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Aminocarbonylation of 4-Iodo-1*H*-imidazoles with an Amino Acid Amide Nucleophile: Synthesis of Constrained H-Phe-Phe-NH_2 Analogues

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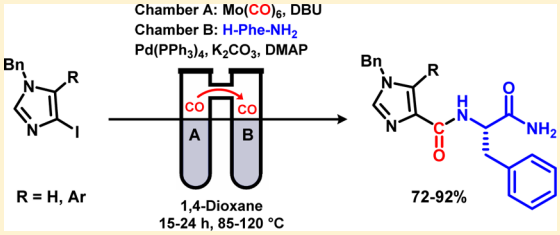
Supporting Information

ABSTRACT: A simple and an expedient process to prepare 5-aryl-1-benzyl-1*H*-imidazole-4-carboxamides by the aminocarbonylation of 5-aryl-4-iodo-1*H*-imidazoles using *ex situ* generation of CO from $Mo(CO)_6$ with an amino acid amide nucleophile is reported. Furthermore, a microwave-assisted protocol for the direct C-5 arylation of 1-benzyl-1*H*-imidazole and a regioselective C-4 iodination method to acquire starting material for our aminocarbonylation are presented. The method can be used to prepare imidazole based peptidomimetics, herein exemplified by the synthesis of constrained H-Phe-Phe-NH_2 analogues.



Heterocyclic compounds have important applications in medicinal chemistry. For example, incorporation of heterocycles into peptide backbones is a common approach in the construction of peptidomimetics in drug discovery.[1−6] Functionalized imidazoles are an important class of heterocycles which are frequently used as the core structure of biologically active agents.[7−10] Commonly, substituted imidazoles are obtained via cyclization reactions resulting in 1,5-, 1,2-, or 4,5-disubstitution patterns directly,[11] or by lithiation of N1-protected imidazoles to give 2- or 2,5-substituted products.[12,13] Few examples are presented in literature in which imidazoles are directly functionalized.[14−16]

In an ongoing medicinal chemistry program aimed at developing constrained H-Phe-Phe-NH_2 mimetics acting as the neuropeptide substance P 1−7 (SP_{1-7}),[17,18] we have explored a simple and fast route to functionalized imidazoles. More precisely, it was planned to introduce an amino acid side chain in the C-5 position and thereafter connect a peptide equivalent, an amino acid amide, in the C-4 position through a carboxamide coupling (forming a peptide bond), as outlined in Figure 1.

The palladium-catalyzed aminocarbonylation between (hetero)aryl halides, carbon monoxide, and amines is a well established synthetic method for the preparation of arylamides.[19,20] The processes of sequential palladium-catalyzed oxidative aminocarbonylation−heterocyclization of alkyne precursors are also worth mentioning in this context.[21−24] The need for facile and high-throughput methods which are suitable for small scale laboratory applications and parallel synthesis have led to the development of solid substitutes for the highly toxic and flammable CO gas, such as $Mo(CO)_6$.[25] The *in situ* CO-releasing ability of $Mo(CO)_6$ has been well explored in our laboratory and demonstrated in a wide range of one-pot carbonylation reactions using a range of different nucleophiles.[26−28] Recently, Skydstrup and co-workers developed a two-chamber system[29−32] utilizing *ex situ* generation of CO, and several aminocarbonylation reactions have been published based on this method.[33,34] Surprisingly, aminocarbonylation reactions with halogenated imidazoles are relatively unexplored. To our knowledge, only a couple of reactions using unsubstituted N1-protected imidazoles as starting material have been reported.[35,36]

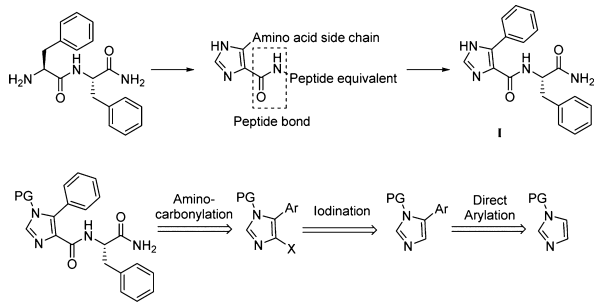


Figure 1. Design of a constrained H-Phe-Phe-NH_2 analogue incorporating an N-terminal imidazole moiety along with a retrosynthetic analysis.

Herein, a versatile and high yielding strategy to prepare 5-aryl-1-benzyl-1*H*-imidazole-4-carboxamides by aminocarbonylation of 5-aryl-1-benzyl-4-iodo-1*H*-imidazole using *ex situ* generation of CO from $Mo(CO)_6$ with an amino acid derived nucleophile is reported. Furthermore, a fast microwave-assisted protocol for direct C-5 arylation of 1-benzyl-1*H*-imidazoles and a regioselective C-4 iodination to generate the starting material for our aminocarbonylation are presented.

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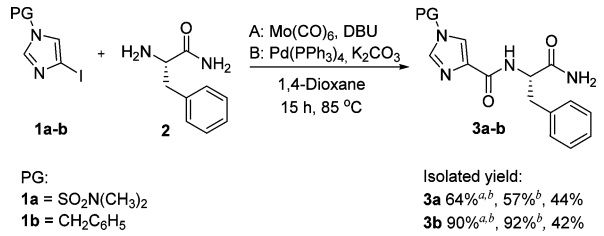
We first sought to explore the preparation of analogues to compound **I** lacking an aryl substituent in the C-5 position utilizing N1-protected 4-iodo-1*H*-imidazoles (**1a**−**b**) as model substrates (Scheme 1). The conditions previously reported by

Scheme 1. Aminocarbonylation of N1-Protected 4-Iodo-1*H*-imidazoles (1a−b) Using *ex Situ* Generation of CO



[a]100 °C. [b] DMAP (0.8 mmol, 2 equiv) was added to chamber B before capping. Reaction conditions: Chamber A: $Mo(CO)_6$ (0.2 mmol, 0.5 equiv), DBU (0.6 mmol, 1.5 equiv) in 1,4-dioxane (3 mL). Chamber B: N1-protected 4-iodo-1*H*-imidazoles **1a**−**b** (0.4 mmol, 1.0 equiv), H-Phe-NH_2·HCl **2** (0.8 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (5 mol %, 0.05 equiv) and K_2CO_3 (0.8 mmol, 2.0 equiv) in 1,4-dioxane (3 mL).

Nordeman et al.[33] were used as a starting point for our investigation. Thus, the CO-releasing vessel (chamber A in the two-chamber system) was charged with $Mo(CO)_6$ (0.5 equiv) and the CO-accepting chamber (chamber B, the reaction vessel) with 1 equiv of *N*,*N*-dimethyl-4-iodo-1*H*-imidazole-1-sulfonamide (**1a**), 2 equiv of phenylalanine amide (**2**) as the nucleophile, and tetrakis(triphenylphosphine)palladium(0) as the palladium catalyst. Encouraged by the work presented by Odell et al. DMAP was also added to chamber B as an acylation catalyst.[37] Subsequently, the system was sealed and flushed with nitrogen and 1,4-dioxane was added to both chambers followed by the addition of DBU to chamber A and Et_3N to chamber B. The two-chamber system was placed into a heating block, and the reaction was stirred at 85 °C for 15 h. Initial investigations identified urea formation originating from two amino acid amide nucleophiles as the major product.[38,39] To minimize the byproduct formation, the base in chamber B was exchanged from Et_3N to K_2CO_3 and compound **3a** was isolated in a 57% yield. In an attempt to reach full conversion, the reaction temperature was increased to 100 °C and full consumption was observed; however, only a slightly higher isolated yield was obtained (64%). Unfortunately, the increased temperature led to the formation of the competing bis-imidazole homocoupling byproduct.[40,41] Since we suspected that the sulfonamide protecting group could enhance dimerization of the imidazole substrate, the N1-protecting group was changed to a benzyl group (**1b**). Repeating the same conditions for 15 h at 85 °C resulted in full conversion of starting material, and an excellent yield of 92% of compound **3b** was isolated. Surprisingly, the homocoupling byproduct formation was not observed in this case and a similar isolated yield was obtained when the temperature was increased to 100 °C (90%). The combination of high temperature, basic reaction conditions, and a chiral nucleophile made us concerned about possible racemization. To investigate this, the products were analyzed using chiral HPLC, showing chromatograms with single and symmetrical peaks. Additionally, the corresponding D-analogue of compound **3b** was synthesized according to above-described method. Specific optical rotation measurements of the two products (L- and D-isomers) revealed equivalent values although of opposite sign ($[\alpha]_D^{20}$ − 46 and +46). Taken together, no racemization of the asymmetric center seems to occur under the reaction conditions used. For the synthesis of **3a** and **3b**, DMAP turned out to be crucial for the reaction, since its removal resulted in a drastic decrease in isolated yield (44% and 42%, respectively).

Having demonstrated the successful aminocarbonylation of **1b** with **2** as the nucleophile, our next step was to access N1-protected 5-aryl-1*H*-imidazoles according to the retrosynthetic analysis in Figure 1. Previously, Bellina et al. published a direct C−H activation method for the selective palladium-catalyzed C-5 arylation of 1-benzyl-1*H*-imidazoles.[15] In that study 5-aryl-1-benzyl-1*H*-imidazoles were synthesized, in 43−73% yield with a variety of aryl bromides using $Pd(OAc)_2$ and $P(2\text{-furyl})_3$ as the catalytic system and conventional heating for 27−88 h. Based on these reaction conditions, we were interested in exploring a microwave-assisted protocol for C-5 arylation in order to reduce the reaction times.[42] Initial experiments, using a sealed reaction vessel with microwave heating and 4-bromotoluene as an arylating agent identified the presence of the 2,5-diarylated byproduct. In order to find optimized reaction conditions to maximize product formation and minimize byproduct formation, an experimental design was used to explore variation in temperature, time, Pd-catalyst loading, and amount of aryl bromide (see Supporting Information). To study the outcome of the different experiments the ratios of product, 2,5-diarylated byproduct, and remaining starting material were examined by ^1H NMR analysis of the crude reaction mixture. Subsequent isolation, using column chromatography, led to the conclusion that the highest isolated yield of **4b** (63%, Table 1, entry 2) could be achieved by running the reaction for 1 h at 160 °C with a low catalyst loading (2 mol %) and 5 equiv of the arylbromide. Furthermore, the addition of 30 mol % pivalic acid was observed to enhance the yield.[43] Using this protocol on electron-deficient and -rich aryl bromides resulted in isolated yields of up to 65% for compounds **4a**−**f** (Table 1). The steric hindrance from *ortho* methyl substituents had a negative impact on the reaction as shown in entries 3 and 4. Compound **3c**, containing one *ortho* substituent, was isolated in 46% yield; however heating to 170 °C improved the yield to 61%. As can be seen from entry 4, the presence of two *ortho* substituents inhibited the arylation reaction (**4d**, 0% yield). Since the isolated yields are in agreement with the previously reported method,[15] the optimized conditions developed for this selective C-5 arylation of 1-benzyl-1*H*-imidazoles indicate that the reaction time can be reduced from 27−88 to 1 h without negatively affecting the yields.

Introduction of iodine in the C-4 position of compounds **4a**−**c** and **4e**−**f** was performed by using a reported method developed for the iodination of electron-rich carbocycles consisting of a combination of NIS with catalytic TFA in MeCN.[44] Extending the scope of the method provided a regioselective iodination, and compounds **5a**−**c** and **5e**−**f** were isolated in good yields (73−84%). Notably, the preparation of **5a**−**c** and **5e**−**f** was greatly influenced by the electronic and steric effects of the C-5 aryl substituent. In a typical reaction the 5-aryl-1-benzyl-1*H*-imidazoles (**4a**−**c**, **4e**−**f**), NIS, TFA, and MeCN were heated at 80 °C for 1 h to reach full conversion. Substrates containing *ortho*-substituent (**4c**) or electron-poor (**4e**) C-5 phenyl groups required 2 or 4 h of heating at 80 °C, respectively. Compound **4f**, carrying an electron-donating 4-methoxy functionality, reached full conversion of the starting material after stirring at 80 °C for only 0.5 h (Scheme 2).

Having demonstrated the C-4 aminocarbonylation of **1b** with an amino acid amide in 92% yield (Scheme 1), we next tried this

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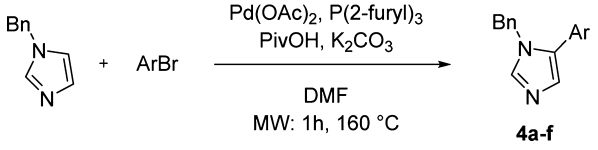
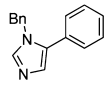
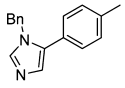
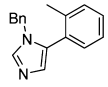
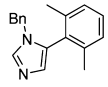
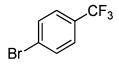
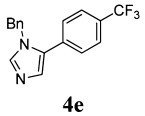
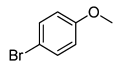
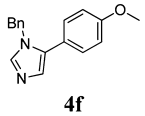
Table 1. Palladium Catalyzed C-5 Arylation of 1-Benzyl-1*H*-imidazole with Aryl Bromides

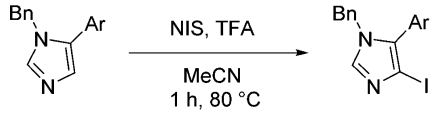


entry	ArBr	Product	Conversion (%) [a]	Yield (%) [b]
1		 **4a**	88	60
2		 **4b**	84	63
3		 **4c**	51 90 [c]	46 61 [c]
4		 **4d**	0	0
5		 **4e**	91	65
6		 **4f**	87	64

[a]Determined by ^{1}H NMR analysis of the crude. [b]Isolated yield. [c]170 °C. Reaction conditions: The reaction was performed under microwave irridation in a sealed vial: 1-Benzyl-1*H*-imidazole (1 mmol, 1.0 equiv), ArBr (5 mmol, 5 eqiuv), $Pd(OAc)_2$ (0.02 mol, 0.02 equiv), $P(2\text{-furyl})_3$ (0.04 mol, 0.04 equiv), PivOH (0.3 mol, 0.3 equiv), and K_2CO_3 (3 mmol, 3 equiv) in 4.0 mL of DMF.

strategy for the C-5 aryl containing compounds (**5a–c**, **5e–f**). We realized that steric congestion of the aryl substituent could negatively affect the yield and, unfortunately, using the same reaction conditions elaborated in Scheme 1 led to incomplete conversion of the substrate and a low isolated yield of compound **6a** (45%, Scheme 3). However, prolonging the reaction time and increasing the temperature resulted in high isolated yields of the desired products **6a–c** and **6e–f** (72–85%). Traces of dehalogenated starting material due to the high reaction temperature were observed, which lowered the yield compared to compound **3b** (Scheme 1). The aminocarbonylation of compound **5c**, having an *ortho* methyl substituent, required a prolonged reaction time of 48 h for full consumption, and the product was isolated as a 1:1 mixture of two atrop-diastereomers according to ^{1}H NMR. Notably, the changes in reaction

Scheme 2. Iodination of 5-Aryl-1-benzyl-1*H*-imidazoles (4a–c, 4e–f) with NIS and TFA



4a-c, 4e-f

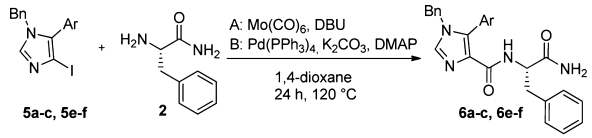
Ar:
4a = C_6H_5
4b = 4-MeC_6H_4
4c = 2-MeC_6H_4
4e = 4-$CF_3C_6H_4$
4f = 4-$OMeC_6H_4$

5a-c, 5e-f

Isolated yield:
5a 79%
5b 79%
5c 73%[a]
5e 81%[b]
5f 84%[c]

[a]2 h. [b] 4 h. [c] 0.5 h. Reaction conditions: 5-aryl-1-benzyl-1*H*-imidazoles **4a–c**, **4e–f** (0.5–1.15 mmol), NIS (1.1 equiv), TFA (0.3 equiv) in MeCN (4–8 mL).

Scheme 3. Aminocarbonylation of the 5-Aryl-1-benzyl-4-iodo-1*H*-imidazoles (5a-c, 5e-f) Using *ex Situ* Generation of CO[a]



Ar:
5a = C_6H_5
5b = 4-MeC_6H_4
5c = 2-MeC_6H_4
5e = 4-$CF_3C_6H_4$
5f = 4-$OMeC_6H_4$

Isolated yield:
6a 72%, 45%[b], 56%[c]
6b 80%
6c 85%[d]
6e 75%
6f 83%

[a]Maximum expected CO pressure in the system is 2.3 bar (see Supporting Information). [b] 15 h at 100 °C. [c] 15 h at 120 °C. [d] 48 h at 120 °C. Reaction conditions: Chamber A: $Mo(CO)_6$ (0.5 equiv), DBU (1.5 equiv) in 1,4-dioxane (3 mL). Chamber B: 5-aryl-1-benzyl-4-iodo-1*H*-imidazoles **5a–c**, **5e–f** (0.38–0.46 mmol), H-Phe-NH_2·HCl **2** (2.0 equiv), $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (2.0 equiv), and DMAP (2.0 equiv) in 1,4-dioxane (3 mL).

conditions did not seem to cause racemization of the product according to chiral HPLC analysis and specific optical rotation of the corresponding D-form, that was prepared for comparison ($[\alpha]_D^{21}$ −42 and +42, for the L- and D-isomer of **6f**, respectively). This observation was in agreement with a previously reported, similar aminocarbonylation of heterocycles at high temperature using phenylalanine ethyl ester as a nucleophile.[36]

The final removal of the N1-protecting group was demonstrated on compounds **3b** and **6a** (Scheme 4). N-Debenzylation using Pd/C and H_2 (1 atm) was unsuccessful. However, full conversion was observed after 6 h at 60 °C with H_2 (10 bar).

In conclusion, we have developed an efficient protocol for the preparation of imidazole containing phenylalanine based peptidomimetics in high and reproducible yields. First, a fast microwave-assisted palladium-catalyzed protocol for the direct C-5 arylation of 1-benzyl-1*H*-imidazole was developed. Microwave heating was able to reduce the reaction time from 24–88 h to 1 h without compromising the yields. Second, after successful introduction of iodine in the C-4 position, aminocarbonylation was performed to yield constrained H-Phe-Phe-NH_2 analogues. This was achieved utilizing $Mo(CO)_6$ as the *ex situ* generating solid CO-source and phenylalanine amide (**2**) as the nucleophile. Aminocarbonylation of 1-benzyl-4-iodine-1*H*-imidazole **1b** lacking an aryl in the C-5 position resulted in an excellent

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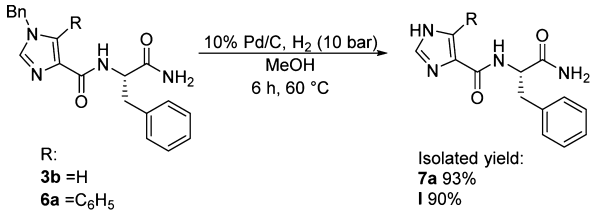
Scheme 4. Palladium Catalyzed N-Debenzylation of Compounds 3b and 6a[a]



[a]Reaction conditions: The reaction was performed in an autoclave: Substrate **3b**/**6a** (0.5 mmol) and 10% Pd/C in MeOH (4 mL).

isolated yield of 92%. Also, aminocarbonylations on the sterically congested C-5 aryl imidazoles (**5a−c**, **5e−f**) were successful and resulted in high isolated yields (72−85%) despite the competing dehalogenation due to the elevated temperature. These are the first reported examples of aminocarbonylation of an iodinated imidazole scaffold using $Mo(CO)_6$ as the *ex situ* generating CO-source with an amino acid amide as the nucleophile, thus providing a method to incorporate imidazole based phenylalanine mimetics into the N-terminal of a peptide chain.

EXPERIMENTAL SECTION

General Information. For technical specifications of the glassware (the two-chamber system) used for the aminocarbonylation, see earlier publications.[33,34] All the C-5 arylation reactions were performed in sealed microwave-transparent process vials designed for 2−5 mL reaction volumes. The microwave heating was performed in an Initiator single mode reactor (or a Smith single mode reactor for the experimental design), producing controlled irradiation at 2450 MHz. The reaction temperature was determined using the built-in online IR-sensor. $Pd(OAc)_2$ was purchased from STREM, and $Pd(PPh_3)_4$, from Sigma-Aldrich. *N*,*N*-Dimethyl-4-iodo-1*H*-imidazole-1-sulfonamide (**1a**), H-Phe-NH_2·HCl (**2**), and H-D-Phe-NH_2 are commercially available and were used without further purification. Analytical thin-layer chromatography was performed on silica gel 60 F-254 plates and visualized with UV light. Flash column chromatography was performed on a silica gel 60 (40−63 μm). ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz, respectively, using CD_3OD, DMSO-d_6, or $CDCl_3$ as a solvent. Chemical shifts for ^1H and ^{13}C are referenced via the residual solvent signal. The HRMS experiment was performed on a 7-T hybrid ion trap (LTQ) FT mass spectrometer modified with a nanospray ion source. Reprosil Chiral NR and NR-R columns (Dr. Maisch GmbH HPLC; 8 μm; 250 mm × 4.6 mm; eluted at 1.5 mL/min; UV 254 nm) were used for ee determination of compounds **3a−b**, **6a−c**, and **6e−f** with iso-hexane/2-propanol.

Caution! Pressurized reactions should not be conducted in a sealed two-chamber system without an appropriate pressure release device. The aminocarbonylation reactions described in this paper should not be repeated in a larger scale, as this could result in an explosion.

1-Benzyl-4-iodo-1*H*-imidazole (1b). Prepared as described by He et al.[45] White solid (218−356 mg, 62−85%); ^1H NMR (400 MHz, CD_3OD) δ 7.67−7.63 (m, 1H), 7.37−7.20 (m, 5H), 7.19−7.15 (m, 1H), 5.15 (s, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 140.7, 137.5, 130.0, 129.4, 128.7, 126.7, 81.2, 51.9. HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{10}H_9IN_2$ 284.9889; found 284.9890.

General Procedure for the Aminocarbonylation of the N1-Protected 4-Iodo-1*H*-imidazoles (1a−b). Chamber A was loaded with $Mo(CO)_6$ (0.2 mmol, 0.5 equiv). Chamber B was loaded with N1-protected 4-iodo-1*H*-imidazole (**1a−b**) (0.4 mmol, 1.0 equiv), H-Phe-NH_2·HCL (**2**) (0.8 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (5 mol %, 0.05 equiv), K_2CO_3 (0.8 mmol, 2.0 equiv), and DMAP (0.8 mmol, 2.0 equiv). The two chambers were capped with a gastight cap, evacuated, and backfilled with nitrogen gas. Thereafter, 1,4-dioxane (3 + 3 mL) was added to both chambers by a syringe under a flow of nitrogen. Next, DBU (0.6 mmol, 1.5 equiv) was added to chamber A by syringe and the two-chamber system was heated in a heating block at 85/100 °C for 15 h under vigorous stirring. The reaction tube was thereafter cooled to rt, excess CO was evacuated carefully, and the crude mixture from chamber B was filtered and evaporated to dryness. The crude reaction product was further purified by flash column chromatography on silica gel with DCM/MeOH/NH_4OH (98:2:0.05) as the eluent. This procedure was employed to prepare compounds **3a−b** (Scheme 1).

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-imidazole-4-carboxamide (3a). Obtained from **1a** (0.4 mmol) as a white solid (94 mg, 64% yield); ^1H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J* = 1.4 Hz, 1H), 7.93 (d, *J* = 1.4 Hz, 1H), 7.29−7.16 (m, 5H), 4.82−4.80 (m, 1H), 3.26−3.20 (m, 1H), 3.10−3.03 (m, 1H), 2.88 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 161.4, 137.6, 136.7, 136.3, 129.4, 128.8, 127.1, 120.2, 54.0, 38.3, 38.1. $[\alpha]_D^{21}$ −30 (*c* 0.5, $CHCl_3$). HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{15}H_{19}N_5O_4S$ 366.1236; found 366.1235.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-1*H*-imidazole-4-carboxamide (3b). Obtained from **1b** (0.4 mmol) as an off-white solid (128 mg, 92% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 1H), 7.50 (d, *J* = 1.4 Hz, 1H), 7.40 (d, *J* = 1.4 Hz, 1H), 7.38−7.13 (m, 10H), 6.37 (s, 1H), 5.75 (s, 1H), 5.07 (s, 2H), 4.86−4.80 (m, 1H), 3.23−3.09 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 162.7, 137.1, 137.0, 136.8, 135.1, 129.5, 129.3, 128.8, 128.7, 127.7, 126.9, 122.7, 53.9, 51.5, 37.8. $[\alpha]_D^{20}$ −46 (*c* 1.0, $CHCl_3$). HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{20}H_{20}N_4O_2$ 349.1665; found 349.1663.

Preparation of the Corresponding D*-Isomer.* (*R*)-*N*-(1-amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-1*H*-imidazole-4-carboxamide. Obtained from **1b** and H-D-Phe-NH_2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 1.4 Hz, 1H), 7.38 (d, *J* = 1.4 Hz, 1H), 7.34−7.10 (m, 10H), 6.58 (s, 1H), 6.08 (s, 1H), 5.03 (s, 2H), 4.90−4.79 (m, 1H), 3.23−3.05 (m, 2H). $[\alpha]_D^{20}$ +46 (*c* 1.0, $CHCl_3$).

General Procedure for Palladium Catalyzed C-5 Arylation of 1-Benzyl-1*H*-imidazole with Aryl Bromides. A 5 mL process vial was charged with 1-benzyl-1*H*-imidazole (158.0 mg, 1.0 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.48 mg, 0.02 mmol, 0.02 equiv), P(2-furyl)$_3$ (9.28 mg, 0.04 mmol, 0.04 equiv), PivOH (30.6 mg, 0.3 mmol, 0.3 equiv), and K_2CO_3 (414.0 mg, 3 mmol, 3 equiv). The vial was capped with a gastight cap, evacuated, and backfilled with nitrogen gas. Thereafter, DMF (4.0 mL) and aryl bromide (5 mmol, 5 equiv) were added by a syringe under a flow of nitrogen. The resulting mixture was exposed to microwave heating at 160 °C for 1 h (compound **4c** heated at 170 °C for 1 h). The reaction tube was thereafter cooled to rt, and the crude mixture was filtered and evaporated to dryness. The crude reaction product was further purified by flash column chromatography on silica gel with iso-hexane/acetone (50:50) as the eluent. This procedure was employed to prepare compounds **4a−f** (Table 1).

1-Benzyl-5-phenyl-1*H*-imidazole (4a).[15]. White solid (144 mg, 61%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.40−7.25 (m, 8H), 7.15 (s, 1H), 7.04−6.99 (m, 2H), 5.15 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.8, 136.9, 133.6, 129.9, 129.0 (2 overlapping signals), 128.8, 128.4, 128.2, 128.0, 126.8, 48.8. HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{16}H_{14}N_2$ 235.1235; found 235.1230.

1-Benzyl-5-(*p*-tolyl)-1*H*-imidazole (4b).[15]. Yellow solid (155 mg, 63%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.33−7.14 (m, 7H), 7.11 (s, 1H), 7.04−6.99 (m, 2H), 5.13 (s, 2H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 138.0, 137.0, 133.6, 129.4, 128.9, 128.9, 128.1, 127.9, 126.8, 126.7, 48.7, 21.3. HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{17}H_{16}N_2$ 249.1392; found 249.1395.

1-Benzyl-5-(*o*-tolyl)-1*H*-imidazole (4c). Colorless oil (151 mg, 61%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34−7.12 (m, 7H), 7.03 (s, 1H), 6.94−6.89 (m, 2H), 4.91 (s, 2H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 137.6, 136.4, 131.7, 131.3, 130.2, 129.2, 129,0, 128.7, 128.5, 127.9, 127.3, 125.7, 48.8, 19.9. HRMS (ES) *m*/*z* calcd for $[M+H^+]$: $C_{17}H_{16}N_2$ 249.1392; found 249.1391.

1-Benzyl-5-(4-(trifluoromethyl)phenyl-1*H*-imidazole (4e).[15] White solid (195 mg, 65%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.60 (m, 2H), 7.59 (s, 1H), 7.41−7.37 (m, 2H), 7.34−7.27 (m, 3H), 7.21 (s, 1H), 7.03−6.98 (m, 2H), 5.17 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.3, 133.4, 132.1, 129.9 (q, J_{CF_3} = 32.6 Hz), 129.4, 129.0, 128.8, 128.1, 126.5, 125.6 (q, J_{CF_3} = 3.8 Hz), 124.0 (q, J_{CF_3} = 272.1

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Hz), 48.9. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{13}F_3N_2$ 303.1109; found 303.1111.

1-Benzyl-5-(4-methoxyphenyl)-1*H*-imidazole (4f).[15] White solid (169 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.38−7.23 (m, 3H), 7.22−7.13 (m, 2H), 7.08 (s, 1H), 7.04−6.98 (m, 1H), 6.92−6.86 (m, 2H), 5.11 (s, 2H), 3.81 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 138.4, 137.1, 133.4, 130.5, 129.0, 128.0, 128.0, 126.8, 122.2, 114.2, 55.4, 48.7. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{16}N_2O$ 265.1341; found 265.1338.

General Procedure for Iodination of 5-Aryl-1-benzyl-1*H*-imidazoles (4a−c, 4e−f) with NIS and TFA. 5-Aryl-1-benzyl-1*H*-imidazole (**4a−c**, **4e−f**) (0.5−1.15 mmol) was dissolved in MeCN (4−8 mL). Thereafter, NIS (1.1 equiv) and TFA (0.3 equiv) were added and the reaction mixture was stirred at 80 °C for 0.5−4 h. After the specified time, the solvent was evaporated to dryness. The crude product was dissolved in DCM, washed with saturated thiosulphate and brine, and dried over Na_2SO_4. The crude product was further purified by flash column chromatography on silica gel with iso-hexane/acetone (50:50) as the eluent. This procedure was employed to prepare compounds **5a−c** and **5e−f** (Scheme 2).

1-Benzyl-4-iodo-5-phenyl-1*H*-imidazole (5a). Obtained from **4a** (0.61 mmol) as a yellow oil (174 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.40−7.36 (m, 3H), 7.28−7.21 (m, 5H), 6.96−6.91 (m, 2H), 5.01 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 136.0, 135.4, 130.6, 129.1, 129.0, 128.8, 128.3, 127.1, 84.6, 50.0. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{16}H_{14}IN_2$ 361.0202; found 361.0195.

1-Benzyl-4-iodo-5-(*p*-tolyl)-1*H*-imidazole (5b). Obtained from **4b** (0.5 mmol) as a yellow oil (147 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.30−7.27 (m, 2H), 7.23−7.19 (m, 2H), 7.17−7.12 (m, 2H), 6.99−6.95 (m, 2H), 5.02 (s, 2H), 2.38 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 139.2, 139.0, 136.1, 135.4, 130.5, 129.5, 129.0, 128.2, 127.0, 125.9, 84.5, 49.9, 21.5. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{15}IN_2$ 375.0358; found 375.0363.

1-Benzyl-4-iodo-5-(*o*-tolyl)-1*H*-imidazole (5c). Obtained from **4c** (0.874 mmol) as a colorless oil (239 mg, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.36−7.17 (m, 6H), 7.07−7.03 (m, 1H), 6.88−6.83 (m, 2H), 4.86 (d, J = 15.1 Hz, 1H), 4.81 (d, J = 15.3 Hz, 1H), 1.92 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 138.7, 135.4, 135.1, 131.4, 130.3, 129.7, 128.7, 128.3, 128.2, 127.6, 125.9, 85.2, 50.1, 19.6. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{15}IN_2$ 375.0358; found 375.0355.

1-Benzyl-4-iodo-5-(4-trifluoromethyl)phenyl-1*H*-imidazole (5e). Obtained from **4e** (1.15 mmol) as a yellow oil (398 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.61 (m, 2H), 7.58 (s, 1H), 7.38−7.33 (m, 2H), 7.29−7.24 (m, 3H), 6.94−6.89 (m, 2H), 5.03 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 135.6, 134.0, 132.8, 131.0 (q, J_{CF_3} = 32.6 Hz), 131.0, 129.2, 128.5, 127.0, 125.7 (q, J_{CF_3} = 3.7 Hz), 124.0 (q, J_{CF_3} = 272.4 Hz), 85.4, 50.2. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{12}F_3IN_2$ 429.0076; found 429.0084.

1-Benzyl-4-iodo-5-(4-methoxyphenyl)-1*H*-imidazole (5f). Obtained from **4f** (0.51 mmol) as a yellow oil (168 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.30−7.27 (m, 3H), 7.19−7.14 (m, 2H), 6.99−6.95 (m, 2H), 6.94−6.90 (m, 2H), 5.02 (s, 2H), 3.84 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 139.2, 136.1, 135.3, 132.0, 129.0, 128.2, 127.1, 121.0, 114.2, 84.7, 55.4, 49.9. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{17}H_{15}IN_2O$ 391.0307; found 391.0310.

General Procedure for Aminocarbonylation of the 5-Aryl-1-benzyl-4-iodo-1*H*-imidazoles (5a−c, 5e−f). Chamber A was loaded with $Mo(CO)_6$ (0.5 equiv). Chamber B was loaded with H-Phe-NH_2·HCl (**2**) (2 equiv), $Pd(PPh_3)_4$ (0.05 equiv), K_2CO_3 (2.0 equiv), and DMAP (2.0 equiv). The two chambers were capped with a gastight cap, evacuated, and backfilled with nitrogen gas. Thereafter, the 5-aryl-1-benzyl-4-iodo-1*H*-imidazole (**5a−c**, **5e−f**) (0.38−0.46 mmol, 1.0 equiv), dissolved in 1,4-dioxane (3 mL), was added by a syringe to chamber B under a stream of nitrogen. Next, 1,4-dioxane (3 mL) and DBU (1.5 equiv) were added to chamber A. The two-chamber system was heated in a heating block at 120 °C for 24 h (compound **5c** heated at 120 °C for 48 h) under vigorous stirring. The reaction tube was thereafter cooled to rt, excess CO was evacuated carefully, and the crude mixture from chamber B was filtered and evaporated to dryness. The crude reaction product was further purified by flash column chromatography on silica gel with DCM/MeOH/NH_4OH (98:2:0.05) as the eluent. This procedure was employed to prepare compounds **6a−c** and **6e−f** (Scheme 3).

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-phenyl-1*H*-imidazole-4-carboxamide (6a). Obtained from **5a** (0.455 mmol) as a yellow solid (140 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 1H), 7.47 (s, 1H), 7.41−7.14 (m, 13H), 6.97−6.89 (m, 2H), 6.35 (s, 1H), 5.17 (s, 1H), 4.93 (s, 2H), 4.91−4.80 (m, 1H), 3.18−3.02 (m, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 162.6, 137.1, 136.6, 135.9, 135.8, 132.0, 130.6, 129.5, 129.1, 129.0, 128.7, 128.5, 128.3, 128.3, 127.1, 126.7, 53.5, 48.9, 38.4. $[\alpha]_D^{20}$ −48 (c 0.65, $CHCl_3$). HRMS (ES) m/z calcd for $[M+H^+]$: $C_{26}H_{24}N_4O_2$ 425.1978; found 425.1974.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-(*p*-tolyl)-1*H*-imidazole-4-carboxamide (6b). Obtained from **5b** (0.377 mmol) as a yellow solid (132 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.38−7.11 (m, 12H), 7.02−6.95 (m, 2H), 6.46 (s, 1H), 5.49 (s, 1H), 4.97 (s, 2H), 4.94−4.85 (m, 1H), 3.20−3.08 (m, 2H), 2.40 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 162.6, 139.0, 137.1, 136.4, 136.0, 135.9, 131.7, 130.4, 129.5, 129.0, 128.9, 128.5, 128.2, 127.0 (2C), 126.7, 125.5, 53.4, 48.7, 38.2, 21.4. $[\alpha]_D^{21}$ −112 (c 0.3, $CHCl_3$). HRMS (ES) m/z calcd for $[M+H^+]$: $C_{27}H_{26}N_4O_2$ 439.2134; found 439.2130.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-(*o*-tolyl)-1*H*-imidazole-4-carboxamide (6c). Obtained from **5c** (0.450 mmol) as a yellow solid (168 mg, 85%) and isolated as a 1:1 mixture of two atrop-diastereomers; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91−7.88 (m, 2H), 7.65 (t, J = 7.9 Hz, 2H), 7.33−7.01 (m, 28H), 6.87−6.82 (m, 4H), 4.95−4.86 (m, 4H), 4.62−4.53 (m, 2H), 3.12−3.03 (m, 3H), 3.00−2.93 (m, 2H), 1.78 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.71, 172.68, 161.3, 161.1, 138.38, 138.37, 137.51, 137.48, 137.3, 137.2, 136.4, 136.3, 135.0, 133.1, 133.0, 132.3, 130.2, 130.1, 129.8, 129.6, 129.2, 128.92, 128.90, 128.73, 128.69, 128.4, 128.2, 128.05, 127.96, 127.6, 127.2, 126.3, 126.2, 125.24, 125.19, 52.9, 52.6, 48.01, 47.96, 38.1, 33.0, 19.2, 19.1. HRMS (ES) m/z calcd for $[M+H^+]$: $C_{27}H_{26}N_4O_2$ 439.2134; found 439.2137.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-(4-(trifluoromethyl)phenyl)-1*H*-imidazole-4-carboxamide (6e). Obtained from **5e** (0.396 mmol) as a yellow solid (146 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 1H), 7.64−7.58 (m, 2H), 7.52 (s, 1H), 7.41−7.34 (m, 2H), 7.32−7.16 (m, 8H), 6.95−6.88 (m, 2H), 6.00 (s, 1H), 5.46 (s, 1H), 4.96 (s, 2H), 4.80−4.70 (m, 1H), 3.14 (d, J = 7.1 Hz, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 162.5, 137.2, 136.9, 135.5, 134.3, 132.6, 132.4, 131.1 (q, J_{CF_3} = 32.2 Hz), 131.1, 129.5, 129.2, 128.7, 128.5, 127.0, 126.9, 125.3 (q, J_{CF_3} = 3.7 Hz, 2C), 123.17 (q, J_{CF_3} = 272.4 Hz), 53.7, 49.1, 38.1. $[\alpha]_D^{21}$ −32 (c 0.5, $CHCl_3$). HRMS (ES) m/z calcd for $[M+H^+]$: $C_{27}H_{23}F_3N_4O_2$ 493.1851; found 493.1856.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-(4-methoxyphenyl)-1*H*-imidazole-4-carboxamide (6f). Obtained from **5f** (0.431 mmol) as a yellow solid (162 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.32−7.23 (m, 8H), 7.20−7.16 (m, 2H), 6.97−6.93 (m, 2H), 6.92−6.87 (m, 2H), 6.17 (s, 1H), 5.28 (s, 1H), 4.95 (s, 2H), 4.84−4.75 (m, 1H), 3.81 (s, 3H), 3.21−3.09 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 162.9, 160.3, 137.1, 136.4, 136.0, 135.9, 131.9, 131.7, 129.6, 129.1, 128.7, 128.3, 127.1, 126.9, 120.5, 113.9, 55.4, 53.6, 48.8, 37.9. $[\alpha]_D^{21}$ −42 (c 0.3, $CHCl_3$). HRMS (ES) m/z calcd for $[M+H^+]$: $C_{27}H_{26}N_4O_3$ 455.2083; found 455.2080.

Preparation of the Corresponding D*-Isomer.* (*R*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1-benzyl-5-(4-methoxyphenyl)-1*H*-imidazole-4-carboxamide. Obtained from **5f** and H-D-Phe-NH_2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.32−7.09 (m, 12H), 6.97 −6.92 (m, 2H), 6.41 (s, 1H), 5.45 (s, 1H), 4.92 (s, 2H), 4.90- 4.81 (m, 1H), 3.17−3.00 (m, 2H), 2.35 (s, 3H). $[\alpha]_D^{21}$ +42 (c 0.3, $CHCl_3$).

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General Procedure for the Pd-Catalyzed N-Debenzylation of Compounds 3b and 6a. 10% Pd/C was added to a solution of the substrate (**3b**/**6a**) (0.5 mmol, 1.0 equiv) in MeOH (4 mL). The resulting mixture was stirred at 60 °C for 6 h in an autoclave under a H_2 atmosphere (10 bar), filtered, and concentrated under reduced pressure. The product was isolated with analytical purity. This procedure was employed to prepare compounds **7a** and **I** (Scheme 4).

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-1*H*-imidazole-4-carboxamide (7a). Obtained from **3b** (0.5 mmol) as a white solid (120 mg, 93%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 1.2 Hz, 1H), 7.29−7.21 (m, 4H), 7.20−7.14 (m, 1H), 4.82−4.77 (m, 1H), 3.25−3.18 (m, 1H), 3.08−3.01 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.5, 157.8, 138.8, 136.5, 130.2, 129.3, 128.0, 127.6, 121.7, 56.1, 38.0. HRMS (ES) m/z calcd for [M+H$^+$]: $C_{13}H_{14}N_4O_2$ 259.1195; found 259.1197.

(*S*)-*N*-(1-Amino-1-oxo-3-phenylpropan-2-yl)-5-phenyl-1*H*-imidazole-4-carboxamide (I). Obtained from **6a** (0.5 mmol) as a white solid (150 mg, 90%); ^{1}H NMR (400 MHz, CD_3OD) δ 7.67 (s, 1H), 7.60−7.55 (m, 2H), 7.40−7.31 (m, 3H), 7.28−7.13 (m, 5H), 4.78 (dd, J = 8.2, 5.7 Hz, 1H), 3.24−3.17 (m, 1H), 3.07−2.98 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.9, 162.0, 137.6, 135.0, 132.9, 130.1, 129.6, 129.2, 128.8, 128.1, 128.0, 127.9, 126.3, 53.1, 38.1. HRMS (ES) m/z calcd for [M+H$^+$]: $C_{19}H_{18}N_4O_2$ 335.1508; found 335.1513.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra, LC-MS, and chiral HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441.
(2) Vagner, J.; Qu, H. C.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292.
(3) Biron, E.; Chatterjee, J.; Kessler, H. *Org. Lett.* **2006**, *8*, 2416.
(4) Hanessian, S.; McNaughtonSmith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
(5) Jones, R. C. F.; Ward, G. J. *Tetrahedron Lett.* **1988**, *29*, 3853.
(6) Petit, S.; Fruit, C.; Bischoff, L. *Org. Lett.* **2010**, *12*, 4928.
(7) Gising, J.; Nilsson, M. T.; Odell, L. R.; Yahiaoui, S.; Lindh, M.; Iyer, H.; Sinha, A. M.; Srinivasa, B. R.; Larhed, M.; Mowbray, S. L.; Karlen, A. *J. Med. Chem.* **2012**, *55*, 2894.
(8) Bolchi, C.; Pallavicini, M.; Bernini, S. K.; Chiodini, G.; Corsini, A.; Ferri, N.; Fumagalli, L.; Straniero, V.; Valoti, E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5408.
(9) Zaman, S.; Mitsuru, K.; Abell, A. D. *Org. Lett.* **2005**, *7*, 609.
(10) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z. J.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453.
(11) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571.
(12) Chadwick, D. J.; Ngochindo, R. I. *J Chem. Soc., Perkin Trans. 1* **1984**, 481.
(13) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1986**, *42*, 2351.
(14) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543.
(15) Bellina, F.; Cauteruccio, S.; Di Fiore, A.; Marchetti, C.; Rossi, R. *Tetrahedron* **2008**, *64*, 6060.
(16) Chatani, N.; Fukuyama, T.; Tatamidani, H.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 4039.
(17) Fransson, R.; Botros, M.; Sköld, C.; Nyberg, F.; Lindeberg, G.; Hallberg, M.; Sandström, A. *J. Med. Chem.* **2010**, *53*, 2383.
(18) Fransson, R.; Sköld, C.; Kratz, J. M.; Svensson, R.; Artursson, P.; Nyberg, F.; Hallberg, M.; Sandström, A. *J. Med. Chem.* **2013**, *56*, 4953.
(19) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402.
(20) Brennfuhrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114.
(21) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R. *Synthesis* **2006**, 4247.
(22) Gabriele, B.; Salerno, G.; Veltri, L.; Mancuso, R.; Li, Z. Y.; Crispini, A.; Bellusci, A. *J. Org. Chem.* **2006**, *71*, 7895.
(23) Gabriele, B.; Plastina, P.; Salerno, G.; Mancuso, R.; Costa, M. *Org. Lett.* **2007**, *9*, 3319.
(24) Gabriele, B.; Mancuso, R.; Ziccarelli, I.; Salerno, G. *Tetrahedron Lett.* **2012**, *53*, 6694.
(25) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.
(26) Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, 685.
(27) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4.
(28) Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750.
(29) Hermange, P.; Lindhardt, A. T.; Taaning, R. H.; Bjerglund, K.; Lupp, D.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 6061.
(30) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444.
(31) Friis, S. D.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Am. Chem. Soc.* **2011**, *133*, 18114.
(32) Burhardt, M. N.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2013**, *15*, 948.
(33) Nordeman, P.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2012**, *77*, 11393.
(34) Borhade, S. R.; Sandström, A.; Arvidsson, P. I. *Org. Lett.* **2013**, *15*, 1056.
(35) Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339.
(36) Qu, B.; Haddad, N.; Han, Z. S.; Rodriguez, S.; Lorenz, J. C.; Grinberg, N.; Lee, H.; Busacca, C. A.; Krishnamurthy, D.; Senanayake, C. H. *Tetrahedron Lett.* **2009**, *50*, 6126.
(37) Odell, L. R.; Sävmarker, J.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 6115.
(38) Enquist, P. A.; Nilsson, P.; Edin, J.; Larhed, M. *Tetrahedron Lett.* **2005**, *46*, 3335.
(39) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741.
(40) Luo, F. T.; Jeevanandam, A.; Basu, M. K. *Tetrahedron Lett.* **1998**, *39*, 7939.
(41) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205.
(42) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.
(43) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
(44) Castanet, A. S.; Colobert, F.; Broutin, P. E. *Tetrahedron Lett.* **2002**, *43*, 5047.
(45) He, Y.; Chen, Y. Z.; Du, H. W.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529.