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Chemoselective Pd-Catalyzed Direct C–H Arylation of 5-Carboxyimidazoles: Unparalleled access to fused Imidazole-Based Tricycles containing 6-, 7- or 8-Membered Rings

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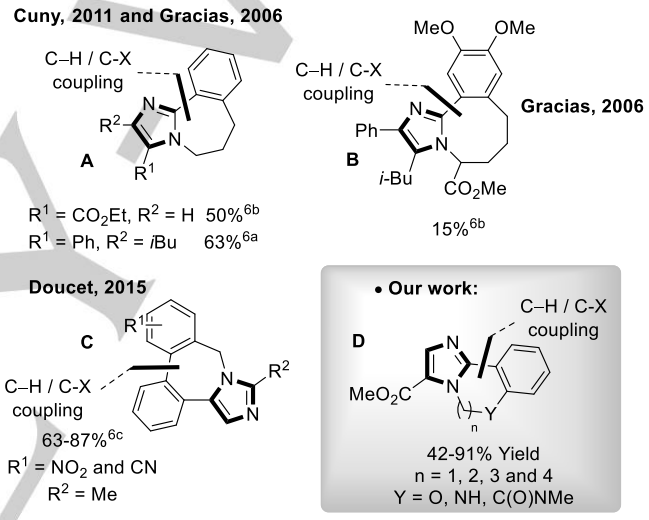
Dedication ((optional))

Abstract: An extensive study of chemoselective Pd-catalyzed inter- and intramolecular direct C–H arylation of *N*-benzylated 5-carboxyimidazoles with halides with and without Cu(I)-assistance in 1,4-dioxane as a poorly polar solvent is reported. The methodology was found suitable for the synthesis of fused imidazole-based tricyclic systems incorporating medium sized rings, including for the first time 8-membered rings valuable in modern drug design.

Introduction

The transition metal-catalyzed direct C–H bond arylation of heterocycles has established itself as one of the key methods for the construction of valuable bis-(hetero)aromatic systems, which are widespread in both natural products and pharmaceuticals.[1] Over the past ten years, efforts have been devoted to the development of methodologies aimed at improving the chemoselectivity of C–H arylation reactions when applied to heterocycles functionalized with diverse atoms or functions such as for example halogen, amine, nitro, ester, cyano.[2]
From this perspective, imidazole, which represents an important class of naturally occurring heterocycle widely employed in pharmalogical sciences in the design of peptidomimetics[3] as well as many other biologically active molecules,[4] is a very attractive target on which to apply C–H arylation in order to access new chemical space.
Fused tricyclic structures containing one non-aromatic ring are becoming ever more present in the literature as valuable scaffolds for medicinal chemistry.[5] Due to the reduction of their planarity through deconjugation of one arene unit, they display improved physicochemical properties, such as better solubility.
To date, only a limited number of imidazole-based tricycles incorporating medium sized central rings and obtained through intramolecular direct C–H arylation, have been reported in the literature (Figure 1, structures A, B and C).[6]

Figure 1. Access to imidazole-based tricyclic heterocycles incorporating medium sized central rings through direct C-H arylation.



More precisely, since the pioneering work by the group of Suzuki on intramolecular direct C–H arylation of *N*-bromophenyl imidazole-4-carboxamide,[7] carboxylated imidazoles have been scarcely used in transition metal-catalyzed direct C–H functionalization reactions. In 2011, Cuny developed the first general Mitsunobu alkylation / intramolecular direct C2–H arylation of ethyl 1*H*-imidazole-5-carboxylate leading to the production of three imidazole-based tricyclic heterocycles including the first example of a 7-membered-ring model (figure 1, Structure A).[6b] More recently, the intramolecular direct C–H arylation was also employed to synthesize 4-carboxamide imidazole-based tricyclic heterocycles with a central 6-membered ring as novel antihistamic agents.[8] In this paper, we report the first general study of base-assisted and palladium catalyzed inter- and intramolecular direct C–H arylation of methyl *N*-benzylated imidazole-5-carboxylate **1a** with bromoarenes. Following our investigations in structurally related 1,3-diazole-4-carboxylate series[9], we reasoned that the presence of an ester moiety should sufficiently reinforce the C2–H acidity to achieve a chemoselective carbonate-assisted CMD-reaction process in a poorly polar solvent, such as 1,4-dioxane, with or without CuI assistance. Indeed, Goreslsky has demonstrated through DFT calculations that CuI assistance dramatically enhances the

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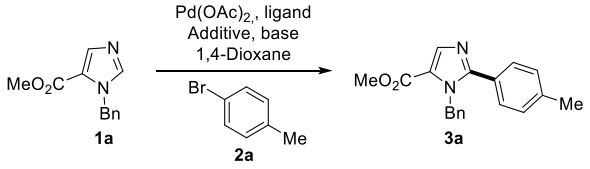
C2–H reactivity of 1,3-diazole in palladium-catalyzed CMD-type reactions through formation of a (N)-CuI pre-complex.[10] Optimization of the C–H arylation procedure led to the production of novel imidazole-5-carboxylate based tricycles with 7- and 8-membered central rings containing different types of tethers such as alkyl, ether and amide (Figure 1, structure D).

Results and Discussion

Table 1. Pd-catalyzed and CuI-assisted intermolecular direct C2–H arylation of **1a**.

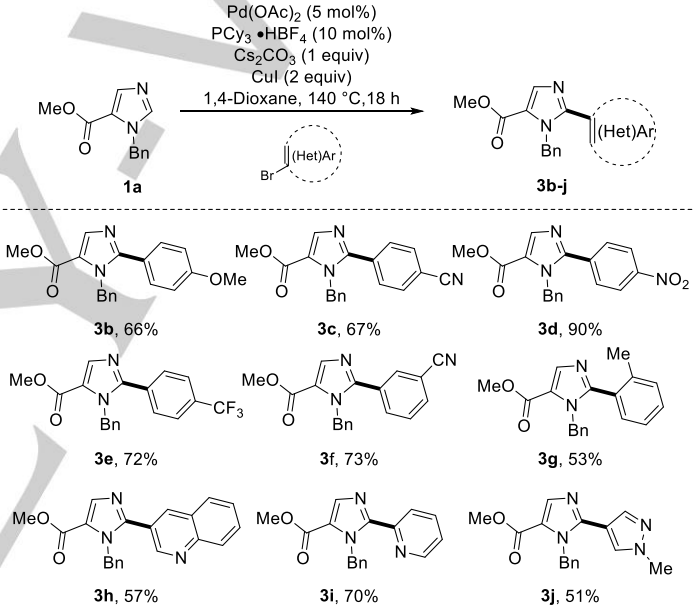


Entry	Ligand	Base	Additive	Yield[b]
1	PPh_3	K_2CO_3	-	5%
2	PPh_3	K_2CO_3		Trace[c]
3	PPh_3	Cs_2CO_3	-	11%
4	PPh_3	K_2CO_3	CuI	57%
5	PPh_3	Cs_2CO_3	CuI	77%
6	**PCy_3•HBF_4**	**Cs_2CO_3**	**CuI**	**81%**
7	PCy_3•HBF_4	Cs_2CO_3	CuI	70%[d, e]

[a] Conditions: **1a** (1 equiv), **2a** (1.2 equiv), $Pd(OAc)_2$ (5 mol%), Ligand (10 mol%), additive (2 equiv), base (1 equiv), 1,4-Dioxane (0.16 M), 140 °C, 18 h. [b] Yield of the isolated product. [c] DMAc and DMF were used as solvent. [d] Using 4-iodotoluene as electrophile. [e] Failed with 4-chlorotoluene as electrophile.

Our study was initiated with the intermolecular $Pd^{(0)}$-catalyzed direct C–H arylation of methyl *N*-benzylimidazole-4-carboxylate **1a**, readily prepared through a Mitsunobu reaction between the commercially available methyl imidazole-4-carboxylate and benzyl alcohol following the Cuny procedure.[6b] First attempts at C–H arylation of **1a** with 4-bromotoluene **2a** under standard CMD-based conditions, which had previously proven to be highly effective in oxazole and thiazole 4-carboxylate series[9] as well as being compatible with the methyl ester moiety, were disappointing. The desired 2-arylated product **3a** was isolated in only 5% yield (Table 1, entry 1), despite the high reaction temperature (140°C). Moreover, surprisingly the use of more polar solvents such as DMF and DMAc - previously reported by Cuny *et al*. to favour the direct intramolecular C–H arylation of a related ethyl *N*-benzyl imidazole-5-carboxylate system - in our case proved unsuccessful (Table 1, entry 2). Switching to electron-rich phosphine ligands (PCy_3•HBF_4, P*t*Bu_3•HBF_4, DavePhos…) as well as exploring two alternative bases (Cs_2CO_3 and KOAc), failed to improve the yield of 2-arylated imidazole-4-carboxylate **3a**.[11] At this stage, we turned our attention to CuI-assitance to target cooperative $Pd^{(0)}$/CuI bis-catalysis through generation of an imidazolylcopper intermediate.[12] Interestingly, we immediately observed a better reactivity with the desired 2-arylated imidazole **3a** being isolated in 57% yield using K_2CO_3 as base (Table 1, entry 4). This encouraging result was further improved by switching to Cs_2CO_3 as base and PCy_3•HBF_4 as the optimal phosphine ligand, providing **3a** in 81% yield (Entry 6). The structure **3a** was confirmed by single crystal X-ray structure determination.[11] The reaction remained effective when employing 4-iodotoluene as electrophile but failed with 4-chorotoluene (Entry 7).

Scheme 1. Scope of (hetero)aryl bromides as coupling partners.

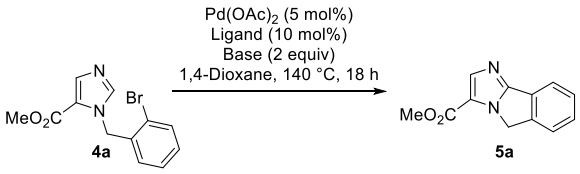


The scope of electrophile was next investigated (Scheme 1). The C2–H arylation of **1a** was successfully achieved with a broad panel of arylbromides substituted at their *para*, *ortho*, or *meta* positions with electron-withdrawing as well as electron-donating substituents, to afford the corresponding coupling products **3b-3f** in a range of 53 to 90% yields (Scheme 1). The methyl 2-arylated 5-carboxyimidazole **3g** was also isolated in an acceptable 53% yield, showing that the methodology can accommodate steric effects. Notably, **1a** was also directly heteroarylated at its C2–H site using 3-bromoquinoline, 2-bromopyridine and *N*-methyl-4-bromopyrazole as coupling partners to afford the 2-heteroarylimidazoles **3h-l** in moderate to good yields.

After achieving the C2–H arylation of **1a** through $Pd^{(0)}$-catalyzed intermolecular direct C–H arylation with (hetero)aryl halides under Cu(I)-assisted CMD-based conditions, we focused on the more entropically favoured intramolecular direct C–H arylation pathway. The *N*-(*ortho*-Bromobenzyl)imidazole-4-

carboxylate **4a**, selected as the prototypical substrate for evaluation, was found surprisingly to be poorly reactive under the conditions for the CuI-assisted intermolecular C2–H arylation previously optimized for **1a**. Indeed, the expected C2-linked 5-membered-ring 5-carboxyimidazole-based tricycle **5a** was isolated in the poor yield of 25% (Table 2, entry 1). However, it was possible to improve yields by adopting Cu(I)-free conditions especially with K_2CO_3 as base (Table 2, entries 2-4) with which compound **5a** was obtained in 72% yield (Table 2, entry 4). After scanning a range of phosphine ligands, an optimal 79% yield of tricycle **5a** was obtained using the electron-rich ligand P^{t}Bu$_2$Me•HBF$_4$, while sterically hindered P^{t}Bu$_3$•HBF$_4$ and poor to highly electron-donor mono and diphosphines [P(4-FPh) and dppb) gave poorer results (Table 2, entries 5-9).

Table 2. Base-assisted CMD-proceeding intramolecular direct C–H arylation of **4a**.[a]

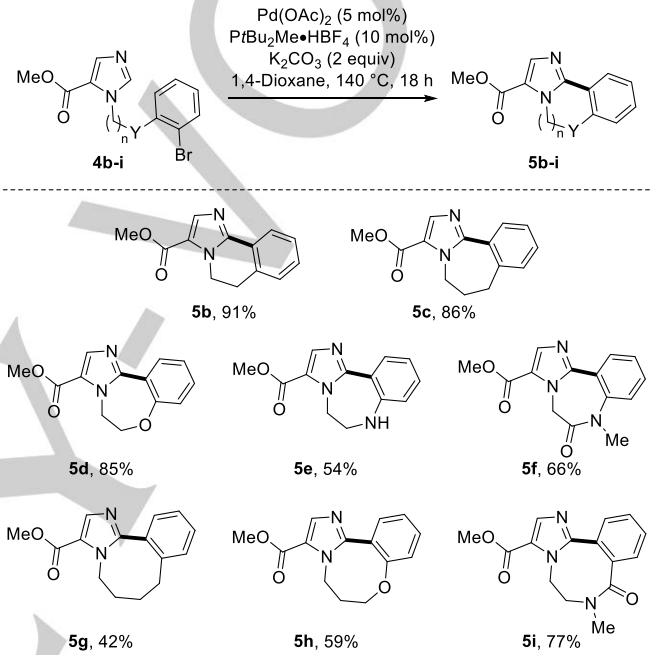


Entry	Ligand	Base	Yield (%)[b]
1	PCy$_3$•HBF$_4$	Cs$_2$CO$_3$	25[c]
2	PCy$_3$•HBF$_4$	Cs$_2$CO$_3$	33
3	PCy$_3$•HBF$_4$	KOAc	25
4	PCy$_3$•HBF$_4$	K$_2$CO$_3$	72
5	P*t*Bu$_2$Me•HBF$_4$	K$_2$CO$_3$	79
6	P*t*Bu$_3$•HBF$_4$	K$_2$CO$_3$	69
7	PPh$_3$	K$_2$CO$_3$	57
8	P(4-FPh)$_3$	K$_2$CO$_3$	65
9	dppb	K$_2$CO$_3$	55

[a] Conditions: **4a** (1 equiv), Pd(OAc)$_2$ (5 mol%), Ligand (10 mol%), base (2 equiv), 1,4-Dioxane (0.16 M), 140 °C, 18 h. [b] Yield of the isolated product. [c] 2 equiv of CuI used as additive.

At this stage, we investigated the scope of this optimized intramolecular C-H arylation protocol to generate novel 7 and 8-membered ring containing tricyclic heterocycles starting from the different methyl *N*-alkylated imidazole-5-carboxylates **4b-4i**. The resulting outcomes are depicted in Scheme 2. First, we checked the performance of the optimized protocol for the ring-closing of the methyl *N*-phenylethyl imidazole-5-carboxylate **4b**. The 6-membered ring tricycle **5b** was isolated in an excellent 91% yield. The protocol was also successfully applied to the intramolecular direct C2–H arylation of methyl *N*-phenylpropyl imidazole-5-carboxylate **4c** affording the 7-membered ring tricyle **5c** in an excellent 86% yield. This novel procedure in 1,4-dioxane as solvent seems to be complementary and, in some cases, more efficient than the one reported by Cuny's team using DMF. Indeed, it allowed compounds **5b** and **5c** to be isolated in better yields especially for the 7-membered ring tricycle **5c** (86% vs 50%[6c]).

Scheme 2. Synthesis of 5-carboxyimidazole-based tricyclic heterocycles incorporating 6-, 7- and 8-membered rings.



We then turned to the more challenging preparation of imidazole-based tricycles with both larger and more complex central rings – for example, embedding oxygen or nitrogen atoms as well as an amide into the linkage-chain. Remarkably, the strict application of the optimized CMD-arylation procedure led to the generation of three new imidazole-5-carboxylate tricycles **5d-f** based around a central 7-membered ring containing respectively ether, amine and amide moieties in the linkage chain which were isolated in moderate to excellent yields (54 to 85% yields). In addition, this optimized ring-closing protocole successfully led to the synthesis of the new 8-membered ring containing imidazole 5-carboxylate tricycles **5g-i** in fair to good yields.

Conclusion

In conclusion, two innovative and convenient carbonate-based procedures under poor basic conditions, using 1,4-dioxane as solvent, were successfully established for the intra- and intermolecular palladium-catalyzed direct C–H arylation of imidazole-5-carboxylates with bromoarenes. To the best of our knowledge, we report here the first carbonate-assisted CMD-

based direct C2–H arylation of imidazole rings in 1,4-dioxane as solvent. The use of such mild basic conditions fully ensures the stability of sensitive functionalities to nucleophilic attack - such as, for example, an ester moiety. This methodology was successfully applied to prepare several new imidazole-based tricycles based around 7- and, for the first time, 8-membered central rings. This methodology opens access to new chemical space with, for example, potential applications in drug-design.

Experimental Section

General information: All reagents were purchased from commercial suppliers and were used without further purification. Extra dry 1,4-Dioxane and DMF were purchased from Sigma-Aldrich® in sealed bottles over 3Å or 4Å molecular sieves and stored under N_2.The reactions were performed without any protection from the light and monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation (λ = 254 nm) and/or spraying TLC stain such as a $KMnO_4$ solution followed by heating at 200 °C. Flash chromatography columns were performed on silica gel 60 (230-400 mesh, 0.040-0.063 mm). ^1H and ^{13}C NMR spectra were recorded at room temperature on a Brucker Advance spectrometer operating at 300 MHz and 75 MHz respectively. Chemical shifts are given in parts per million from tetramethylsilane (TMS) as internal standard. The following abbreviations are used for the proton spectra multiplicities: s: singulet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet, br: broad. Coupling constants (*J*) are reported in Hertz (Hz). Signals were assigned as far as possible by means of two-dimensional NMR spectroscopy: ^1H-^1H-COSY, ^1H-^{13}C-COSY (HSQC: Heteronuclear Single Quantum Coherence). HRMS were recorder on a LC Waters Acquity coupled to a Waters LCT Premier XE instrument. The infrared spectra of compounds were recorded on a Perkin Elmer Spectrum 100 FT IR spectrometers. Melting points (mp [°C]) were taken on open capillary tubes and are uncorrected, performed on a Stuart SMP3.

General Procedure for the Pd-catalyzed intermolecular direct C–H heteroarylation of 5-carboxyimidazole 1a (Method A): Methyl *N*-benzylimidazole-4-carboxylate **1a** (50 mg, 0.230 mmol, 1 eq) and the appropriate halide **2a-i** (1.2 eq) were placed in a dry sealed tube containing a magnetic stir bar with $Pd(OAc)_2$ (2.5 mg, 11 µmol, 5 mol%), PCy_3•HBF_4 (8.5 mg, 23 µmol, 10 mol%), CuI (88 mg, 0.460 mmol, 2 eq) and anhydrous Cs_2CO_3 (150 mg, 0.460 mmol, 2 eq). The tube was evacuated and filled back with N_2 three time before adding anhydrous 1,4-dioxane (1 mL). The tube was sealed and heated to 140 °C for 18 hours. The reaction mixture was filtered over a Celite® pad (washed with EtOAc) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

General Procedure for the synthesis of various methyl bromo-N-substituted imidazole-4-carboxylate, Mitsunobu reaction (Method B):[6c] A solution of an alcohol (1.1 eq) in anhydrous THF (0.55 M) was added dropwise to a stirred solution of of methyl 1*H*-imidazole-4-carboxylate (1 eq) and triphenylphosphine (1.3 eq) in anhydrous THF (0.7 M) at –40°C. Then a solution of di-*tert*-butyl azodicarboxylate (1.35 eq.) in anhydrous THF (0.7 M) was added dropwise to the reaction mixture at –40°C and then stirred at this temperature for 30 minutes. The reaction mixture was warmed up to room temperature and stirred overnight. The crude mixture was then evaporated to dryness and directly purified by flash chromatography using a mixture of petroleum ether and ethyl acetate to give the expected compound.

General Procedure for the Pd-catalyzed intramolecular direct C–H heteroarylation of bromo *N*-substituted-imidazoles 4b-i (Method C): Bromo *N*-substituted-imidazole **4a-i** (0.16 mmol, 1 equiv.) was placed in a dry sealed tube containing a magnetic stir bar with an appropriate $Pd(OAc)_2$ (2 mg, 8 µmol, 5 mol%), Pd*t*Bu_2Me•HBF_4 (4.6 mg, 16 µmol, 10 mol%), K_2CO_3 (44 mg, 0.32 mmol, 2.0 eq). The tube was evacuated and filled back with N_2 three time before adding anhydrous 1,4-dioxane (1 ml). The tube was sealed and heated to 140 °C for 18 hours. The reaction mixture was filtered over a Celite® pad (washed with EtOAc) and the solvents were removed under reduced pressure. The crude product was then purified by flash column chromatography.

Methyl 1-benzyl-2-(*p*-tolyl)-1*H*-imidazole-5-carboxylate 3a: Compound **3a** was prepared according to the *method A* with 4-bromotoluene **2a** (48 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 8:2) to afford **3a** in 81% (57 mg, 0.186 mmol) as a colorless solid. mp: 104 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2919, 1710, 1523, 1444, 1257, 1185 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.31-7.28 (m, 3H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 6.7 Hz, 2H), 5.65 (s, 2H), 3.80 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (C), 153.5 (C), 140.0 (C) 138.0 (CH), 137.7 (C), 129.4 (2xCH), 129.1 (2xCH), 128.8 (2xCH), 127.4 (CH), 126.8 (C), 125.7 (2xCH), 123.2 (C), 51.5 (CH_3), 49.2 (CH_2), 21.4 (CH_3); HMRS (ESI-TOF): calc. for $C_{19}H_{19}N_2O_2$; 307.1447: found 307.1450.

Methyl 1-benzyl-2-(4-methoxyphenyl)-1*H*-imidazole-5-carboxylate 3b: Compound **3b** was prepared according to the *method A* with 4-bromoanisole **2b** (52 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 6:4) to afford **3b** in 66% (49 mg, 0.152 mmol) as a colorless solid. mp: 138 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2948, 1708, 1450, 1295, 1249, 1174, 128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.34-7.27 (m, 3H), 6.99-6.96 (m, 2H), 6.92. (d, *J* = 8.8 Hz, 2H), 5.63 (s, 2H), 3.83 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (C), 160.7 (C), 153.3 (C), 137.9 (CH), 137.7 (C), 130.6 (2xCH), 128.9 (2xCH), 127.5 (CH), 125.7 (2xCH), 123.1 (C), 122.1 (C), 114.2 (2xCH), 55.4 (CH_3), 51.5 (CH_3), 49.3 (CH_2); HMRS (ESI-TOF)**:** calc. for $C_{19}H_{19}N_2O_3$; 323.1396: found 323.1395.

Methyl 1-benzyl-2-(4-cyanophenyl)-1*H*-imidazole-5-carboxylate 3c: Compound **3c** was prepared according to the *method A* with *p*-bromobenzonitrile **2c** (50 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc 8:2) to afford **3c** in 67% (49 mg, 0.154 mmol) as a yellow oil. IR (neat) *ν*max: 2923, 1711, 1447, 1322, 1261, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.69-7.62 (m, 4H), 7.34-27 (m, 3H), 6.94-6.90 (m, 2H), 5.64 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 150.9 (C), 138.1 (CH), 136.9 (C), 133.9 (C), 132.5 (2xCH), 129.7 (2xCH), 129.1 (2xCH), 127.8 (CH), 125.5 (2xCH), 124.3 (C), 118.2 (C), 113.4 (C), 51.5 (CH_3), 49.3 (CH_2); HMRS (ESI-TOF): calc. for $C_{19}H_{16}N_3O_2$; 318.1243: found 318.1228.

Methyl 1-benzyl-2-(4-nitrophenyl)-1*H*-imidazole-5-carboxylate 3d: Compound **3d** was prepared according to the *method A* with 1-bromo-4-nitrobenzene **2d** (56 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 4:6) to afford **3d** in 90% (70 mg, 0.207 mmol) as a colorless solid. mp: 146 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2959, 1711, 1516, 1446, 1346, 1087 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.28-7.18 (m, 3H), 6.89-6.86 (m, 2H), 5.61 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.4 (C), 150.6 (C), 148.4 (C), 138.2 (CH), 136.8 (C), 135.7 (C), 130.0 (2xCH), 129.2 (2xCH), 127.9

(CH), 125.5 (2xCH), 124.5 (C), 124.0 (CH), 51.8 (CH_3), 49.4 (CH_2); HMRS (ESI-TOF)**:** calc. for $C_{19}H_{16}N_3O_4$; 338.1141: found 338.1128.

Methyl 1-benzyl-2-(4-(trifluoromethyl)phenyl)-1*H*-imidazole-5-carboxylate 3e: Compound **3e** was prepared according to the *method A* with *p*-bromobenzotrifluoride **2e**(62 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 7:3) to afford **3e** in 72% (60 mg, 0.167 mmol) as a colorless solid. mp: 107 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2923, 1711, 1447, 1322, 1261, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.58 (bs, 4H), 7.27-7.18 (m, 3H), 6.88-6.85 (m, 2H), 5.57 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 150.5 (C), 138.9 (CH), 137.7 (C), 133.2 (C), 131.7 (*J* = 34.8 Hz, C), 129.5 (2xCH), 129.0 (2xCH), 127.7 (CH), 125.8 (*J* = 3.7 Hz, 2xCH), 125.6 (2xCH), 124.0 (C), 123.9 (*J* = 271 Hz, C), 51.5 (CH_3), 49.3 (CH_2); HMRS (ESI-TOF): calc. for $C_{19}H_{16}F_3N_2O_2$; 361.1164: found 361.1161.

Methyl 1-benzyl-2-(3-cyanophenyl)-1*H*-imidazole-5-carboxylate 3f: Compound **3f** was prepared according to the *method A* with 3-bromo-benzonitrile **2f** (50 mg, 0.276 mmol, 1 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 3:7) to afford **3f** in 73% (53 mg, 0.168 mmol) as a colorless solid. mp: 115 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2951, 2231, 1711, 1447, 1250, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.82 (t, *J* = 1.7 Hz, 1H), 7.73-7.69 (m, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.35-7.28 (m, 3H), 6.94-6.91 (m, 2H), 5.64 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (C), 150.7 (C), 138.0 (CH), 136.9 (C), 133.2 (2xCH), 132.9 (CH), 131.1 (C), 129.7 (CH), 129.1 (2xCH), 125.6 (CH), 124.2 (2xCH), 124.2 (C), 118.0 (C), 113.3 (C), 51.8 (CH_3), 49.4 (CH_2); HMRS (ESI-TOF): calc. for $C_{19}H_{16}N_3O_2$; 318.1243: found 318.1239.

Methyl 1-benzyl-2-(*m*-tolyl)-1*H*-imidazole-5-carboxylate 3g: Compound **3g** was prepared according to the *method A* with 2-iodotoluene **2g** (60 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 3:7) to afford **3g** in 53% (37 mg, 0.121 mmol) as a colorless oil. IR (neat) *v*max: 2912, 2862, 1707, 1441, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.29-7.24 (m, 1H), 7.19 – 7.09 (m, 6H), 6.76-72 (m, 1H), 5.34 (s, 2H), 3.75 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.0 (C), 152.9 (C), 138.6 (C), 137.7 (CH), 137.0 (C), 130.6 (CH), 130.2 (CH), 130.0 (CH), 129.5 (C), 128.5 (2xCH), 127.5 (CH), 126.6 (2xCH), 125.8 (CH), 122.4 (C), 51.8 (CH_3), 49.4 (CH_2); HMRS (ESI-TOF): calc. for $C_{19}H_{19}N_2O_2$; 307.1447: found 307.1449.

Methyl 1-benzyl-2-(quinolin-3-yl)-1*H*-imidazole-5-carboxylate 3h: Compound **3h** was prepared according to the *method A* with 3-bromoquinoline **2h** (58 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:1 to 3:7) to afford **3h** in 57% (45 mg, 0.131 mmol) as a colorless solid. mp: 133 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2965, 1716, 1438, 1309, 1181 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.1 Hz, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.95 (s, 1H), 7.70 (ddd, *J* = 1.5, 6.8 and 8.4 Hz, 1H), 7.65-7.62 (m, 1H), 7.50 (ddd, *J* = 1.1, 6.8 and 8.0, 1H), 7.29-7.19 (m, 3H), 6.93-6.89 (m, 2H), 5.65 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 150.5 (C), 149.9 (CH), 148.1 (C), 138.3 (CH), 137.2 (C), 136.5 (CH), 130.9 (CH), 129.5 (CH), 129.1 (2xCH),128.4 (2xCH), 127.8 (CH), 127.6 (CH), 127.0 (C), 125.6 (2xCH), 124.2 (C), 123.0 (C), 51.8 (CH_3), 49.5 (CH_2); HMRS (ESI-TOF): calc. for $C_{21}H_{18}N_3O_2$; 344.1399: found 344.1391.

Methyl 1-benzyl-2-(pyridine-2-yl)-1*H*-imidazole-4-carboxylate 3i: Compound **3i** was prepared according to the *method A* with 2-bromopyridine **2i** (44 mg, 0.276 mmol, 1 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc 3:7) to afford **3i** in 70% (47 mg, 0.159 mmol) as a colorless solid. mp: 144 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2942, 1711, 1523, 1378, 1268 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 1.7 and 5.9 Hz, 1H), 8.11 (ddt, *J* = 1.08 and 7.9 Hz, 1H), 7.79 (td, *J* = 1.8 and 7.9 Hz, 1H), 7.31-7.18 (m, 4H), 7.07-7.04 (m, 2H), 6.47 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 150.0 (C), 149.2 (C), 148.6 (CH), 138.2 (C), 137.8 (CH), 136.9 (CH), 128.4 (2xCH), 127.1 (CH), 126.7 (2xCH), 124.5 (CH), 124.5 (C), 123.7 (CH), 51.6 (CH_3), 49.2 (CH_2); HMRS (ESI-TOF): calc. for $C_{17}H_{16}N_3O_2$; 294.1243: found 294.1242.

Methyl 1-benzyl-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-imidazole-5-carboxylate 3j: Compound **3j** was prepared according to the *method A* with 4-bromo-*N*-methylpyrazole **2j** (45 mg, 0.276 mmol, 1.2 eq) as halide. The crude product was purified by flash chromatography (PE/EtOAc from 1:1 to 0:1) to afford **3j** in 51% (35 mg, 0.117 mmol) as a colorless solid. mp: 148 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2921, 2852, 1716, 1258, 1015 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.82 (s, 1H), 7.68 (s, 1H), 7.33-7.21 (m, 3H), 6.94 (d, *J* = 7.4 Hz, 1H), 5.74 (s, 2H), 3.83 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.9 (C), 146.7 (C), 137.8 (CH), 137.5 (CH), 137.1 (C), 130.6 (CH), 128.7 (2xCH), 127.2 (CH), 15.5 (2xCH), 122.1 (C), 111.0 (C), 51.3 (CH_3), 47.8 (CH_2), 38.7 (CH_3); HMRS (ESI-TOF): calc. for $C_{16}H_{17}N_4O_2$; 297.1352: found 297.1352.

Methyl 1-(2-bromobenzyl)-1*H*-imidazole-5-carboxylate 4a: Compound **4a** was prepared according to the *method B* using *o*-bromobenzyl alcohol (3.26 g, 17.44 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 7:3 to 1:1) to afford **4a** in 54% (2.51 g, 8.53 mmol) as a colorless solid. mp: 130 °C (CH_2Cl_2/PE); IR (neat) *v*max: 3110, 2941, 1700, 1434, 1119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.61-7.58 (m, 2H), 7.27-7.14 (m, 2H), 6.76 (dt, *J* = 1.9 and 7.5 Hz, 1H), 5.60 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6 (C), 142.6 (CH), 138.2 (CH); 135.8 (C), 133.1 (CH), 129.7 (CH), 128.3 (CH), 128.1 (CH), 122.8 (C), 122.7 (C), 51.8 (CH_3), 50.3 (CH_2); HMRS (ESI-TOF): calc. for $C_{12}H_{12}BrN_2O_2$; 395.0082: found 295.0083.

Methyl 1-(2-bromophenethyl)-1*H*-imidazole-5-carboxylate 4b: Compound **4b** was prepared according to the *method B* using 2-bromophenylethanol (173 mg, 0.870 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 8:2 to 6:4) to afford **4b** in 57% (140 mg, 0.454 mmol) as a colorless solid. mp: 93 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2952, 2229, 1710, 1449, 1257; 1178; 1086 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.54 (dd, *J* = 1.4 and 7.8 Hz, 1H), 7.25 (s, 1H), 7.16 (td, *J* = 1.4 and 7.4 Hz, 1H), 7.08 (td, *J* = 2.0 and 7.8 Hz, 1H), 6.96 (dd, *J* = 2.0 and 7.4 Hz, 1H), 4.53 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.21 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (C), 142.3 (CH), 138.2 (CH), 136.8 (C), 133.0 (CH), 131.2 (CH), 128.9 (CH), 127.9 (CH), 124.4 (C), 122.1 (C), 51.8 (CH_3), 46.5 (CH_2), 37.8 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{14}BrN_2O_2$; 309.0239: found 309.0236.

Methyl 1-(3-(2-bromophenyl)propyl)-1H-imidazole-5-carboxylate 4c: Compound **4c** was prepared according to the *method B* using 2-bromophenylpropanol (2.816 g, 13.09 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 1:1) to afford **4c** in 52% (1.99 g, 6.16 mmol) as a yellow oil. IR (neat) *v*max: 3416, 2941, 1709, 1360, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.60 (s, 1H), 7.52 (dd, *J* = 1.0 and 8.6, 1H), 7.24-7.21 (m, 1H), 7.18 (dd, *J* = 1.8 and 7.6, 1H), 7.06 (td, *J* = 1.8 and 7.6 Hz, 1H), 4.36 (t, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 2.76-2.73 (m, 2H), 2.15-2.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.7 (C), 142.1 (CH), 140.0 (C), 138.3 (CH), 133.0 (CH), 130.3 (CH), 128.1 (CH), 127.7 (CH), 124.5 (C), 122.4 (C), 51.6 (CH_3), 46.6 (CH_2), 33.2 (CH_2), 31.2 (CH_2); HMRS (ESI-TOF): calc. for $C_{14}H_{16}BrN_2O_2$; 323.0393: found 323.0395.

Methyl 1-(2-(2-bromophenoxy)ethyl)-1H-imidazole-5-carboxylate 4d: Compound **4d** was prepared according to the *method B* using 2-bromophenoxyethanol (413 mg, 1.903 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 8:2 to 6:4) to afford **4d** in 51% (288 mg, 0.889 mmol) as a colorless solid. mp: 84 °C (CH_2Cl_2/PE); IR (neat) *v*max: 3062, 2941, 1705, 1208, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.1 Hz, 1H), 7.75 (d, *J* = 1.1 Hz, 1H), 7.50 (dd, *J* = 1.6 and 7.8 Hz, 1H), 7.21 (td, *J* = 1.6 and 7.8, 1H), 6.86-6.78 (m, 2H), 4.78 (t, *J* = 4.7 Hz, 2H), 4.27 (t, *J* = 4.7 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (C), 154.5 (C), 144.2 (CH), 138.2 (CH), 133.6 (CH), 128.5 (CH), 122.6 (CH), 121.7 (C), 112.9 (CH), 112.2 (C), 67.6 (CH_2), 51.6 (CH_3), 46.2 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{14}BrN_2O_3$; 325.0188: found 325.0186.

Methyl 1-(2-((2-bromophenyl)amino)ethyl)-1*H*-imidazole-5-carboxylate 4e: Compound **4e** was prepared according to the *method B* using 2-((2-bromophenyl)amino)ethan-1-ol[13] (500 mg, 2.313 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 3:7 to 7:3) to afford **4e** in 63% (429 mg, 1.33 mmol) as a colorless solid. mp: 82 °C (CH_2Cl_2/PE); IR (neat) *v*max: 3346, 3089, 1703, 1372, 1222, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.51 (s, 1H), 7.42 (dd, *J* = 1.4 and 7.8 Hz, 1H), 7.20-7.13 (m, 1H), 6.65 (dd, *J* = 1.4 and 8.2 Hz, 1H), 6.60 (td, *J* = 1.4 and 7.8 Hz 1H), 4.52 (t, *J* = 6.1 Hz, 2H), 4.48 (t, *J* = 6.1 Hz, NH), 3.87 (s, 3H), 3.62 (q, *J* = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0 (C), 143.8 (C), 142.7 (CH), 138.4 (CH), 132.9 (CH), 128.7 (CH), 122.2 (C), 118.6 (CH), 111.0 (CH), 110.1 (C), 51.8 (CH_3), 45.7 (CH_2), 44.2 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{15}BrN_3O_2$; 324.0348: found 324.0354.

Methyl 1-(2-((2-bromophenyl)(methyl)amino)-2-oxoethyl)-1*H*-imidazole-5-carboxylate 4f: Compound **4f** was prepared according to the *method B* using *N*-(2-bromophenyl)-2-hydroxy-*N*-methylacetamide[11] (300 mg, 1.23 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 3:7 to EtOAc/MeOH 98:2) to afford **4f** in 30% (128 mg, 0.365 mmol) as a colorless solid. mp: 123 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2947, 1711, 1659, 1433, 1290, 1125 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 1.4 and 8.1 Hz, 1H), 7.71 (s, 1H), 7.59 (dd, *J* = 1.6 and 7.9 Hz, 1H), 7.53 (s, 1H), 7.49 (td, *J* = 1.4 and 7.7 Hz, 1H), 7.32 (td, *J* = 1.6 and 7.8 Hz, 1H), 5.00 (d, *J* = 16.5 Hz, 1H), 4.46 (d, *J* = 16.5 Hz, 1H), 3.82 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0 (C), 160.9 (C), 143.2 (CH), 140.9 (C), 137.5 (CH), 134.2 (CH), 130.7 (CH), 130.4 (CH), 129.7 (CH), 123.4 (C), 122.7 (C), 51.6 (CH_3), 48.3 (CH_2), 36.4 (CH_2); HMRS (ESI-TOF): calc. for $C_{14}H_{15}BrN_3O_3$; 352.0297: found 352.0294.

Methyl 1-(4-(2-bromophenyl)butyl)-1*H*-imidazole-5-carboxylate 4g: Compound **4g** was prepared according to the *method B* using 2-bromophenylbutanol[14] (170 mg, 0.748 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 1:1) to afford **4g** in 50% (126 mg, 0.375 mmol) as a colorless oil. IR (neat) *v*max: 2941, 2867, 1709, 1435, 1220, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.57 (s, 1H), 7.51 (dd, *J* = 1.2 and 7.9 Hz, 1H), 7.21 (td, *J* = 1.2 and 7.9 Hz, 1H), 7.16 (dd, *J* = 1.8 and 7.6 Hz, 1H), 7.04 (td, *J* = 1.8 and 7.6 Hz, 1H), 4.31 (t, *J* = 7.3 Hz, 2H), 3.84 (s, 3H), 2.74 (t, *J* = 7.8 Hz, 2H), 1.83 (p, *J* = 7.3 Hz, 2H), 1.65-1.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (C), 142.1 (CH), 141.0 (C), 138.2 (CH), 132.9 (CH), 130.4 (CH), 127.8 (CH), 127.5 (CH), 124.4 (C), 122.2 (C), 51.5 (CH_3), 46.8 (CH_2), 35.6 (CH_2), 30.7 (CH_2), 26.8 (CH_2); HMRS (ESI-TOF): calc. for $C_{15}H_{18}BrN_2O_2$; 337.0052: found 337.0052.

Methyl 1-(3-(2-bromophenoxy)propyl)-1*H*-imidazole-5-carboxylate 4h: Compound **4h** was prepared according to the *method B* using 2-bromophenoxyethanol (1.8 g, 7.789 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 7:3 to 1:1) to afford **4h** in 51% (1.14 g, 3.37 mmol) as a yellow oil. IR (neat *v*max: 2948, , 1708, 1467, 1246, 1126, 1029 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.62 (s, 1H), 7.54 (dd, *J* = 1.6 and 7.8 Hz, 1H), 7.23 (ddd, *J* = 1.6, 7.8 and 8.3 Hz, 1H), 6.85 (td, *J* = 1.4 and 7.8 Hz, 1H), 6.81 (dd, *J* = 1.4 and 8.3 Hz, 1H), 4.61 (t, *J* = 6.3 Hz, 2H), 3.90 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 3H), 2.32 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8 (C), 154.7 (C), 143.0 (CH), 138.4 (CH), 133.5 (CH), 128.7 (CH), 122.4 (CH), 122.1 (C), 113.1 (CH), 112.2 (C), 64.6 (CH_2), 51.6 (CH_3), 43.6 (CH_2), 30.0 (CH_2); HMRS (ESI-TOF)**:** calc. for $C_{14}H_{16}BrN_2O_3$; 339.0344: found 339.0353.

Methyl 1-(3-((2-bromo-phenyl)(methyl)amino)-3-oxopropyl)-1*H*-imidazole-5-carboxylate 4i: Compound **4i** was prepared according to the *method B* using *N*-(2-bromophenyl)-3-hydroxy-*N*-methylpropanamide[14] **7** (1.57 g, 8.72 mmol). The crude product was purified by flash chromatography (PE/EtOAc from 8:2 to 1:1) to afford **4i** in 40% (1.154 g) as a colorless solid.[16]

Methyl 5*H*-imidazo[2,1-*a*]isoindole-3-carboxylate 5a: Compound **5a** was prepared according to the *method C* using **4a** (50 mg, 0.16 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 8:2) to afford **5a** in 79% (27 mg, 0.126 mmol) as a colorless solid. mp: 180 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2923, 1695, 1550, 1440, 1243 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.5 Hz, 1H), 7.85 (s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.42 (td, *J* = 1.2 and 7.5 Hz, 1H), 5.09 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7 (C), 156.8 (C), 143.1 (C), 140.1 (CH), 129.2 (C), 128.8 (CH), 128.7 (CH), 123.7 (CH), 121.8 (C), 120.9 (CH), 51.8 (CH_3), 48.3 (CH_2); HMRS (ESI-TOF): calc. for $C_{12}H_{11}N_2O_2$; 215.0825: found 215.0821.

Methyl 5,6-dihydroimidazo[2,1-*a*]isoquinoline-3-carboxylate 5b: Compound **5b** was prepared according to the *method C* using **4b** (50 mg, 0.16 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 8:2) to afford **5b** in 91% (33 mg, 0.145 mmol) as a colorless solid. mp: 123 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2938, 2851, 1707, 1440, 1234, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07-8.05 (m, 1H), 7.82 (s, 1H), 7.37-7.33 (m, 2H), 7.27-7.25 (m, 1H), 4.61 (t, *J* = 7.0 Hz, 2H), 3.87 (s, 3H), 3.16 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.1 (C), 148.4 (C), 138.0 (CH), 133.3 (C), 129.9 (CH), 127.8 (CH), 127.7 (CH), 126.4 (C), 124.8 (CH), 122.3 (C), 51.6 (CH_3), 42.3 (CH_2), 28.3 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{13}N_2O_2$; 229.0977: found 229.0974.

Methyl 6,7-dihydro-5*H*-benzo[c]imidazo[1,2-*a*]azepine-3-carboxylate 5c: Compound **5c** was prepared according to the *method C* using **4c** (50 mg, 0.15 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 7:3) to afford **5c** in 86% (33 mg, 0.136 mmol) as a colorless solid. mp: 87 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2940, 1705, 1440, 1184, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.78-7.76 (m, 1H), 7.41-7.36 (m, 2H), 7.30-7.28 (m, 1H), 4.34 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.37 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (C), 153.7 (C), 138.9 (C), 137.4 (CH), 130.5 (C), 130.1 (CH), 129.4 (CH), 129.1 (CH), 127.3 (CH), 122.8 (C), 51.6 (CH_3), 42.7 (CH_2), 31.9 (CH_2), 30.6 (CH_2); HMRS (ESI-TOF): calc. for $C_{14}H_{15}N_2O_2$; 243.1134: found 243.1130.

Methyl 5,6-dihydrobenzo[*f*]imidazo[1,2-*d*][1,4]oxazepine-3-carboxylate 5d: Compound **5d** was prepared according to the *method C* using **4d** (50 mg, 0.154 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 8:2) to afford **5d** in 85% (32 mg, 0.131 mmol) as a colorless solid. mp: 148 °C (CH_2Cl_2/PE); IR (neat) *v*max: 2965, 1703, 1481, 1373, 1185 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 1.8 and 8.1 Hz, 1H), 7.85 (s, 1H), 7.32 (ddd, *J* = 1.8, 7.3

and 8.7 Hz, 1H), 7.12 (ddd, *J* = 1.2, 7.3 and 8.2 Hz, 1H), 7.04 (dd, *J* = 1.2 and 8.2 Hz, 1H), 4.86-7.83 (m, 2H), 4.49-4.46 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2 (C), 156.2 (C), 149.8 (C), 137.9 (CH), 131.2 (CH), 131.1 (CH), 123.6 (C), 122.8 (CH), 120.6 (CH), 117.9 (C), 69.2 (CH_2), 51.7 (CH_3), 48.8 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{13}N_2O_3$; 245.0926: found 245.0932.

Methyl 6,7-dihydro-5H-benzo[f]imidazo[1,2-d][1,4]diazepine-3-carboxylate 5e: Compound **5e** was prepared according to the *method C* using **4e** (50 mg, 0.154 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 1:1) to afford **5e** in 54% (20 mg, 0.083 mmol) as a colorless solid. mp: 159 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 3247, 2979, 2898, 1709, 1427, 1065 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 1.6 and 8.1 Hz, 1H), 7.84 (s, 1H), 7.17 (ddd, *J* = 1.5, 7.1 and 8.4 Hz, 1H), 6.85 (ddd, *J* = 1.1, 7.1 and 8.1 Hz, 1H), 6.67 (dd, *J* = 1.1 and 8.2 Hz, 1H), 4.79-4.76 (m, 2H), 4.57 (bs, NH), 3.84 (s, 3H), 3.62-3.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4 (C), 152.0 (C), 145.4 (C), 137.8 (CH), 131.9 (CH), 130.6 (CH), 122.8 (C), 118.7 (CH), 118.0 (CH), 113.4 (C), 51.5 (CH_3), 48.5 (CH_2), 46.1 (CH_2); HMRS (ESI-TOF): calc. for $C_{13}H_{13}N_2O_3$; 244.1086: found 244.1090.

Methyl 7-methyl-6-oxo-6,7-dihydro-5*H*-benzo[*f*]imidazo[1,2-*d*][1,4]diazepine-3-carboxylate 5f: Compound **5f** was prepared according to the *method C* using **4f** (50 mg, 0.142 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 1:1) to afford **5f** in 66% (25 mg, 0.092 mmol) as a colorless solid. mp: 214 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2953, 1672, 1709, 1388, 1257, 1098 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 1.6 and 7.8 Hz, 1H), 7.89 (s, 1H), 7.57 (td, *J* = 1.6 and 7.9 Hz, 1H), 7.39-7.35 (m, 2H), 6.09 (bs, 1H), 4.18 (bs, 1H), 3.90 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 167.0 (C), 160.7 (C), 149.7 (C), 140.8 (C), 138.2 (CH), 131.2 (CH), 130.3 (CH), 126.2 (CH), 122.9 (C), 122.8 (C), 122.6 (CH), 51.9 (CH_3), 47.2 (CH_2), 37.0 (CH_3); HMRS (ESI-TOF): calc. for $C_{14}H_{14}N_3O_2$; 272.1035: found 272.1041.

Methyl 5,6,7,8-tetrahydrobenzo[*c*]imidazo[1,2-*a*]azocine-3-carboxylate 5g: Compound **5g** was prepared according to the *method C* using **4g** (50 mg, 0.148 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 7:3) to afford **5g** in 42% (16 mg, 0.062 mmol) as a colorless solid. mp: 109-111 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2931, 2855, 1706, 1470, 1235, 1106 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.52 (dd, *J* = 1.4 and 7.6 Hz, 1H), 7.44 (td, *J* = 1.4 and 7.5 Hz, 1H), 7.33-7.29 (m, 2H), 4.86-4.82 (m, 1H), 3.46-.39 (m, 1H), 2.89-2.85 (m, 1H), 2.17-2.11 (m, 3H), 1.85-1.60 (m, 1H), 1.60-1.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1 (C), 153.3 (C), 143.3 (C), 137.6 (CH), 130.7 (CH), 130.1 (CH), 130.0 (CH), 128.9 (C), 126.4 (CH), 122.5 (C), 51.5 (CH_3), 45.4 (CH_2), 32.9 (CH_2), 28.6 (CH_2), 28.0 (CH_2); HMRS (ESI-TOF): calc. for $C_{15}H_{17}N_2O_2$; 257.1290: found 257.1285.

Methyl 6,7-dihydro-5*H*-benzo[*b*]imidazo[2,1-*d*][1,5]oxazocine-3-carboxylate 5h: Compound **5h** was prepared according to the *method C* using **4h** (50 mg, 0.147 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 8:2) to afford **5h** in 59% (22 mg, 0.085 mmol) as a colorless solid. mp: 153 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2972, 1701, 1476, 1224, 1088, 1046 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.71 (dd, *J* = 1.7 and 7.9 Hz, 1H), 7.38 (td, *J* = 1.7 and 7.8 Hz, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 4.51 (bs, 2H), 4.09 (t, , *J* = 5.4 Hz 2H), 3.87 (s, 3H), 2.07 (p, *J* = 5.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0 (C), 158.2 (C), 151.9 (C), 138.1 (CH), 133.3 (CH), 131.7 (CH), 122.4 (CH), 122.1 (C), 120.9 (CH), 117.2 (C), 67.4 (CH_2), 51.6 (CH_3), 42.1 (CH_2), 28.7 (CH_2); HMRS (ESI-TOF): calc. for $C_{14}H_{15}N_2O_3$; 259.1183: found 259.1190.

Methyl 7-methyl-8-oxo-5,6,7,8-tetrahydrobenzo[*f*]imidazo[1,2-*d*][1,4]diazocine-3-carboxylate 5i: Compound **5i** was prepared according to the *method C* using **4i**[16] (50 mg, 0.136 mmol, 1.0 eq). The crude product was purified by flash chromatography (PE/EtOAc from 1:0 to 1:1) to afford **5i** in 77% (30 mg, 0.105 mmol) as a colorless solid. mp: 173 °C (CH_2Cl_2/PE); IR (neat) *ν*max: 2946, 1717, 1643, 1329, 1196 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.61-53 (m, 4H), 5.62-5.50 (m, 1H), 4.30-4.19 (m, 1H), 3.90-3.85 (m, 1H), 3.85 (s, 3H), 3.42-3.35 (m, 1H), 3.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C), 161.1 (C), 150.5 (C), 138.6 (CH), 134.9 (C), 131.3 (CH), 130.5 (CH), 130.3 (CH), 129.5 (C), 128.0 (CH), 124.0 (C), 51.7 (CH_3), 47.2 (CH_2), 43.8 (CH_2), 32.5 (CH_3); HMRS (ESI-TOF): calc. for $C_{15}H_{16}N_3O_3$; 286.1192: found 286.1181.

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[16] Product **4i** was not pure enough to be properly characterized and has been used as is for the Pd-catalyzed intramolecular direct C–H heteroarylation.

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