EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201150

Diversely Substituted Imidazo[1,2-*a*]pyrazine-8-oxo-3-carbaldehydes: An Iodine-Mediated Cyclization/Oxidation Approach

Nigam M. Mishra,[a] Dipak D. Vachhani,[a] Sachin G. Modha,[a] and Erik V. Van der Eycken*[a]

Keywords: Synthetic methods / Nitrogen heterocycles / Iodine / Oxidation / Cyclization / Cross-coupling / Alkynes

A mild and efficient iodine-mediated intramolecular heteroannulation approach for the construction of the imidazo[1,2-*a*]pyrazinone core has been developed. Under ambient conditions, this metal-free protocol allows easy access to densely functionalized imidazo[1,2-*a*]pyrazinone-3-carbaldehydes or (aminomethyl)imidazo[1,2-*a*]pyrazinones from substrates containing terminal alkynes by cyclization and subsequent oxidation or amination. Further diversification may be introduced by using substrates containing an internal alkyne and/or Suzuki coupling after cyclization to generate polysubstituted (dihydro)imidazo[1,2-*a*]pyrazinones.

Introduction

Imidazo[1,2-*a*]pyrazinones[1] are a very important class of heterocyclic compounds, as many of them have been developed into, for example, GABAA agonists,[1a,1d] antiarrhythmic agents,[1e] and kinase modulators.[1c] As a result, imidazo[1,2-*a*]pyrazinones have generated considerable interest in the last two decades, and different synthetic approaches have been reported. However, most of these approaches rely on long synthetic sequences[1b,1e] and lack the possibility to generate diversity.[1]

Metal-catalyzed[2] intra- or intermolecular carbocyclizations[3] and heteroannulations[4] of alkynes have been extensively used in recent years for the construction of diversely substituted heterocycles.[5] Although selective and high-yielding, such metal-catalyzed approaches have a drawback, which is that traces of the metals must be removed after the reaction. This has inspired organic chemists to develop metal-free approaches for the synthesis of such biologically important heterocycles.[6] Iodine activates alkynes very well, and most often, an iodo group will remain in the molecule after cyclization, allowing the introduction of additional functionalities.[4a,7] Thus, iodine-mediated metal-free approaches are generating interest in organic chemistry.[8] As part of our continuing research into transformations of the 3,5-dichloropyrazinone[9,10] skeleton and the development of diversity-orientated concise routes for the synthesis of biologically interesting heterocycles,[3,11] we developed an iodine-mediated intramolecular heteroannulation approach for the synthesis of the imidazo[1,2-*a*]pyrazinone core.

Results and Discussion

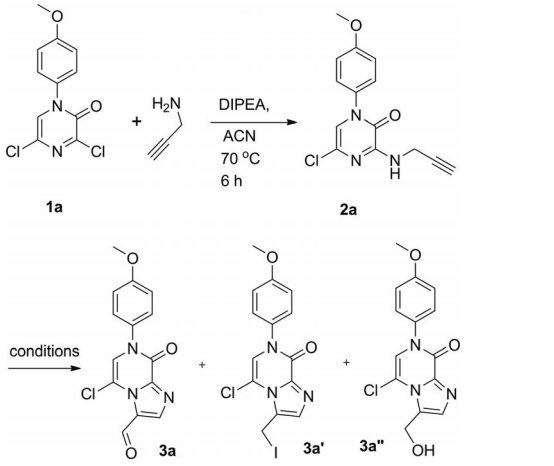
Following on from our recent report on the chemoselective Ag^I- and Au^I-catalyzed synthesis of pyrazino[2,1-*b*]-quinazolines and 3-indolylpyrazin-2(1*H*)-ones,[4b] we envisioned that iodine may be used for this heteroannulation. To investigate this idea, we synthesized starting compound **2a** by treatment of readily available 3,5-dichloropyrazin-2(1*H*)-one[12] **1a** with propargylamine and diisopropylethylamine (DIPEA) in acetonitrile at 70 °C for 6 h (Table 1). Compound **2a** was stirred with I_2 (3 equiv.) in CH_2Cl_2 at room temp. TLC and MS analysis indicated that **2a** was entirely consumed after 12 h. Surprisingly, MS and NMR spectroscopic analysis of the purified product showed that aldehyde[7a,7b,13] **3a** had been formed (Table 1, entry 1), whereas MS analysis during the reaction had shown the presence of iodine-containing compound **3a′**, as well as the corresponding hydrolyzed compound (i.e., **3a′′**). We concluded that oxidation of this primary alcohol (i.e., **3a′′**) to aldehyde **3a** due to the presence of air during the reaction and column chromatography must have occured. Further optimization of the conditions was required to exploit the tendency of this alcohol to be oxidized. To our satisfaction, the yield of **3a** increased dramatically to 80%, when hydrogen peroxide (50% in water, 8.0 mmol) was added after complete consumption of **2a** (Table 1, entry 2). Importantly, the amount of iodine could be decreased to 2 equiv. without a significant drop in the yield. However a further decrease seemed to be deleterious for the reaction (Table 1, entries 3

[a] Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven, Celestijnenlaan 200F, Heverlee 3001, Leuven, Belgium
Fax: +32-16-327-990
E-mail: erik.vandereycken@chem.kuleuven.be
Homepage: http://chem.kuleuven.be/organ/lomac/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201150.

and 4). To further enhance the reaction performance, different solvents were evaluated, and THF was found to be the best solvent (Table 1, entries 5–7). Using iodine monochloride (ICl) or *N*-iodosuccinimide (NIS) as the iodine source resulted in lower yields (Table 1, entries 8 and 9). Finally, of the different oxidants examined, H_2O_2 was found to be the best (Table 1, entries 10, 12, and 13). The amount of oxidant could be decreased from 8.0 mmol to 5.0 mmol without compromising the yield (Table 1, entries 10 and 11).

Table 1. Optimization of the iodine-mediated intramolecular heteroannulation.[a]

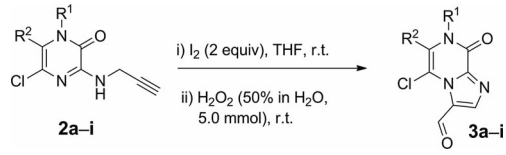


Entry	Solvent	Iodine source (equiv.)	Oxidant	Yield[b] of **3a** [%]
1	CH_2Cl_2	I_2 (3)	–	30
2	CH_2Cl_2	I_2 (3)	H_2O_2 (8.0 mmol)	80
3	CH_2Cl_2	I_2 (2)	H_2O_2 (8.0 mmol)[c]	75
4	CH_2Cl_2	I_2 (1.5)	H_2O_2 (8.0 mmol)	45
5	MeCN	I_2 (2)	H_2O_2 (8.0 mmol)	95
6	acetone	I_2 (2)	H_2O_2 (8.0 mmol)	50
7	THF	I_2 (2)	H_2O_2 (8.0 mmol)	99
8	THF	ICl (2)	H_2O_2 (8.0 mmol)	65
9	THF	NIS (2)[d]	H_2O_2 (8.0 mmol)	74
10	THF	I_2 (2)	H_2O_2 (5.0 mmol)	99
11	THF	I_2 (2)	H_2O_2 (3.0 mmol)	80
12	THF	I_2 (2)	aq. $K_2Cr_2O_3$ (2 equiv.)	50
13	THF	I_2 (2)	aq. *m*CPBA (2 equiv.)	57

[a] All reactions were carried out with **2a** (0.3 mmol) in the indicated solvent (5 mL) at room temp. for 12 h. Then the oxidant was added, and the mixture was stirred for 2–4 h. [b] Isolated yields. [c] H_2O_2 (50% in water). [d] NIS = *N*-Iodosuccinimide.

With the optimum conditions established (Table 1, entry 10), the scope of this newly developed process was evaluated. A set of diversely substituted propynylaminopyrazinones **2b**–**i** was synthesized from the corresponding 3,5-dichloropyrazin-2(1*H*)-ones (i.e., **1b**–**i**), and was subjected to the reaction conditions. In most cases, complete conversion was obtained in 12–14 h at room temp., yielding imidazo[1,2-*a*]pyrazinone-3-carbaldehydes **3b**–**i** in good to excellent yields, regardless of the substitution pattern of the pyrazinone (Table 2).

Table 2. One-pot sequential cyclization/oxidation approach towards imidazo[1,2-*a*]pyrazinone-3-carbaldehyde.[a]

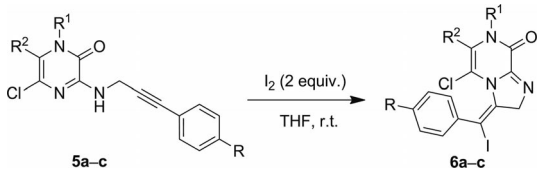


Entry	Product	R^1	R^2	Yield[b] [%]
1	**3a**	PMP	H	99
2	**3b**	Ph	Me	72
3	**3c**	Me	Me	72
4	**3d**	Me	Ph	72
5	**3e**	Bn	H	80
6	**3f**	PMB	H	72
7	**3g**	PMP	PMP	88
8	**3h**	Ph	2-$MeOC_6H_4$	99
9	**3i**	PMB	PMP	74

[a] Conditions: **2** (0.3 mmol) and I_2 (2 equiv.) in THF, room temp., 12–14 h, then H_2O_2 (50% in water, 5.0 mmol), room temp., 2–4 h. [b] Isolated yields.

To further evaluate the utility of the protocol on alkyne-substituted propynylaminopyrazinones, substrates **5a**–**c** were synthesized by Sonogashira coupling of **2a**,**b** with the aryl iodides iodobenzene (**4a**) and 1-iodo-4-methoxybenzene (**4b**) by treatment with $Pd(PPh_3)_2Cl_2$ (2 mol-%) and CuI (3 mol-%) in a mixture of Et_3N/DMSO (3:1) at 40 °C for 1 h. When the resulting (arylpropynylamino)pyrazinones **5a**–**c** were subjected to the reaction conditions, the iodine-mediated heteroannulation proceeded very well, and we were able to isolate the 3-iodomethylene 2,3-dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-ones **6a**–**c** containing an (*E*)-configured exocyclic double bond (Table 3).[14] However, upon addition of an oxidant, these compounds decomposed completely.

Table 3. Iodine-mediated heteroannulation of (arylpropynylamino)-pyrazinones **5a**–**c**.[a]

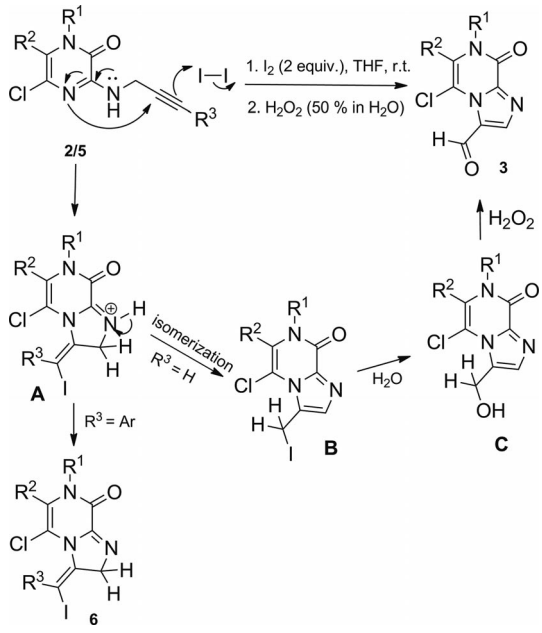


Entry	Product	R^1	R^2	R	Yield[b] [%]
1	**6a**	PMP	H	H	68
2	**6b**	Ph	CH_3	H	48
3	**6c**	PMP	H	OCH_3	91

[a] Conditions: **5** (0.3 mmol) and I_2 (2 equiv.) in THF, room temp., 12–15 h. [b] Isolated yields.

On the basis of literature reports[7] and our experimental observations, a plausible mechanism for the iodine-mediated heteroannulation is shown in Scheme 1. Nucleophilic attack of nitrogen on the activated alkyne generates inter-

mediate **A**, which, after deprotonation and subsequent isomerization of the double bond, produces **B**. This intermediate produces the final carbaldehydes (i.e., **3**) by hydrolysis and subsequent oxidation. However, in case of an internal alkyne **5**, deprotonation of intermediate **A** results in **6**, without further hydrolysis.

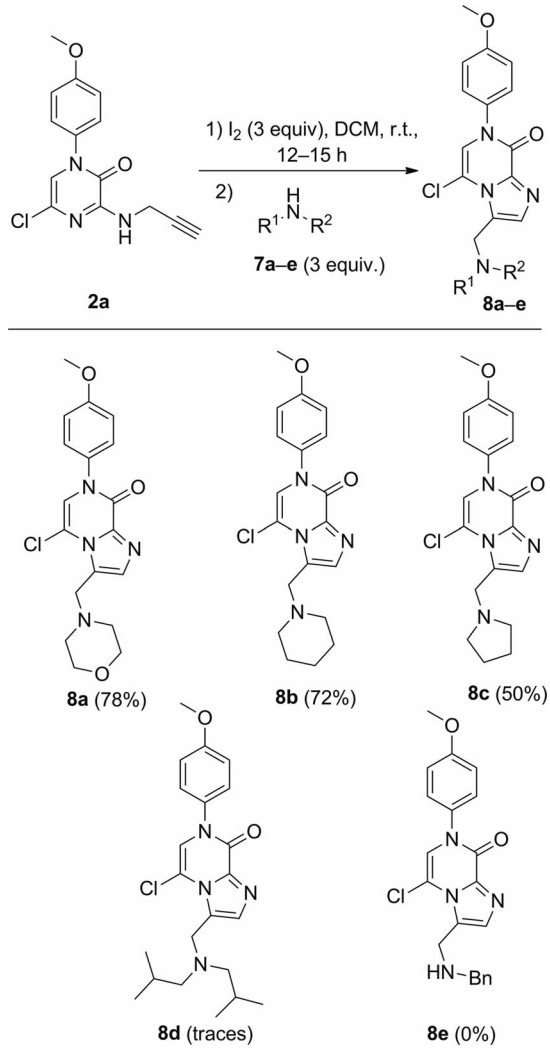


Scheme 1. Plausible mechanism for the iodine-mediated regioselective 5-*exo*-*dig* heteroannulation of propynylaminopyrazinones.

Next, we became interested in using highly reactive intermediate **B** to generate amino-substituted imidazo[1,2-*a*]pyrazinones. To our delight, when the reaction mixture was treated with an excess (3 equiv.) of cyclic secondary amines after the cyclization step was complete, the reaction worked well and amino-substituted products **8a**–**c** were formed (Table 4). However, only traces of product or even no reaction was observed when the reaction was attempted with an acyclic secondary amine (i.e, diisobutylamine) or a primary amine (i.e., benzylamine).

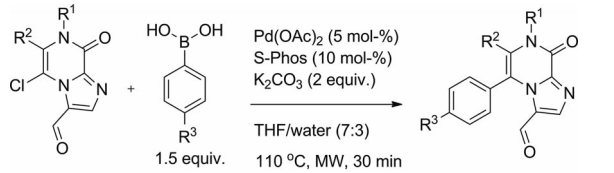
Finally, to further decorate the synthesized imidazo[1,2-*a*]pyrazin-3-carbaldehydes **3a**,**b**,**e**, the 5-Cl group was used as a convenient synthetic handle. It is worth mentioning that such a Suzuki coupling could not be performed before the heteroannulation had been done.[15] Using imidazopyrazinone **3** (1 equiv.), boronic acid **9** (1.5 equiv.), $Pd(OAc)_2$ (5 mol-%), S-Phos (10 mol-%), and K_2CO_3 (2 equiv.) in THF/water (7:3) at 110 °C for 30 min under microwave irradiation, we could generate further diversity at the 5-position (Table 5). This newly developed protocol allowed the installation of diverse substituents on both the 5- and 6-positions of the imidazo-pyrazinone, which is rather difficult to achieve otherwise.[1] However, when compound **6c** was subjected to Suzuki coupling, diarylated product **11** was isolated in 65% yield as the sole product (Scheme 2).

Table 4. One-pot sequential cyclization/amination approach towards aminomethyl-imidazo[1,2-*a*]pyrazinone.[a]



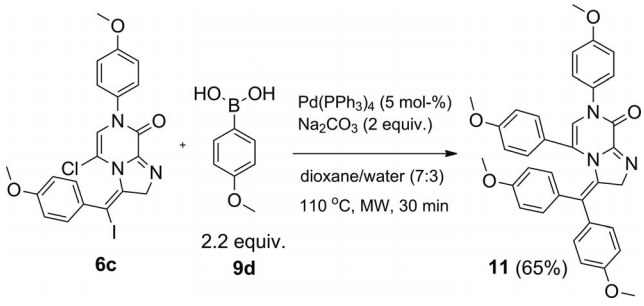
[a] Conditions: **2a** (0.3 mmol) and I_2 (3 equiv.) in CH_2Cl_2, room temp., 12–15 h, then amine **7** (3 equiv.), room temp., 3–5 h. Isolated yields.

Table 5. Synthesis of polysubstituted imidazo[1,2-*a*]pyrazin-3-carbaldehydes.[a]



Entry	Product	R^1	R^2	R^3	Yield[b] [%]
1	**10a**	PMP	H	OC_2H_5	53
2	**10b**	Bn	H	H	85
3	**10c**	Ph	CH_3	H	32
4	**10d**	PMP	H	CH_3	63

[a] Isolated yield. [b] **3** (0.3 mmol), boronic acid **9** (1.5 equiv.), $Pd(OAc)_2$ (5 mol-%), S-Phos (10 mmol-%) and K_2CO_3 (2 equiv.) in THF/water (7:3; 2 mL), 110 °C, 30 min.



Scheme 2. Synthesis of polysubstituted dihydroimidazo[1,2-*a*]-pyrazinone **11**.

Conclusions

In summary, we have developed an efficient and mild iodine-mediated approach for the synthesis of (dihydro)imidazo[1,2-*a*]pyrazinones using a 5-*exo*-*dig* intramolecular heteroannulation strategy. For terminal alkynes, a hydrolysis and oxidation sequence or an amination gives direct access to imidazo[1,2-*a*]pyrazinone-3-carbaldehydes or aminomethylimidazo[1,2-*a*]pyrazinones in a one-pot process. Mild reaction conditions, good to excellent yields, and tolerance of a range of substituents are merits of this protocol. Moreover, the above approach also allowed convenient access to polysubstituted (dihydro)imidazo[1,2-*a*]pyrazinones by Suzuki coupling.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 MHz instrument using $CDCl_3$ or [D_6]DMSO as solvent unless otherwise stated. The ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane using the residual solvent signal as an internal reference. Mass spectra were recorded using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150–250 °C, as required. High-resolution electron impact (EI) mass spectra were performed with a resolution of 10000. The low-resolution spectra were obtained with a HP5989A MS instrument. For TLC, analytical TLC plates (Alu-gram SIL G/UV254) and 70–230 mesh silica gel (E. M. Merck) were used.

Microwave Irradiation Experiments: All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation with a maximum power of 300 W. The reactions were carried out in 10 mL glass vials sealed with a Teflon® septum and placed in the microwave cavity. Initially, the temperature was raised to the desired reaction temperature. Once this temperature was reached, the reaction mixture was held at the same temperature for the required time. The reaction mixture was magnetically stirred continuously during the reaction. The temperature was measured with an IR sensor on the outer surface of the vial. After the irradiation was complete, the reaction vessel was cooled rapidly to ambient temperature by an air jet.

General Procedure for the Synthesis of 3-(Prop-2-ynylamino)pyrazin-2(1*H*)-ones 2a–i: Propargylamine (3 mmol, 1.5 equiv.) and diisopropylethylamine (DIPEA; 6 mmol, 3 equiv.) were added to a solution of substituted 3,5-dichloropyrazine-2(1*H*)-one (**1**) (2 mmol, 1 equiv.) in THF (25 mL). The reaction mixture was stirred at 60 °C for 6–10 h. After the reaction was complete, THF was removed under reduced pressure, and the mixture was partitioned between ethyl acetate (2× 50 mL) and water (50 mL). The organic phase was separated, washed with brine, and dried with Na_2SO_4. The solvent was distilled off, and the residue was subjected to silica gel chromatography (30–60% ethyl acetate in heptane) to give compounds **2a**–**i**.

5-Chloro-1-(4-methoxyphenyl)-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2a): Pale yellow solid, 84% yield, m.p. 170–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 6.68 (s, 1 H), 6.52 (s, 1 H, NH), 4.26 (dd, J = 2.4, 5.5 Hz, 2 H, CH_2), 3.85 (s, 3 H), 2.28 (s, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.4, 144.8, 144.5, 126.4, 121.5, 121.3, 109.4, 109.1, 73.7, 66.7, 50.3, 25.6 ppm. HRMS (EI): calcd. for $C_{14}H_{12}ClN_3O_2$ 289.0618; found 289.0591.

5-Chloro-6-methyl-1-phenyl-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2b): Pale yellow solid, 66% yield, m.p. 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.48 (m, 3 H), 7.17 (d, J = 6.5 Hz, 2 H), 6.29 (s, 1 H, NH), 4.23 (dd, J = 2.4, 5.3 Hz, 2 H, CH_2), 2.25 (t, J = 2.49 Hz, 1 H, alkyne-CH), 1.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.4, 147.8, 137.3, 129.9, 129.4, 127.4, 125.0, 120.5, 79.3, 71.6, 30.6, 16.9 ppm. HRMS (EI): calcd. for $C_{14}H_{12}ClN_3O$ 273.0668; found 273.0662.

5-Chloro-1,6-dimethyl-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2c): White solid, 30% yield, m.p. 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.25 (s, 1 H, NH), 4.19 (dd, J = 2.4, 5.5 Hz, 2 H, CH_2), 3.53 (s, 3 H), 2.35 (s, 3 H), 2.25 (t, J = 2.4 Hz, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.3, 147.1, 125.0, 120.5, 79.4, 71.6, 32.0, 30.6, 15.9 ppm. HRMS (EI): calcd. for $C_9H_{10}ClN_3O$ 211.0512; found 211.0514.

5-Chloro-1-methyl-6-phenyl-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2d): Yellow solid, 90% yield, m.p. 119–121 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.45 (m, 3 H), 7.33–7.28 (m, 2 H), 6.41 (br. s, 1 H, NH), 4.27 (dd, J = 2.5, 5.5 Hz, 2 H, CH_2), 3.22 (s, 3 H), 2.28 (t, J = 2.3 Hz, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.0, 148.2, 132.2, 130.2, 129.4, 129.0, 125.7, 124.8, 79.2, 71.8, 34.2, 30.7 ppm. HRMS (EI): calcd. for $C_{14}H_{12}ClN_3O$ 273.0669; found 273.0680.

1-Benzyl-5-chloro-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2e): Off-white solid, 80% yield, m.p. 170–172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 3 H), 7.31–7.27 (m, 2 H), 6.53–6.50 (m, 2 H, NH, Ar), 5.01 (s, 2 H, CH_2Ar), 4.21 (dd, J = 2.4, 5.4 Hz, 2 H, CH_2NH), 2.26 (t, J = 2.4 Hz, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.1, 149.5, 134.7, 129.0, 128.6, 128.3, 126.7, 112.9, 78.9, 72.0, 51.8, 30.8 ppm. HRMS (EI): calcd. for $C_{14}H_{12}ClN_3O$ 273.0668; found 273.0668.

5-Chloro-1-(4-methoxybenzyl)-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2f): Pale yellow solid, 85% yield, m.p. 197–199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24 (d, J = 8.4 Hz, 2 H), 6.88 (d, J = 8.4 Hz, 2 H), 6.52 (s, 1 H), 6.44 (br. s, 1 H, NH), 4.94 (s, 2 H, CH_2Ar), 4.21 (dd, J = 2.4, 5.4 Hz, 2 H, CH_2NH), 3.80 (s, 3 H), 2.26 (s, 1 H, alkyne-CH) ppm. . ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 159.7, 150.2, 150.1, 130.1, 128.5, 125.3, 114.7, 113.9, 81.1, 72.9, 55.7, 51.0, 30.3 ppm. HRMS (EI): calcd. for $C_{15}H_{14}ClN_3O_2$ 303.0774; found 303.0771.

5-Chloro-1,6-bis(4-methoxyphenyl)-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2g): Yellow solid, 88% yield, m.p. 137–139 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.98 (d, J = 8.6 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 6.75–6.67 (m, 4 H), 6.50 (t, J = 5.4 Hz, 1 H, NH), 4.29 (dd, J = 2.4, 5.6 Hz, 2 H, CH_2), 3.72 (s, 6 H), 2.28 (t, J =

2.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 159.0, 151.3, 148.6, 132.2, 130.0, 129.1, 126.0, 125.1, 124.5, 114.2, 113.4, 79.3, 71.7, 55.3, 55.1, 30.71 ppm. HRMS (EI): calcd. for $C_{21}H_{18}ClN_3O_3$ 395.1036; found 395.1030.

5-Chloro-6-(2-methoxyphenyl)-1-phenyl-3-(prop-2-ynylamino)-pyrazin-2(1*H*)-one (2h): Yellow solid, 78% yield, m.p. 223–225 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.11 (m, 5 H), 7.09 (d, J = 1.8 Hz, 1 H), 7.07 (d, J = 1.7 Hz, 1 H), 6.90 (d, J = 4.7 Hz, 1 H), 6.61 (d, J = 8.2 Hz, 1 H), 6.49 (br. s, 1 H, NH), 4.31 (dd, J = 2.4, 5.6 Hz, 2 H, CH_2), 3.64 (s, 3 H), 2.29 (t, J = 2.4 Hz, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.7, 151.0, 148.8, 137.2, 132.5, 130.8, 128.5, 128.3, 128.2, 127.9, 127.5, 126.2, 122.1, 121.1, 120.1, 110.5, 79.3, 71.8, 55.0, 30.7 ppm. HRMS (EI): calcd. for $C_{21}H_{18}ClN_3O_2$ 365.0931; found 365.0875.

5-Chloro-1-(4-methoxybenzyl)-6-(4-methoxyphenyl)-3-(prop-2-ynylamino)pyrazin-2(1*H*)-one (2i): Yellow solid, 35% yield, m.p. 113–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.01 (d, J = 8.6 Hz, 2 H), 6.89 (d, J = 8.6 Hz, 2 H), 6.74 (m, 4 H), 6.50 (t, J = 5.5 Hz, 1 H, NH), 4.94 (s, 2 H, CH_2Ar), 4.26 (dd, J = 2.4, 5.4 Hz, 2 H, CH_2NH), 3.84 (s, 3 H), 3.75 (s, 3 H), 2.28 (t, J = 2.3 Hz, 1 H, alkyne-CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 159.0, 151.1, 148.6, 132.1, 128.8, 127.8, 126.6, 124.4, 124.0, 113.9, 113.7, 79.2, 71.9, 55.3, 55.2, 48.8 ppm. HRMS (EI): calcd. for $C_{22}H_{20}ClN_3O_3$ 409.1193; found 409.1200.

General Procedure for the Synthesis of Imidazo[1,2-*a*]pyrazinone-3-carbaldehydes 3a–i: Compound **2** (0.3 mmol, 1 equiv.) was dissolved in THF (5 mL) in a 25 mL round-bottomed flask fitted with a condenser, and iodine (0.6 mmol, 2 equiv.) was added. The mixture was stirred at room temp. for 12–14 h. After complete consumption of **2**, H_2O_2 (50% in H_2O, 5.0 mmol) was added, and stirring was continued for 2–4 h at room temp. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. $Na_2S_2O_3$ (satd. aq., 25 mL) was added to the resulting crude material, and the mixture was extracted with ethyl acetate (2 × 25 mL). The organic extracts were washed with water (25 mL) and brine (25 mL), and dried with Na_2SO_4. The solvent was distilled off, and the residue was subjected to silica gel chromatography (50–70% ethyl acetate in heptane) to give compounds **3a**–**i**.

5-Chloro-7-(4-methoxyphenyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (3a): Yellow solid, 99% yield, m.p. 263–265 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.63 (s, 1 H), 8.28 (s, 1 H), 7.83 (s, 1 H), 7.48 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 2 H), 3.88 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 180.4, 159.0, 151.6, 140.4, 138.8, 131.4, 131.2, 127.9, 121.9, 114.2, 108.2, 55.4 ppm. HRMS (EI): calcd. for $C_{14}H_{10}ClN_3O_3$ 303.0410; found 303.0409.

5-Chloro-6-methyl-8-oxo-7-phenyl-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (3b): Yellow solid, 86% yield, m.p. 211–213 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.69 (s, 1 H), 8.26 (s, 1 H), 7.60–7.52 (m, 3 H), 7.27–7.23 (m, 2 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 152.7, 140.2, 139.8, 136.7, 132.0, 130.1, 129.8, 128.1, 127.8, 107.6, 17.9 ppm. HRMS (EI): calcd. for $C_{14}H_{10}ClN_3O_2$ 287.0461; found 287.0481.

5-Chloro-6,7-dimethyl-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (3c): Yellow solid, 72% yield, m.p. 241–243 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.64 (s, 1 H), 8.23 (s, 1 H), 3.66 (s, 3 H), 2.56 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 152.9, 140.2, 139.4, 131.8, 127.7, 107.4, 31.9, 16.7 ppm. HRMS (EI): calcd. for $C_9H_8ClN_3O_2$ 225.0305; found 225.0306.

5-Chloro-7-methyl-8-oxo-6-phenyl-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (3d): Yellow solid, 82% yield, m.p. 311–313 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.63 (s, 1 H), 8.28 (s, 1 H), 7.65–7.55 (m, 3 H), 7.40 (t, J = 7.31 Hz, 2 H), 3.29 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.6, 152.8, 140.3, 139.8, 132.0, 131.8, 130.8, 130.6, 129.6, 129.4, 108.7, 34.2 ppm. HRMS (EI): calcd. for $C_{14}H_{10}ClN_3O_2$ 287.0461; found 287.0460.

7-Benzyl-5-chloro-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (3e): Yellow solid, 80% yield, m.p. 181–183 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.60 (s, 1 H), 8.24 (s, 1 H), 7.45–7.32 (s, 5 H), 6.92 (s, 1 H), 5.19 (s, 2 H, CH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 152.0, 140.4, 140.2, 134.6, 131.8, 129.2, 128.9, 128.5, 119.6, 109.2, 51.0 ppm. HRMS (EI): calcd. for $C_{14}H_{10}ClN_3O_2$ 287.0461; found 287.0460.

5-Chloro-7-(4-methoxybenzyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (3f): Yellow solid, 72% yield, m.p. 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.60 (s, 1 H), 8.26 (s, 1 H), 7.31 (d, J = 8.6 Hz, 2 H), 6.91 (d, J = 8.6 Hz, 2 H), 6.85 (s, 1 H), 5.12 (s, 2 H, CH_2Ar), 3.81 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 180.4, 158.9, 151.5, 138.6, 129.5, 128.1, 120.9, 113.9, 108.3, 55.0, 49.8 ppm. HRMS (EI): calcd. for $C_{15}H_{11}ClN_2O_3$ 317.0567; found 317.0607.

5-Chloro-6,7-bis(4-methoxyphenyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (3g): Yellow solid, 94% yield, m.p. 228–230 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.68 (s, 1 H), 8.30 (s, 1 H), 7.08 (d, J = 8.6 Hz, 2 H), 6.96 (d, J = 8.8 Hz, 2 H), 6.76 (t, J = 8.8 Hz, 4 H), 3.77 (s, 3 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 160.1, 159.2 152.9, 140.3, 140.2, 132.3, 132.2, 131.7, 129.8, 129.3, 122.9, 114.3, 113.9, 108.9, 55.3, 55.2 ppm. HRMS (EI): calcd. for $C_{22}H_{17}ClN_3O_4$ 409.0825; found 409.0829.

5-Chloro-6-(2-methoxyphenyl)-8-oxo-7-phenyl-7,8-dihydroimidazo-[1,2-*a*]pyrazine-3-carbaldehyde (3h): Yellow solid, 99% yield, m.p. > 320 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.71 (s, 1 H), 8.33 (s, 1 H), 7.30–7.15 (m, 5 H), 7.13–7.09 (m, 2 H), 6.87 (t, J = 7.5 Hz, 1 H), 6.71 (d, J = 8.2 Hz, 1 H), 3.73 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 183.1, 159.0, 154.9, 142.8, 141.9, 139.7, 134.7, 134.5, 134.3, 131.6, 131.2, 131.1, 130.8, 122.9, 122.6, 114.0, 111.2, 58.1 ppm. HRMS (EI): calcd. for $C_{21}H_{15}ClN_3O_3$ 379.0723; found 379.0717.

5-Chloro-7-(4-methoxybenzyl)-6-(4-methoxyphenyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (3i): Yellow solid, 74% yield, m.p. 185–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.61 (s, 1 H), 8.29 (s, 1 H), 7.06 (d, J = 8.6 Hz, 2 H), 6.97 (d, J = 8.6 Hz, 2 H), 6.78 (d, J = 8.6 Hz, 2 H), 6.69 (d, J = 8.6 Hz, 2 H), 5.06 (s, 2 H, CH_2Ar), 3.89 (s, 3 H), 3.74 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.7, 160.9, 159.2, 153.1, 140.3, 140.1, 132.1, 131.6, 131.5, 129.1, 127.9, 122.4, 114.4, 113.7, 109.4, 55.4, 55.2, 48.4 ppm. HRMS (EI): calcd. for $C_{22}H_{18}ClN_3O_4$ 423.0985; found 423.0972.

General Procedure for the Synthesis of Compounds 5a–c: Compound **2** (0.7 mmol, 1 equiv.), aryl iodide **4** (0.77 mmol, 1.1 equiv.), $Pd(PPh_3)_2Cl_2$ (2 mol-%), and CuI (3 mol-%) were added to an oven-dried 25 mL two-necked flask equipped with a stirrer-bar under argon. The flask was evacuated and refilled with argon (3×). Dry Et_3N/DMSO (4:1; 10 mL) were added by syringe, and the resulting suspension was allowed to stir at 45 °C for 1 h. After completion of reaction, as indicated by TLC and MS analysis, the mixture was cooled to room temperature. The crude mixture was diluted with ethyl acetate (50 mL), and washed with H_2O (50 mL). The organic phase was washed with brine (50 mL), and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude sample was purified by silica gel column chromatography (35–40% ethyl acetate in heptane) to give compounds **5a**–**c**.

5-Chloro-1-(4-methoxyphenyl)-3-(3-phenylprop-2-ynylamino)-pyrazin-2(1*H*)-one (5a): Yellow solid, 72% yield, m.p. 95 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.39 (m, 2 H), 7.35–7.27 (m, 5 H), 6.98 (d, J = 8.5 Hz, 2 H), 6.66–6.63 (m, 2 H, Ar, NH), 4.27 (d, J = 5.5 Hz, 2 H, CH_2), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 150.2, 149.7, 131.7, 128.4, 128.3, 126.8, 126.7, 122.5, 114.66, 114.1, 84.2, 83.7, 55.6, 31.7 ppm. HRMS (EI): calcd. for $C_{20}H_{16}N_3O_2$ 365.0931; found 365.0930.

5-Chloro-6-methyl-1-phenyl-3-(3-phenylprop-2-ynylamino)pyrazin-2(1*H*)-one (5b): Yellow solid, 80% yield, m.p. 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.48 (m, 3 H), 7.47–7.41 (m, 2 H), 7.31–7.28 (m, 3 H), 7.17 (d, J = 6.7 Hz, 2 H), 6.35 (br. s, 1 H, NH), 4.46 (d, J = 5.2 Hz, 2 H, CH_2), 1.93 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.5, 147.8, 137.4, 131.7, 129.9, 129.3, 128.3, 128.2, 127.4, 125.1, 122.6, 120.3, 84.6, 83.5, 31.5, 16.9 ppm. HRMS (EI): calcd. for $C_{20}H_{16}ClN_3O$ 349.0982; found 349.0961.

5-Chloro-1-(4-methoxyphenyl)-3-[3-(4-methoxyphenyl)prop-2-ynylamino]pyrazin-2(1*H*)-one (5c): Yellow solid, 84% yield, m.p. 130–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, J = 8.8 Hz, 2 H), 7.30 (d, J = 9.0 Hz, 2 H), 6.98 (d, J = 9 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 6.66–6.61 (m, 2 H, NH, Ar), 4.45 (d, J = 5.4 Hz, 2 H, CH_2), 3.83 (s, 3 H), 3.79 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.7, 159.6, 150.1, 149.7, 133.2, 131.7, 126.8, 126.6, 114.6, 114.5, 114.0, 113.9, 83.7, 82.8, 55.5, 55.2, 31.8 ppm. HRMS (EI): calcd. for $C_{21}H_{18}ClN_3O_3$ 395.1036; found 395.1023.

General Procedure for the Synthesis of Dihydroimidazo[1,2-*a*]-pyrazinones 6a–c: Compound **5** (0.3 mmol, 1 equiv.) was dissolved in THF (5 mL) in a 25 mL round-bottomed flask fitted with a condenser, and iodine (0.6 mmol, 2 equiv.) was added. The mixture was stirred at room temp. for 12–15 h. After complete consumption of **5**, the reaction mixture was concentrated under reduced pressure. $Na_2S_2O_3$ (satd. aq., 25 mL) was added to the resulting crude material, and the mixture was extracted with ethyl acetate (2 × 25 mL). The organic phase was washed with water (25 mL) and brine (25 mL), and dried with Na_2SO_4. The solvent was distilled off, and the residue was subjected to silica gel chromatography (60–70% ethyl acetate in heptane) to give compounds **6a**–**c**.

(*E*)-5-Chloro-3-[iodo(phenyl)methylene]-7-(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-one (6a): Yellow solid, 68% yield, m.p. 122–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.42 (m, 3 H), 7.34–7.31 (m, 4 H), 6.98 (d, J = 9 Hz, 2 H), 6.09 (s, 1 H), 4.75 (s, 2 H, CH_2), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 155.2, 146.0, 138.3, 134.8, 131.5, 129.6, 129.3, 128.5, 126.9, 114.7, 113.8, 112.8, 73.6, 59.8, 55.5 ppm. HRMS (EI): calcd. for $C_{20}H_{15}ClIN_3O_2$ 490.9897; found 490.9879.

(*E*)-5-Chloro-3-[iodo(phenyl)methylene]-6-methyl-7-phenyl-2,3-dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-one (6b): Yellow solid, 48% yield, m.p. 175–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.42 (m, 7 H), 7.33–7.31 (m, 2 H), 7.24 (s, 1 H), 4.72 (s, 2 H, CH_2), 1.68 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 146.0, 138.8, 136.9, 134.9, 130.0, 129.6, 129.2, 129.0, 128.4, 128.1, 118.6, 112.2, 72.7, 59.9, 16.5 ppm. HRMS (EI): calcd. for $C_{20}H_{15}ClIN_3O$ 474.9948; found 474.9966.

(*E*)-5-Chloro-3-[iodo(4-methoxyphenyl)methylene]-7-(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-one (6c): Yellow solid, 91% yield, m.p. 188–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32 (d, J = 9 Hz, 2 H), 7.24 (d, J = 8.6 Hz, 2 H), 6.96 (t, J = 8.4 Hz, 4 H), 6.09 (s, 1 H), 4.72 (s, 2 H, CH_2), 3.85 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.2, 159.3, 155.3, 145.9, 138.1, 131.6, 130.9, 126.99, 126.90, 114.7, 113.9, 113.8, 112.7, 72.4, 59.8, 55.5, 55.3 ppm. HRMS (EI): calcd. for $C_{21}H_{17}ClIN_3O_3$ 521.0003; found 521.0021.

General Procedure for the Synthesis of 3-Aminomethylimidazo[1,2-*a*]pyrazinones 8a–c: Compound **2** (0.3 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (5 mL) in a 25 mL round-bottomed flask fitted with a condenser, and iodine (0.9 mmol, 3 equiv.) was added. The mixture was stirred at room temp. for 12–15 h. After complete consumption of **2**, amine (0.9 mmol, 3 equiv.) was added, and the mixture was stirred for 3–5 h at room temp. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (25 mL) and washed with $Na_2S_2O_3$ (satd. aq., 25 mL). The organic phase was washed with brine and dried with Na_2SO_4. The solvent was distilled off, and the residue was purified by silica gel chromatography (2–4% methanol in CH_2Cl_2) to give pure product **8a**–**c**.

5-Chloro-7-(4-methoxyphenyl)-3-(morpholinomethyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (8a): Yellow solid, 78% yield, m.p. 200–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.33 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.83 (s, 1 H), 3.88 (s, 2 H, CH_2Ar), 3.84 (s, 3 H), 3.69 (t, J = 4.3 Hz, 4 H), 2.51 (t, J = 4.3 Hz, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 152.1, 139.3, 135.2, 131.4, 128.1, 127.4, 119.3, 114.7, 109.7, 66.9, 55.6, 53.2, 52.8 ppm. HRMS (EI): calcd. for $C_{18}H_{19}ClN_4O_3$ 374.1145; found 374.1146.

5-Chloro-7-(4-methoxyphenyl)-3-(piperidin-1-ylmethyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (8b): Yellow solid, 72% yield, m.p. 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 7.33 (d, J = 8.8 Hz, 2 H), 6.99 (d, J = 8.8 Hz, 2 H), 6.79 (s, 1 H), 3.84 (s, 3 H), 3.83 (s, 2 H, CH_2Ar), 2.49–2.40 (m, 4 H), 1.62–1.44 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 152.2, 139.0, 135.0, 131.5, 129.3, 127.5, 119.1, 114.7, 109.6, 55.6, 54.3, 53.3, 25.9, 24.2 ppm. HRMS (EI): calcd. for $C_{19}H_{21}ClN_4O_2$ 372.1353; found 372.1360.

5-Chloro-7-(4-methoxyphenyl)-3-(pyrrolidin-1-ylmethyl)imidazo-[1,2-*a*]pyrazin-8(7*H*)-one (8c): Yellow solid, 50% yield, m.p. 142–144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 7.32 (d, J = 8.8 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 6.80 (s, 1 H), 4.07 (s, 2 H, CH_2Ar), 3.83 (s, 3 H), 2.66–2.53 (m, 4 H), 1.84–1.77 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5, 152.2, 138.8, 134.4, 131.5, 130.0, 127.5, 119.2, 114.7, 109.6, 55.6, 54.0, 50.4, 23.5 ppm. HRMS (EI): calcd. for $C_{18}H_{19}ClN_4O_2$ 358.1196; found 358.1222.

General Procedure for the Synthesis of Polysubstituted Imidazo[1,2-*a*]pyrazine-8(7*H*)-ones by Suzuki Coupling 10a–d: Boronic acid **9** (0.45 mmol, 1.5 equiv.), $Pd(OAc)_2$ (0.015 mmol, 5 mol-%), S-Phos (0.03 mmol, 10 mol-%), and K_2CO_3 (0.6 mmol, 2 equiv.) were added to a 10 mL reaction vial containing compound **3** (0.3 mmol, 1 equiv.). Then a THF/water mixture (7:3; 2 mL) was added, and the vial was sealed tightly with a Teflon® cap. The mixture was irradiated for 30 min at a pre-selected temperature of 110 °C, with a maximum irradiation power of 300 W. After the reaction was complete, as monitored by TLC and MS analysis, water (25 mL) was added, and the crude mixture was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (25 mL), and dried with Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure, and the crude product was subjected to silica gel column chromatography (70–80% ethyl acetate in heptane) to give compounds **10a**–**d**.

5-(4-Ethoxyphenyl)-7-(4-methoxyphenyl)-8-oxo-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (10a): Light yellow solid, 53% yield, m.p. 66–68 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.19 (s, 1 H), 7.45 (d, J = 8.6 Hz, 2 H), 7.39 (d, J = 8.8 Hz, 2 H), 7.07–6.97 (m, 4 H), 6.81 (s, 1 H), 4.09 (q, J = 6.9 Hz, 2 H), 3.84 (s, 3 H), 1.46 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 160.8, 159.7, 152.4, 140.6, 140.0, 131.5, 130.9, 130.8, 127.4, 122.8, 121.9, 119.6, 115.8, 114.8, 63.8, 55.6, 14.6 ppm. HRMS (EI): calcd. for $C_{22}H_{19}N_3O_4$ 389.1375; found 389.1375.

7-Benzyl-8-oxo-5-phenyl-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (10b): Yellow solid, 85% yield, m.p. 98–100 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 8.17 (s, 1 H), 7.55–7.42 (m, 5 H), 7.41–7.30 (m, 5 H), 6.68 (s, 1 H), 5.22 (s, 2 H, CH_2Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.7, 152.7, 140.6, 140.2, 135.2, 131.2, 130.8, 130.6, 129.9, 129.2, 129.1, 128.6, 128.5, 120.4, 120.2, 50.8 ppm. HRMS (EI): calcd. for $C_{20}H_{15}N_3O_2$ 329.1164; found 329.1147.

6-Methyl-8-oxo-5,7-diphenyl-7,8-dihydroimidazo[1,2-*a*]pyrazine-3-carbaldehyde (10c): Yellow solid, 32% yield, m.p. 240–242 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 8.16 (s, 1 H), 7.66–7.46 (m, 8 H), 7.34–7.29 (m, 2 H), 1.76 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.6, 153.6, 139.9, 139.8, 136.9, 132.4, 131.1, 130.9, 130.7, 130.5, 130.0, 129.4, 128.3, 127.8, 116.7, 17.8 ppm. HRMS (EI): calcd. for $C_{20}H_{15}N_3O_2$ 329.1164; found 329.1159.

7-(4-Methoxyphenyl)-8-oxo-5-(*p*-tolyl)-7,8-dihydroimidazo[1,2-*a*]-pyrazine-3-carbaldehyde (10d): Yellow solid, 63% yield, m.p. 152–154 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.20 (s, 1 H), 7.45–7.32 (m, 6 H), 7.00 (d, J = 8.6 Hz, 2 H), 6.82 (s, 1 H), 3.84 (s, 3 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.1, 159.7, 152.4, 141.2, 140.7, 140.1, 131.5, 130.8, 130.7, 129.1, 128.1, 127.4, 121.9, 119.8, 114.8, 55.6, 21.4 ppm. HRMS (EI): calcd. for $C_{21}H_{17}N_3O_3$ 359.1269; found 359.1259.

3-[bis(4-Methoxyphenyl)methylene]-5,7-bis(4-methoxyphenyl)-2,3-dihydroimidazo[1,2-*a*]pyrazin-8(7*H*)-one (11): (*p*-Methoxyphenyl)-boronic acid (**9d**) (0.44 mmol, 2.2 equiv.), $Pd(PPh_3)_4$ (0.01 mmol, 5 mol-%), and Na_2CO_3 (0.4 mmol, 2 equiv.) were added to a 10 mL reaction vial containing compound **6c** (0.2 mmol, 1 equiv.). Then a mixture of dioxane/water (7:3; 2 mL) was added, and the vial was sealed tightly with a Teflon® cap. The mixture was irradiated for 30 min at a pre-selected temperature of 110 °C, with maximum irradiation power of 300 W. After the reaction was complete, as monitored by TLC and MS analysis, water (25 mL) was added, and the mixture was extracted with ethyl acetate (2× 30 mL). The combined organic extracts were washed with brine (25 mL), and dried with Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure, and the crude product was subjected to silica gel column chromatography (70–80% ethyl acetate in heptane) to give compound **11**. Yellow solid, 65% yield, m.p. 53–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 9.0 Hz, 2 H), 7.0 (d, J = 9.0 Hz, 2 H), 6.90 (d, J = 2.1 Hz, 2 H), 6.87 (d, J = 2.1 Hz, 2 H), 6.6–6.5 (m, 6 H), 6.47 (d, J = 9 Hz, 2 H), 6.03 (s, 1 H), 3.84 (s, 3 H), 3.72 (s, 2 H), 3.71 (s, 3 H), 3.68 (s, 3 H), 3.67 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 158.7, 158.1, 156.3, 147.8, 134.3, 132.6, 130.9, 130.7, 129.8, 127.5, 127.2, 126.9, 124.6, 116.1, 114.9, 114.6, 116.1, 113.6, 113.4, 113.1, 112.0, 55.5, 55.2, 55.1, 55.0, 52.1 ppm. HRMS (EI): calcd. for $C_{35}H_{31}N_3O_5$ 573.2263; found 573.2272.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C spectra of all new compounds.

Acknowledgments

The authors wish to thank the Fund for Scientific Research, Flanders, Belgium (FWO) and the Research Fund of the University of Leuven (KU Leuven) for financial support. N. M. and D. V. are grateful to the Erasmus Mundus External Cooperation Window (EMECW), Lot 13) for a doctoral scholarship. The authors thank Ir. B. Demarsin for HRMS measurements.

[1] a) S. G. Goodacre, D. J. Hallett, R. W. Carling, J. L. Castro, D. S. Reynolds, A. Pike, K. A. Wafford, R. Newman, J. R. Atack, L. J. Street, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1582–1385; b) D. D. Davey, *J. Org. Chem.* **1987**, *52*, 4379–4381; c) Q. Liu, D. G. Batt, G. V. Delucca, Q. Shi, A. J. Tebben, U. S. Patent US 2010/0160303 A1, **2010**; d) W. R. Carling, J. L. Castro-Pineiro, S. C. Goodacre, D. J. Hallett, L. J. Street, PCT Int. Appl. WO 2004/041826 A1, **2004**; e) B. Plouvier, D. Fedida, G. N. Beatch, D. Chou, A. Yifru, G. Jung, PCT Int. Appl. WO 2005/034837 A2, **2005**; f) D. D. Vachhani, S. G. Modha, A. Sharma, E. V. Van der Eycken, *Tetrahedron* **2013**, *69*, 359–365.

[2] a) A. De Meijere, F. Diederich (Eds.), *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Wiley-VCH, Weinheim, Germany, **2004**; b) E. I. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340–348; c) P. Knochel, M. I. Calaza, E. Hupe, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, Germany, **2004**, chapter 11; d) M. Beller, C. Bolm (Eds.), *Transition Metals for Organic Synthesis* 2nd ed., Wiley-VCH, Weinheim, Germany, **2004**; e) E. A. V. Kentchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824–2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813.

[3] a) P. A. Donets, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken, *Org. Lett.* **2009**, *11*, 3618–3621; b) V. A. Peskov, S. Van Hove, P. A. Donets, O. P. Pereshivko, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken, *Eur. J. Org. Chem.* **2011**, 1837–1840.

[4] a) V. P. Mehta, S. G. Modha, D. Ermolat'ev, K. Van Hecke, L. Van Meervelt, E. Van der Eycken, *Aust. J. Chem.* **2009**, *62*, 27–41; b) D. D. Vachhani, V. P. Mehta, S. G. Modha, K. Van Hecke, L. Van Meervelt, E. V. Van der Eycken, *Adv. Synth. Catal.* **2012**, *354*, 1593–1599.

[5] For a thematic special issue on coinage metals in organic Synthesis see: *Chem. Rev.* **2008**, *108*, 2793–3442.

[6] a) P. T. Parvatkar, P. S. Parameswaran, S. G. Tilve, *Chem. Eur. J.* **2012**, *18*, 5460–5489; b) C. Chen, S. Yang, M. Wu, *J. Org. Chem.* **2011**, *76*, 10269–10274; c) A. Sniady, K. A. Wheeler, R. Dembinski, *Org. Lett.* **2005**, *7*, 1769–1772; d) D. W. Knight, A. L. Redfern, J. Gilmore, *J. Chem. Soc. Perkin Trans. 1* **2001**, 2874–2883; e) D. Yue, R. C. Larock, *Org. Lett.* **2004**, *6*, 1037–1040.

[7] a) S. Li, Z. Li, Y. Yuan, D. Peng, Y. Li, L. Zhang, Y. Wu, *Org. Lett.* **2012**, *14*, 1130–1133; b) D. Sucunza, A. Samadi, M. Chioua, D. B. Silva, C. Yunta, L. Infantes, M. C. Carreiras, E. Soriano, J. Marco-Contelles, *Chem. Commun.* **2011**, *47*, 5043–5045; c) S. K. Sharma, A. K. Mandadapu, B. Kumar, B. Kundu, *J. Org. Chem.* **2011**, *76*, 6798–6805; d) M. J. Mphahlele, *Molecules* **2009**, *14*, 4814–4837; e) H. Togo, S. Iida, *Synlett* **2006**, 2159–2175; f) F. M. da Silva, J. J. Junior, M. C. S. de Mattos, *Curr. Org. Synth.* **2005**, *2*, 393–414; g) S. Mehta, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 1652–1658; h) R. Mancuso, S. Mehta, B. Gabriele, G. Salerno, W. S. Jenks, R. C. Larock, *J. Org. Chem.* **2010**, *75*, 897–901.

[8] a) B. Alcaide, P. Almendros, G. Cabrero, R. Callejo, M. P. Ruiz, M. Arno, L. R. Domingo, *Adv. Synth. Catal.* **2010**, *352*, 1688–1700; b) W. Lee, H. Shen, W. Hu, W. Lo, C. Murali, J. K. Vandavasi, J. Wang, *Adv. Synth. Catal.* **2012**, *354*, 2218; c) K. Xu, Y. Hu, S. Zhang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 9793–9797; d) S. Das, R. Borah, R. R. Devi, A. J. Thakur, *Synlett* **2008**, *18*, 2741–2762.

[9] For an early review, see: a) G. Hoornaert, *Bull. Soc. Chim. Belg.* **1994**, *103*, 583–589; for a recent review, see: b) V. G. Pawar, W. M. De Borggraeve, *Synthesis* **2006**, 2799–2814; using microwave irradiation, see: c) V. P. Mehta, P. Appukkuttan, E. Van der Eycken, *Curr. Org. Chem.* **2011**, *15*, 265–283; d) E. Van der Eycken, C. O. Kappe (Eds.), *Topics in Heterocyclic Chemistry*, Springer, Berlin, **2006**, vol. 1, p. 267; e) N. Kaval, K. Bisztrav, W. Dehaen, C. O. Kappe, E. Van der Eycken, *Mol. Diversity* **2003**, *7*, 125–134; f) N. Kaval, B. K. Singh, D. S. Erm-

olat'ev, S. Claerhout, J. Van der Eycken, E. Van der Eycken, *J. Comb. Chem.* **2007**, *9*, 446–453.
[10] a) V. P. Mehta, A. Sharma, E. Van der Eycken, *Adv. Synth. Catal.* **2008**, *350*, 2174–2178; b) V. P. Mehta, A. Sharma, E. Van der Eycken, *Org. Lett.* **2008**, *10*, 1147–1150; c) V. P. Mehta, S. G. Modha, E. Van der Eycken, *J. Org. Chem.* **2009**, *74*, 6870–6873; d) N. M. Mishra, V. A. Peshkov, O. P. Pereshivko, S. G. Modha, E. V. Van der Eycken, *Tetrahedron Lett.* **2012**, *53*, 4676–4678.
[11] a) S. G. Modha, D. D. Vachhani, J. Jacobs, L. Van Meervelt, E. V. Van der Eycken, *Chem. Commun.* **2012**, *48*, 6550–6552; b) S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2012**, *51*, 9572–9575; c) S. G. Modha, A. Kumar, D. D. Vachhani, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Chem. Commun.* **2012**, *48*, 10916–10918.
[12] a) J. Vekemans, C. Pollers-Wieërs, G. Hoornaert, *J. Heterocycl. Chem.* **1983**, *20*, 919–923; for recent microwave-assisted Synthesis see: b) J. Gising, P. Örtqvist, A. Sandström, M. Larhed, *Org. Biomol. Chem.* **2009**, *7*, 2809–2815.
[13] I. Kim, S. G. Kim, J. Y. Kim, G. H. Lee, *Tetrahedron Lett.* **2007**, *48*, 8976–8981.
[14] The geometry of the double bond was confirmed by 2D NMR spectroscopy (NOESY). For more details, see Supporting Information.
[15] a) V. P. Mehta, A. Sharma, K. Van Hecke, L. Van Meervelt, E. Van der Eycken, *J. Org. Chem.* **2008**, *73*, 2382–2388; b) R. Azzam, W. De Borggraeve, F. Compernolle, G. Hoornaert, *Tetrahedron Lett.* **2004**, *45*, 1885–1888.

Received: August 22, 2012
Published Online: December 11, 2012

