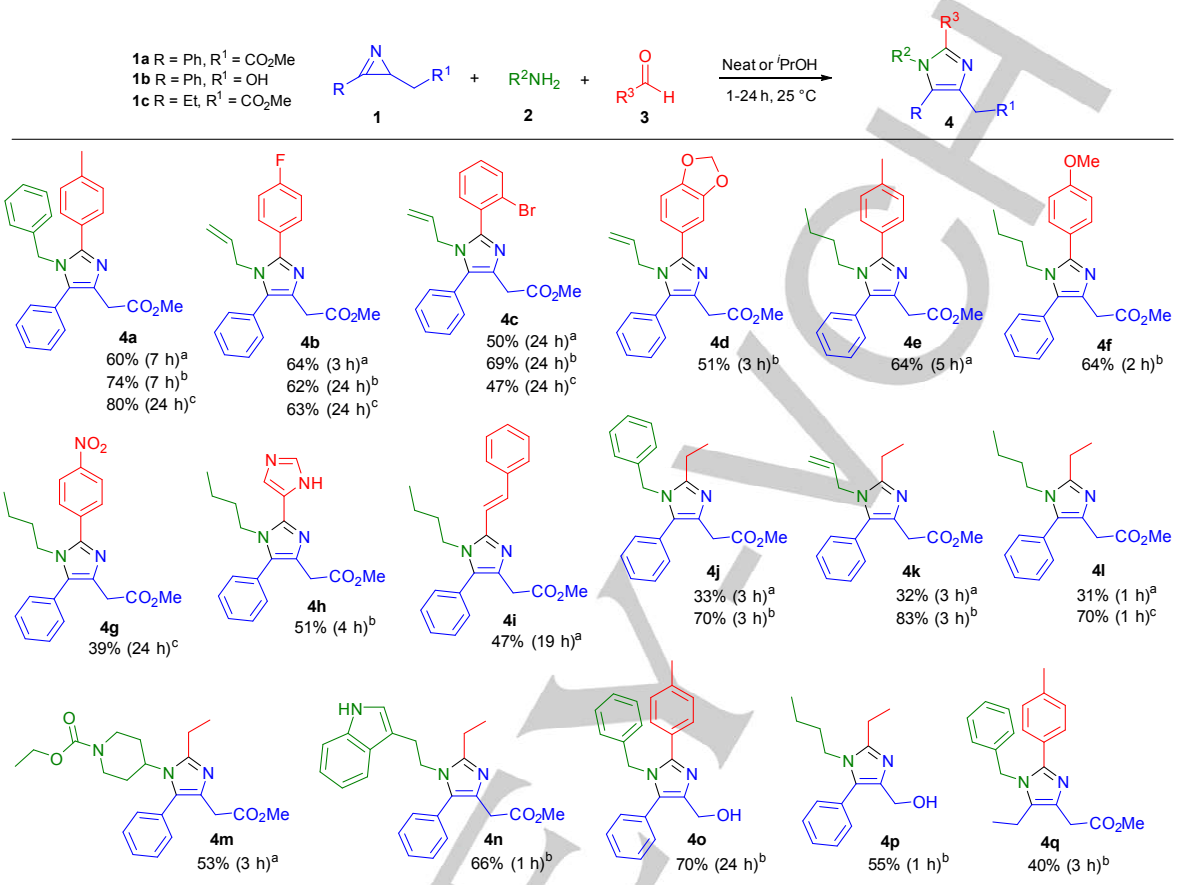
Entry	2a (equiv)	3a (equiv)	Solvent	Time (h)	Yield (%)[b]
1	1.3	1.1	EtOAc	24	- [c]
2	1.3	1.1	CH_3CN	7	67
3	1.3	1.1	PEG	7	51
4	1.3	1.1	H_2O	7	52
5	1.3	1.1	^{t}BuOH	7	56
6	1.3	1.1	^{i}PrOH	7	74
7	1.3	1.1	-	7	60
8	1.0	1.0	^{i}PrOH	24	- [c]
9	1.1	1.3	^{i}PrOH	24	- [c]
10	1.5	1.1	^{i}PrOH	7	73
11	1.3	1.1	^{i}PrOH[d]	24	80

[a] The reaction was monitored by TLC until the total consumption of azirine **1a**. [b] Yields of isolated imidazole **4a** after column chromatography. [c] Incomplete conversion to **4a** (< 80%, measured by ^{1}H NMR). [d] Na_2SO_4 (350 mg/mmol **1a**) was added to the reaction.

The reactions using aromatic aldehydes performed satisfactorily under neat conditions as well as with ^{i}PrOH as the solvent. For the aliphatic aldehydes, however, the solvent-free conditions were generally inefficient and the best yields were achieved in alcoholic medium. The reaction also worked well with substituted azirines **1b** and **1c**, giving the expected imidazoles **4o-q** in moderate-to-good yields.

For the preparative synthesis of imidazoles **4**, the multicomponent reaction starting from 3 mmol of the corresponding azirine **1** was carried out to give the expected product in yield and purity comparable to those obtained from a 0.5-mmol scale.

Imidazole-4-acetates **4** were fully characterized by spectroscopic analysis, including 2D NMR techniques, which confirmed the proposed structure and ruled out the formation of the regioisomeric imidazole-5-acetate (Supp Info: Fig. S52 and S53). The unequivocal structural determination of multisubstituted imidazoles **4** was also achieved by single crystal X-ray methods after crystallizing **4a** in methanol and **4l** in ether/hexane (Fig. 1).[29]



[a] Reaction conducted without solvent (neat conditions); [b] Using iPrOH as the solvent; [c] Using iPrOH as the solvent with addition of Na_2SO_4.

Scheme 3. Multicomponent synthesis of tetrasubstituted imidazoles **4**.

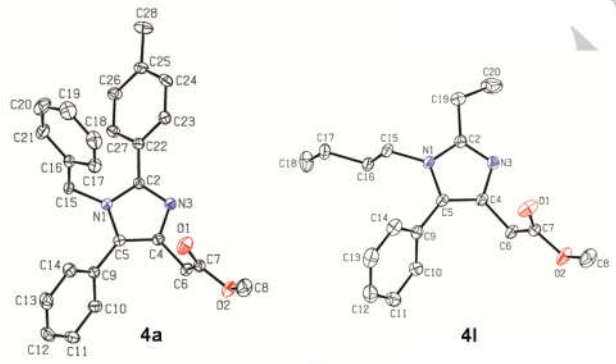


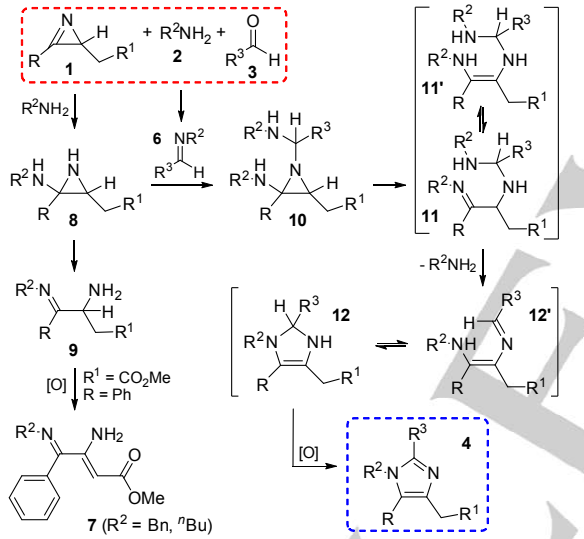
Figure 1. ORTEP plots of imidazoles **4a** and **4l**; ellipsoids are drawn at the 40% probability level

To rationalize the mechanism of this multicomponent process, the reaction profile was studied in more detail. Monitoring the reaction by NMR and LC-MS revealed, as expected, the presence of imine **6** as an intermediate, originating from a fast condensation involving amine **2** and aldehyde **3** (Scheme 4). In fact, imine **6a** (prepared from amine **2a** and aldehyde **3a** through conventional methods)[30] was found to react with azirine **1a** to give the expected imidazole **4a**. However, the reaction rate was much slower (24 h, 55%) than the multicomponent reaction starting from the precursors **2a** and **3a**. Repeating the reaction between equimolar amounts of azirine **1a** and imine **6a**, but in the presence of 0.2 equiv of amine **2a**, led to a complete conversion to imidazole **4a** with a reaction rate comparable to that observed for the multicomponent process. This result is in line with the previous observation that a slight excess of amine is highly beneficial in terms of the reaction rate (see Table 1, entries 6, 8-10).

Therefore, it seems clear that amine **2** exerts a dual role, acting not only as a reagent but also as a reaction promoter. In fact, when azirine **1a** is treated with amine **2** in the absence of aldehyde, both starting materials are rapidly consumed to give rise to a γ-imino-β-enamino ester **7** as the major product (Scheme 4). This transformation can be rationalized by considering an initial attack of amine **2** on the electrophilic C=N bond in azirine **1** to generate the addition adduct **8**, which could be evidenced by

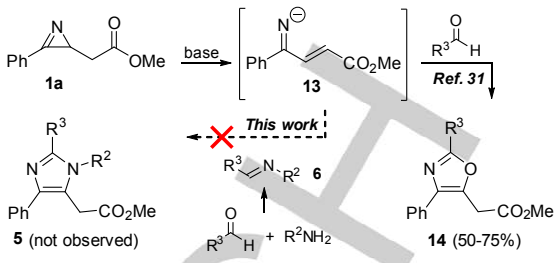
monitoring the reaction profile by mass spectrometry (R = Ph, R^1 = CO_2Me, R^2 = Bn: MH^+, m/z = 297). Subsequent ring opening of aziridine **8** followed by spontaneous air oxidation of **9** would lead to **7**, which had its structure assigned through ^1H NMR, ^{13}C NMR, IR, and HRMS analyses. However, full characterization was precluded due to its partial decomposition on attempted purification by chromatography.

All of these observations are interconnected and support the following mechanistic pathway (Scheme 4). Initially, there is competition between the reversible nucleophilic attack of amine **2** on aldehyde **3** (to form imine **6**) and that on azirine **1** (to generate adduct **8**). Once they are formed, these two intermediates react with each other in the next step through nucleophilic addition to furnish the tetracomponent adduct **10**, which may isomerize to the ring-opening forms **11** followed by the elimination of amine **2**, which gives rise to one or more of the isomers **12**, as noted from the MS analysis (R = Ph, R^1 = CO_2Me, R^2 = Bn, R^3 = 4-MePh: MH^+, m/z = 399). Subsequent air oxidation in the last step provides the aromatic imidazole framework **4**.



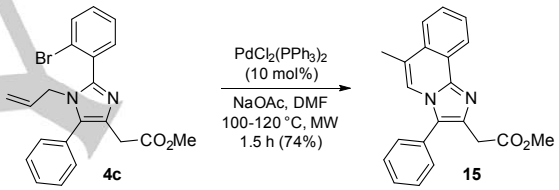
Scheme 4. Proposed mechanism for the multicomponent synthesis of tetrasubstituted imidazoles **4.**

As reported previously,[31] azirine-2-acetate **1a** was employed in a two-step synthesis of oxazole-5-acetates **14**. In this particular case, the presence of an activated methylene group adjacent to the azirine ring enabled a base-mediated ring-opening process with the formation of a stabilized iminyl anion **13**, which reacts with aldehydes to furnish oxazoles **14** after a subsequent oxidation step (Scheme 5). However, this mechanism is ruled out in the present case because a pre-formed imine **6** would lead to the regioisomeric imidazole-5-acetate **5**, which was not observed in the crude reaction. In addition, the formation of the expected imidazole-4-methanol **4o,p** from the cinnamyl-derived azirine **1b** also excludes the involvement of an enolate-type intermediate **13**.



Scheme 5. Proposed base-mediated mechanism for the ring-opening of azirine **1**.

The tetrasubstituted imidazoles **4** obtained by this method are structurally diverse scaffolds that can be readily manipulated to improve the chemical complexity. To further demonstrate the synthetic potential of imidazoles **4** as useful building blocks, we designed an intramolecular palladium-catalyzed Heck reaction[32] for the synthesis of an analogue of zolpidem,[33] a sedative used for the treatment of sleep disturbances. Accordingly, starting from imidazole **4c**, the microwave-assisted intramolecular coupling was successfully achieved in a short time to give the expected fused tricycle **15** in good isolated yield (Scheme 6).



Scheme 6. Synthesis of imidazo[2,1-*a*]isoquinoline **15** from **4c** through intramolecular Pd-catalyzed coupling.

Conclusions

We have developed a simple and straightforward procedure to access structurally diverse imidazoles **4** through a three-component process involving the reaction of azirines **1** with aldehydes and amines in the absence of any additive or metallic catalyst. The key features of this environmentally friendly method include the use of readily available starting materials, together with high atom economy, good yields, and excellent functional group tolerance, leading to multisubstituted imidazoles **4** in a single step. The proposed reaction mechanism through nucleophilic catalysis described here is novel and conceptually different from the known Lewis acid-mediated preparation of imidazoles from azirines.[24,25] The synthetic usefulness of imidazoles **4** was verified by direct post-transformation to an exquisite fused tricyclic scaffold. Although being broad in scope, one limitation of this multicomponent reaction concerns the use of aromatic amines, such as substituted anilines, which did not work under the conditions presented here. Nevertheless, further studies are currently being carried out to expand this methodology to other classes of compounds, as well as to uncover its mechanistic intricacies, which will be reported in due course.

Experimental Section

General Experimental Methods

All chemicals were of reagent grade and were used as received. Melting points were determined using a hot plate apparatus and are uncorrected. Infrared spectra were acquired with a FT-IR spectrometer (range 4000-400 cm^{-1}) using KBr. ^1H NMR spectra were recorded at 400 MHz or at 200 MHz and ^{13}C NMR spectra (fully decoupled) were recorded at 100 MHz or at 50 MHz. Splitting patterns are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), ddd (doublet of doublet of doublet), ddt (doublet of doublet of triplet), t (triplet), tt (triplet of triplet), q (quartet), qt (quintet), sx (sextet), m (multiplet), apt (apparent triplet), apdt (apparent doublet of triplet). Coupling constants (*J*) are measured in Hertz (Hz). Chemical shifts were recorded in parts per million (ppm, δ) relative to TMS or solvent peak ($CDCl_3$ at 7.26 ppm for ^1H NMR, and $CDCl_3$ at 77.16 ppm for ^{13}C NMR) as the internal standard. Column chromatography was performed using silica gel (70-230 mesh) as the stationary phase and hexane/ethyl acetate as the eluent, except for the indole-substituted imidazole **4n**, which was purified by chromatography using alumina (neutral, ~150 mesh) instead of silica gel. TLC analysis was performed in silica gel plates. The ESI-QTOF mass spectrometer was operated in the positive ion mode at 4.5 kV and at a desolvation temperature of 180 °C. The standard electrospray ion (ESI) source was used to generate the ions. The instrument was calibrated in the range *m/z* 50-3000 using a calibration standard (low concentration tuning mix solution) and data were processed with the aid of computer software. Microwave assisted reactions were performed in 10 mL sealed tubes in a monomode microwave CEM Explorer reactor instrument with infrared temperature monitoring and a noninvasive pressure transducer (maximum pressure = 200 psi, t = 1 min ramp, 1 min cooling, stirring mode "on"). Complete experimental procedure for the preparation of azirines **1a-c** is described in the Supporting Information.

General Procedure for the Synthesis of Imidazoles 4

Method A (solvent-free): To a flask containing azirine **1** (0.5 mmol) was added an aldehyde (0.50-0.55 mmol) and an amine (0.60-0.65 mmol) then the mixture was stirred at 25 °C. The reaction was accompanied by TLC until consumption of the starting azirine (1-24 h). Then, the volatile components were evaporated under reduced pressure and the crude product was directly purified by column chromatography (gradient: hexane/EtOAc 8:2 → hexane/EtOAc 1:1 or hexane/EtOAc 8:2 → 100% EtOAc).

Method B: To a stirred solution of azirine **1** (0.5 mmol) in ^{i}PrOH (1.0 mL) was added an aldehyde (0.50-0.55 mmol) and an amine (0.60-0.65 mmol) then the mixture was stirred at 25 °C. The reaction was accompanied by TLC until consumption of the starting azirine (1-24 h). Then, the volatile components were evaporated under reduced pressure and the crude product was purified by column chromatography as described for method A.

Method C: Identical to method B, but with the addition of anhydrous Na_2SO_4 (350 mg/mmol azirine) in the beginning of the reaction.

*Methyl 1-benzyl-5-phenyl-2-(4-tolyl)-1H-imidazole-4-acetate (**4a**)*. Method A: yield 60% (119 mg); method B: yield 74% (147 mg); method C: yield 80% (159 mg); yellow solid, mp 135.5-136.0 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (s, 3H), 3.63 (s, 2H), 3.66 (s, 3H), 5.13 (s, 2H), 6.75-6.80 (m, 2H), 7.12-7.35 (m, 10H), 7.47 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3 (CH_3), 33.6 (CH_2), 48.5 (CH_2), 51.9 (CH_3), 125.9 (2 × CH), 127.3 (CH), 127.9 (C), 128.4 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 128.9 (2 × CH), 129.2 (2 × CH), 129.8 (C), 130.4 (2 × CH), 131.9 (C), 132.5 (C), 137.7 (C), 138.7 (C), 148.1 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3029, 2949, 1738, 1605, 1450, 1201, 1158, 732, 702. HRMS (ESI+): calcd. for $C_{26}H_{25}N_2O_2^+$ $[M+H]^+$ 397.1911; found 397.1906.

*Methyl 1-allyl-2-(4-fluorophenyl)-5-phenyl-1H-imidazole-4-acetate (**4b**)*. Method A: yield 64% (112 mg); method B: yield 62% (109 mg); method C: yield 63% (110 mg); yellow solid, mp 76.3-77.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.59 (s, 2H), 3.67 (s, 3H), 4.47-4.49 (m, 2H), 4.83 (d, *J* = 17.1 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.74 (ddt, *J* = 17.1, 10.5, 4.4 Hz, 1H), 7.09-7.14 (m, 2H), 7.40-7.44 (m, 5H), 7.64-7.69 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.6 (CH_2), 47.2 (CH_2), 51.9 (CH_3), 115.5 (d, *J* = 20.5 Hz, 2 × CH), 117.2 (CH_2), 127.1 (d, *J* = 4.4 Hz, C), 128.65 (2 × CH), 128.68 (CH), 129.8 (C), 130.6 (2 × CH), 130.9 (d, *J* = 8.8 Hz, 2 × CH), 132.0 (C), 132.4 (C), 133.8 (CH), 146.6 (C), 163.2 (d, *J* = 249.4 Hz, C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3057, 2953, 1734, 1605, 1530, 1352, 1212, 1163, 991, 848, 785, 708. HRMS (ESI+): calcd. for $C_{21}H_{20}FN_2O_2^+$ $[M+H]^+$ 351.1503; found 351.1505.

*Methyl 1-allyl-2-(2-bromophenyl)-5-phenyl-1H-imidazole-4-acetate (**4c**)*. Method A: yield 50% (103 mg); method B: yield 69% (144 mg); method C: yield 47% (97 mg); yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (s, 2H), 3.67 (s, 3H), 4.34-4.36 (m, 2H), 4.62 (dd, *J* = 17.1, 1.0 Hz, 1H), 4.93 (dd, *J* = 10.3, 1.0 Hz, 1H), 5.53 (ddt, *J* = 17.1, 10.3, 4.9 Hz, 1H), 7.28-7.45 (m, 7H), 7.49 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.65 (dd, *J* = 7.7, 1.2 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 33.7 (CH_2), 47.2 (CH_2), 52.0 (CH_3), 116.9 (CH_2), 124.6 (C), 127.3 (CH), 128.5 (CH), 128.7 (2 × CH), 129.7 (C), 130.4 (2 × CH), 130.9 (CH), 131.1 (C), 132.1 (C), 132.7 (C), 132.8 (CH), 132.9 (CH), 133.0 (CH), 146.0 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3059, 2949, 1740, 1607, 1452, 1399, 1201, 1161, 1026, 757, 704. HRMS (ESI+): calcd. for $C_{21}H_{20}BrN_2O_2^+$ $[M+H]^+$ 411.0703; found 411.0702.

*Methyl 1-allyl-2-(3,4-methylenedioxyphenyl)-5-phenyl-1H-imidazole-4-acetate (**4d**)*. Method B: yield 51% (96 mg); yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 3.56 (s, 2H), 3.65 (s, 3H), 4.46-4.48 (m, 2H), 4.81 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 10.5 Hz, 1H), 5.71 (ddt, *J* = 17.1, 10.5, 4.4 Hz, 1H), 5.98 (s, 2H), 6.84 (d, *J* = 9.0 Hz, 1H), 7.12-7.15 (m, 2H), 7.37-7.42 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.7 (CH_2), 47.2 (CH_2), 51.9 (CH_3), 101.4 (CH_2), 108.3 (CH), 109.6 (CH), 117.1 (CH_2), 123.2 (CH), 124.9 (C), 128.57 (CH), 128.61 (2 × CH), 130.0 (C), 130.6 (2 × CH), 131.7 (C), 132.2 (C), 134.0 (CH), 147.3 (C), 147.8 (C), 148.3 (C), 172.0 (C). IR

(KBr, cm^{-1}): ν = 3079, 2951, 2898, 1738, 1471, 1250, 1167, 1038, 932, 820, 704. HRMS (ESI+): calcd. for $C_{22}H_{21}N_2O_4^+$ $[M+H]^+$ 377.1496; found 377.1497.

*Methyl 1-butyl-5-phenyl-2-(4-tolyl)-1H-imidazole-4-acetate (**4e**)*. Method A: yield 64% (115 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.60 (t, *J* = 7.4 Hz, 3H), 0.94 (sx, *J* = 7.4 Hz, 2H), 1.28 (qt, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 3.59 (s, 2H), 3.64 (s, 3H), 3.94 (t, *J* = 7.4 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.38-7.53 (m, 7H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.2 (CH_3), 19.4 (CH_2), 21.3 (CH_3), 32.4 (CH_2), 33.5 (CH_2), 44.8 (CH_2), 51.8 (CH_3), 128.3 (CH), 128.5 (C), 128.7 (2 × CH), 129.0 (2 × CH), 129.2 (2 × CH), 130.3 (2 × CH), 130.4 (C), 131.4 (C), 132.0 (C), 138.6 (C), 147.7 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3028, 2957, 2931, 2872, 1740, 1607, 1471, 1436, 1158, 1020, 826, 704. HRMS (ESI+): calcd. for $C_{23}H_{27}N_2O_2^+$ $[M+H]^+$ 363.2067; found 363.2072.

*Methyl 1-butyl-2-(4-methoxyphenyl)-5-phenyl-1H-imidazole-4-acetate (**4f**)*. Method B: yield 64% (121 mg); brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.60 (t, *J* = 7.3 Hz, 3H), 0.95 (sx, *J* = 7.3 Hz, 2H), 1.24-1.32 (m, 2H), 3.59 (s, 2H), 3.65 (s, 3H), 3.84 (s, 3H), 3.92 (t, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.40-7.48 (m, 5H), 7.56 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.3 (CH_3), 19.4 (CH_2), 32.4 (CH_2), 33.5 (CH_2), 44.8 (CH_2), 51.9 (OCH_3), 55.3 (CH_3), 114.0 (2 × CH), 123.7 (C), 128.3 (CH), 128.7 (2 × CH), 130.3 (2 × CH), 130.4 (C), 130.5 (2 × CH), 131.3 (C), 131.8 (C), 147.7 (C), 160.0 (C), 172.1 (C). IR (KBr, cm^{-1}): ν=3033, 2957, 1740, 1611, 1534, 1469, 1250, 1175, 1028, 838, 704. HRMS (ESI+): calcd. for $C_{23}H_{27}N_2O_3^+$ $[M+H]^+$ 379.2016; found 379.2015.

*Methyl 1-butyl-2-(4-nitrophenyl)-5-phenyl-1H-imidazole-4-acetate (**4g**)*. Method C: yield 39% (77 mg); orange solid, mp 69.3-73.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (t, *J* = 7.3 Hz, 3H), 0.98 (sx, *J* = 7.3 Hz, 2H), 1.33 (qt, *J* = 7.3 Hz, 2H), 3.60 (s, 2H), 3.67(s, 3H), 4.02 (t, *J* = 7.3 Hz, 2H), 7.42-7.53 (m, 5H), 7.87 (d, *J* = 8.6 Hz, 2H), 8.32 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2 (CH_3), 19.4 (CH_2), 32.5 (CH_2), 33.5 (CH_2), 45.3 (CH_2), 51.9 (CH_3) 123.9 (2 × CH), 128.87 (CH), 128.93 (2 × CH), 129.5 (2 × CH), 129.6 (C), 130.4 (2 × CH), 133.4 (C), 133.5 (C), 137.6 (C), 145.0 (C), 147.7 (C), 171.7 (C). IR (KBr, cm^{-1}): ν = 3059, 2962, 2929, 1736, 1599, 1522, 1348, 1210, 1148, 863, 708. HRMS (ESI+): calcd. for $C_{22}H_{24}N_3O_4^+$ $[M+H]^+$ 374.1761; found 394.1759.

*Methyl 1-butyl-2-[4(5)-imidazoyl]-5-phenyl-1H-imidazole-4-acetate (**4h**)*. Method B: yield 51% (86 mg); white solid, mp 170.6-173.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.67 (t, *J* = 7.3 Hz, 3H), 1.07 (sx, *J* = 7.3, 2H), 1.45 (qt, *J* = 7.3 Hz, 2H), 3.54 (s, 2H), 3.60 (s, 3H), 4.28 (t, *J* = 7.3 Hz, 2H), 7.36-7.50 (m, 6H), 7.68 (d, *J* = 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3), 19.6 (CH_2), 32.6 (CH_2), 33.3 (CH_2), 44.8 (CH_2), 52.0 (CH_3), 118.9 (C), 128.6 (CH), 128.8 (2 × CH), 129.8 (C), 130.6 (2 × CH), 131.0 (C), 131.5 (C), 136.2 (2 × CH), 141.7 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3068, 2964, 2900-2500, 1742, 1415, 1348, 1197, 1165, 828, 706. HRMS (ESI+): calcd. for $C_{19}H_{23}N_4O_2^+$ $[M+H]^+$ 339.1816; found 339.1819.

*Methyl (E)-1-butyl-5-phenyl-2-styryl-1H-imidazole-4-acetate (**4i**)*. Method A: yield 47% (88 mg); yellow solid, mp 82.3-83.7 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.78 (t, *J* = 7.3 Hz, 3H), 1.09-1.28 (m, 2H), 1.50-1.65 (m, 2H), 3.58 (s, 2H), 3.65 (s, 3H), 3.90 (t, *J* = 7.6 Hz, 2H), 6.91 (d, *J* = 15.7 Hz, 1H), 7.25-7.55 (m, 10H), 7.66 (d, *J* = 15.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.6 (CH_3), 19.8 (CH_2), 33.4 (CH_2), 33.7 (CH_2), 43.6 (CH_2), 52.0 (CH_3), 113.8 (CH), 126.8 (2 × CH), 128.2 (CH), 128.5 (CH), 128.8 (4 × CH), 129.9 (C), 130.5 (2 × CH), 131.5 (C), 132.6 (CH), 132.7 (C), 137.0 (C), 144.7 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3029, 2957, 1730, 1687, 1420, 1269, 1240, 1156, 1020, 957, 753, 704. HRMS (ESI+): calcd. for $C_{24}H_{27}N_2O_2^+$ $[M+H]^+$ 375.2067; found 375.2065.

*Methyl 1-benzyl-2-ethyl-5-phenyl-1H-imidazole-4-acetate (**4j**)*. Method A: yield 33% (55 mg); method B: yield 70% (119 mg); yellow solid, mp 82.5-88.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.6 Hz, 3H), 2.59 (q, *J* = 7.6, 2H), 3.59 (s, 2H), 3.67 (s, 3H), 4.99 (s, 2H), 6.90 (d, *J* = 7.3 Hz, 2H), 7.23-7.34 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (CH_3), 20.8 (CH_2), 33.7 (CH_2), 47.3 (CH_2), 51.9 (CH_3), 125.9 (2 × CH), 127.5 (CH), 128.3 (CH), 128.7 (2 × CH), 128.9 (2 × CH), 130.0 (C), 130.4 (2 × CH), 130.8 (C), 131.0 (C), 137.4 (C), 149.5 (C), 172.2 (C). IR (KBr, cm^{-1}): ν = 3059, 2976, 2933, 1734, 1605, 1495, 1450, 1358, 1201, 1161, 738, 704. HRMS (ESI+): calcd. for $C_{21}H_{23}N_2O_2^+$ $[M+H]^+$ 335.1754; found 335.1754.

*Methyl 1-allyl-2-ethyl-5-phenyl-1H-imidazole-4-acetate (**4k**)*. Method A: yield 32% (46 mg); method B: yield 83% (118 mg); yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.6 Hz, 3H), 2.62 (q, *J* = 7.6 Hz, 2H), 3.47 (s, 2H), 3.59 (s, 3H), 4.27-4.31 (m, 2H), 4.79 (d, *J* = 17.0 Hz, 1H), 5.11 (d, *J* = 10.5 Hz, 1H), 5.75 (ddt, *J* = 17.0, 10.5, 4.4 Hz, 1H), 7.24-7.35 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (CH_3), 20.4 (CH_2), 33.4 (CH_2), 45.9 (CH_2), 51.8 (CH_3), 116.5 (CH_2), 128.1 (CH), 128.5 (2 × CH), 129.8 (C), 130.0 (2 × CH), 130.2 (C), 130.3 (C), 133.3 (CH), 149.1 (C), 172.2 (C). IR (KBr, cm^{-1}): ν =, 3057, 2980, 1738, 1644, 1609, 1436, 1199, 1161, 1020, 761, 704. HRMS (ESI+): calcd. for $C_{17}H_{21}N_2O_2^+$ $[M+H]^+$ 285.15975; found 285.15977.

*Methyl 1-butyl-2-ethyl-5-phenyl-1H-imidazole-4-acetate (**4l**)*. Method A: yield 31% (47 mg); method C: yield 70% (105 mg); yellow solid, mp 81.5-83.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 7.3 Hz, 3H), 1.14 (sx, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.6 Hz, 3H), 1.42-1.49 (m, 2H), 2.74 (q, *J* = 7.6, 2H), 3.50 (s, 2H), 3.64 (s, 3H), 3.74 (t, *J* = 7.8 Hz, 2H), 7.30-7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.4 (CH_3), 13.4 (CH_3), 19.6 (CH_2), 20.6 (CH_2), 32.6 (CH_2), 33.3 (CH_2), 43.5 (CH_2), 51.7 (CH_3), 128.0 (CH), 128.5 (2 × CH), 129.9 (C), 130.2 (2 × CH), 130.33 (C), 130.34 (C), 148.6 (C), 172.1 (C). IR (KBr, cm^{-1}): ν = 3029, 2947, 2872, 1746, 1611, 1428, 1350, 1187, 1163, 765, 712. HRMS (ESI+): calcd. for $C_{18}H_{25}N_2O_2^+$ $[M+H]^+$ 301.1911; found 301.1908.

*Methyl 1-(1-ethoxycarbonylpiperidin-4-yl)-2-ethyl-5-phenyl-1H-imidazole-4-acetate (**4m**)*. Method A: yield 53% (106 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.39 (t, *J* = 7.6 Hz, 3H), 1.80-1.82 (m, 2H), 1.92-1.96 (m, 2H), 2.61-2.67 (m, 2H), 2.80 (q, *J* = 7.6 Hz, 2H) 3.40 (s, 2H), 3.62 (s, 3H), 3.96

(tt, *J* = 12.4, 3.9 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.15-4.32 (m, 2H), 7.26-7.30 (m, 2H), 7.40-7.46 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.0 (CH_3), 14.6 (CH_3), 22.2 (CH_2), 31.7 (2 × CH_2), 33.2 (CH_2), 43.8 (2 × CH_2), 51.7 (CH_3), 54.8 (CH), 61.5 (CH_2), 128.5 (2 × CH), 128.6 (CH), 129.9 (C), 130.7 (C), 131.06 (C), 131.11 (2 × CH), 148.3 (C), 155.2 (C), 171.9 (C). IR (KBr, cm^{-1}): ν = 3055, 2978, 2937, 1740, 1697, 1611, 1434, 1238, 1150, 1016, 767, 706. HRMS (ESI+): calcd. for $C_{22}H_{30}N_3O_4^+$ $[M+H]^+$ 400.2231; found 400.2227.

*Methyl 1-(2-(1H-indol-3-yl)ethyl)-2-ethyl-5-phenyl-1H-imidazole-4-acetate (**4n**)*. Method B: yield 66% (128 mg); brown solid, mp 155.3-158.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J* = 7.6 Hz, 3H), 2.56 (q, *J* = 7.6, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 3.53 (s, 2H), 3.62 (s, 3H), 4.03 (t, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 2.2, 1H), 6.97-7.45 (m, 9H), 8.73 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.6 (CH_3), 20.6 (CH_2), 26.7 (CH_2), 33.5 (CH_2), 44.8 (CH_2), 51.9 (CH_3), 111.4 (C + CH), 118.2 (CH), 119.5 (CH), 122.1 (CH), 122.4 (CH), 127.1 (C), 128.3 (CH), 128.9 (2 × CH), 130.0 (C), 130.55 (2 × CH), 130.63 (C), 130.9 (C), 136.4 (C), 149.3 (C), 172.4 (C). IR (KBr, cm^{-1}): ν = 3184, 3057, 2978, 2925, 1748, 1615, 1436, 1344, 1205, 1159, 744, 704. HRMS (ESI+): calcd. for $C_{24}H_{26}N_3O_2^+$ $[M+H]^+$ 388.2020; found 388.2018.

*1-Benzyl-5-phenyl-2-(4-tolyl)-1H-imidazole-4-methanol (**4o**)*. Method B: yield 70% (124 mg); white solid, mp 149.0-152.2 °C. 1H NMR (200 MHz, CDCl3): δ 2.33 (s, 3H), 4.60 (s, 2H), 4.98 (br s, 1H), 5.15 (s, 2H), 6.74-6.78 (m, 2H), 7.13-7.33 (m, 10H), 7.44 (d, J = 8.1 Hz, 2H). 13C NMR (50 MHz, CDCl3): δ 21.4 (CH3), 48.6 (CH2), 57.2 (CH2), 126.1 (2 × CH), 127.4 (CH), 127.6 (C), 128.4 (CH), 128.6 (2 × CH), 128.7 (2 × CH), 128.9 (2 × CH), 129.4 (2 × CH), 129.5 (C), 130.5 (2 × CH), 131.4 (C), 137.5 (C), 139.0 (C), 139.1 (C), 148.3 (C). IR (KBr, cm-1): ν = 3200, 3029, 2919, 2860, 1448, 1354, 1026, 728, 698. HRMS (ESI+): calcd. for $C_{24}H_{23}N_2O^+$ $[M+H]^+$ 355.1805; found 355.1802.

1-Butyl-2-ethyl-5-phenyl-1H-imidazole-4-methanol (**4p**). Method B: yield 55% (71 mg); white solid, mp 117.8-118.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 7.3 Hz, 3H), 1.15 (sx, *J* = 7.3 Hz, 2H), 1.37 (t, *J* = 7.6 Hz, 3H), 1.41-1.49 (m, 2H), 2.74 (q, *J* = 7.6, 2H), 3.78 (t, *J* = 7.8 Hz, 2H), 4.50 (s, 2H), 7.35-7.46 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.5 (CH_3), 13.5 (CH_3), 19.8 (CH_2), 20.6 (CH_2), 32.8 (CH_2), 43.6 (CH_2), 56.5 (CH_2), 128.1 (CH), 128.6 (2 × CH), 129.6 (C), 130.2 (C), 130.4 (2 × CH), 137.6 (C), 149.0 (C). IR (KBr, cm^{-1}): ν = 3170, 3051, 2976, 2937, 2876, 1509, 1422, 1026, 1004, 779, 710. HRMS (ESI+): calcd. for $C_{16}H_{23}N_2O^+$ $[M+H]^+$ 259.1805; found 259.1807.

*Methyl 1-benzyl-5-ethyl-2-(4-tolyl)-1H-imidazole-4-acetate (**4q**)*. Method B: yield 40% (67 mg); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.04 (t, *J* = 7.6 Hz, 3H), 2.32 (s, 3H), 2.47 (q, *J* = 7.6 Hz, 2H), 3.69 (s, 2H), 3.71 (s, 3H), 5.17 (s, 2H), 6.98 (d, *J* = 7.1 Hz, 2H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.25-7.38 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 17.2 (CH_2), 21.3 (CH_3), 33.8 (CH_2), 47.9 (CH_2), 52.0 (CH_3), 125.7 (2 × CH), 127.6 (CH), 128.1 (C), 128.8 (2 × CH), 129.0 (2 × CH), 129.2 (2 × CH), 130.7 (C), 131.5 (C), 137.6 (C), 138.5 (C), 147.1 (C), 172.0 (C). IR (KBr, cm^{-1}): ν = 3029, 2950, 1740, 1673, 1634, 1454, 1356, 1197, 1159, 1016, 824, 734. HRMS (ESI+): calcd. for $C_{22}H_{25}N_2O_2^+$ $[M+H]^+$ 349.1911; found 349.1913.

*Methyl 2-(6-methyl-3-phenylimidazo[2,1-a]isoquinolin-2-yl)acetate (**15**).* To a solution of imidazole **4c** (82 mg, 0.20 mmol) in DMF (1.0 mL), placed into a microwave tube, was added NaOAc (20 mg, 0.24 mmol) and $PdCl_2(PPh_3)_2$ (14 mg, 10 mol%). After degassing the mixture under N_2, the sealed tube was heated under microwave radiation (100-120 °C, 50 W) for 90 min. Next, the mixture was treated with 6 M NH_4Cl and extracted with EtOAc, the organic extract was dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc 8:2) to give tricycle **15** as a yellow solid (49 mg, 74%), mp 135.7-138.2 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.44 (d, *J* = 1.0 Hz, 3H), 3.71 (s, 3H), 3.87 (s, 2H), 7.47-7.78 (m, 9H), 8.70-8.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5 (CH_3), 34.2 (CH_2), 52.2 (CH_3), 119.2 (CH), 119.3 (C), 123.8 (CH), 124.0 (CH), 124.9 (C), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.0 (C), 129.3 (CH), 129.8 (C), 130.1 (CH), 130.3 (C), 134.9 (C), 142.3 (C), 171.8 (C). IR (KBr, cm^{-1}): ν = 3027, 2947, 2916, 1724, 1601, 1450, 1389, 1261, 1008, 765, 708. HRMS (ESI+): calcd. for $C_{21}H_{19}N_2O_2^+$ $[M+H]^+$ 331.1441; found 331.1442.

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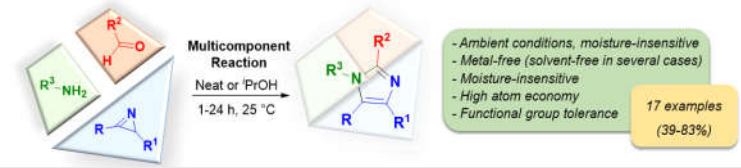

A straightforward method for the synthesis of tetrasubstituted imidazoles was developed, employing readily available starting materials and environmentally benign conditions.

Green Synthesis*

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Multicomponent Synthesis of Structurally Diverse Imidazoles Featuring Azirines, Amines and Aldehydes