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Note

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Aryl azides as forgotten electrophiles in the Van Leusen reaction: a multicomponent transformation affording 4-tosyl-1-arylimidazoles

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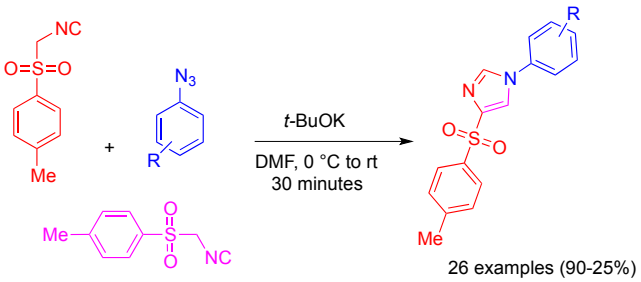
TABLE OF CONTENTS



26 examples (90-25%)

ABSTRACT

Considering aryl azides as electrophilic partners for the TosMIC mediated Van Leusen reaction, a novel multicomponent synthesis of 4-tosyl-1-arylimidazoles is reported. In this transformation, two molecules of TosMIC participate in the reaction mechanism in two different ways, with the second molecule undergoing a novel type of fragmentation resulting in the incorporation of a C-H into the final product.

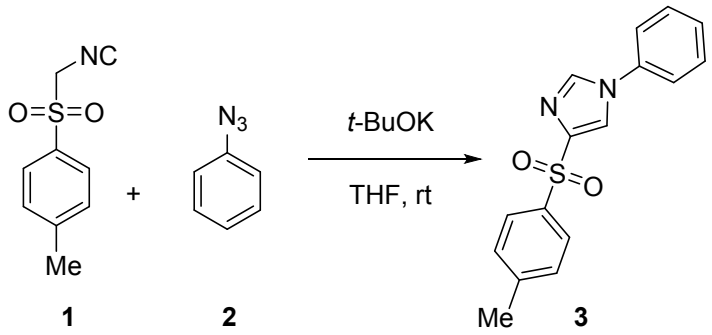
Serendipitously obtained in low yield (14%) by irradiating tosyldiazomethane in liquid hydrogen cyanide by the Dutch Professor Jan Strating and his former student Albert Van Leusen in 1967,[1] toluenesulfonylmethyl isocyanide (TosMIC) rapidly turned from a chemical curiosity to the most important and versatile functionalized isocyanides ever synthesized.[2]

Indeed, in 1972 the same authors presented a safer and scalable synthetic route for TosMIC[3] and in the same year Albert Van Leusen started his independent career on TosMIC chemistry demonstrating the versatility of this non-smelling, shelf stable isocyanide as a valuable reagent in organic synthesis. Preparations of substituted oxazoles and thiazoles by reacting TosMIC and carbonyl compounds[4] or carboxymethyl dithioates,[5] respectively, were published. Over the course of the years, Professor Van Leusen and his group were able to expand the chemical boundaries of TosMIC, recognizing that the consecutive presence of an isocyanide, an acidic CH, and a leaving group allowed for unprecedent transformations with different reactants. Imidazoles, 1,2,4-triazoles, and pyrroles could be easily obtained by reacting TosMIC with different electrophiles such as imines,[6] aryldiazonium salts,[7] and Michael acceptors.[8] Furthermore, TosMIC could also be used as a reagent for converting a ketone to a nitrile in aprotic solvents,[9] or as masked formaldehyde reagent to form symmetrical and unsymmetrical ketones[10] or benzyl derivatives.[11] The versatility of TosMIC was then recognized by other chemists who, with their imagination and intuition, pushed further the boundaries of its chemistry. Excellent reviews on TosMic appeared in the literature covering the period from 1972 to 2018.[12]

The most rationale use of TosMIC is to exploit its α-acidity (pKa= 12-14)[13] in order to favor the nucleophilic attack of the TosMIC anion to an electrophile, and finally use the isocyano group as a carbenoid to form a five-membered rings in a 5-*endo trig* ring closure.[14] Following this strategy, successful examples have been reported with the following electrophiles: carbonyls, imines, carbon disulfide, nitriles, isothiocyanates, Michael adducts, pyridine *N*-oxides, isoquinolines, acyl chlorides, diazonium salts and ketimines. On the basis of the electrophile strength, better results

were obtained using strong bases for less electrophilic partners. Recently, the use of transition metals has amplified and modified the chemical reactivity of TosMIC, opening a new chapter in its already rich history. For example, the metal assisted syntheses of *E*-vinyl sulfones,[15] α-sulfonated ketones,[16] and sulfonyl benzofurans[17] have been reported.

Reflecting on the electrophiles reported in the literature able to react with the TosMIC anion, we became aware that no reports on the reaction between TosMIC and aryl azides were available. Although azides are almost always considered as 1,3-dipolar species or nitrenes precursors of via thermal or photochemical degradation, the terminal nitrogen atom can be intercepted by nucleophiles and azides can also be considered electrophilic reagents. Example of reactions where azides behave like electrophiles are the Dimroth triazole synthesis and the Staudiger reaction.[18] For this reason, we decided to evaluate the reaction of TosMIC with aryl azides. As a model reaction, we chose TosMIC (**1**) and phenyl azide (**2**). When the reaction was carried out in THF at room temperature in the absence of a base, no reaction occurred. But when under the same reaction conditions, *t*-BuOK was added, the reaction proceeded very fast, and we noticed a rapid evolution of gas. The main product was isolated, and its structure unequivocally determined by single crystal X-ray diffraction to be the 4-tosyl-1-phenylimidazole (**3**) obtained in 12% yield (Scheme 1).



Scheme 1. Reaction between TosMIC and phenyl azide affords 4-tosyl-1-phenylimidazole and ORTEP[19] view of **3** and the relative arbitrary atom numbering scheme (thermal ellipsoids at 40% probability).

A literature search showed that 4-tosyl-1-arylimidazoles were already reported via different synthetic strategies. For example, they could be prepared by reacting arylazasulfones **5** with TosMIC[20] or via oxidation of dilithiated 1-phenyl-4-tosyl-1*H*-imidazole-5-thiol **6** with alkaline potassium ferricyanide[21] or, finally via reaction between aryl formamidate **7** or aryl formamidines and TosMIC in the presence of sodium hydride (Figure 1).[22]

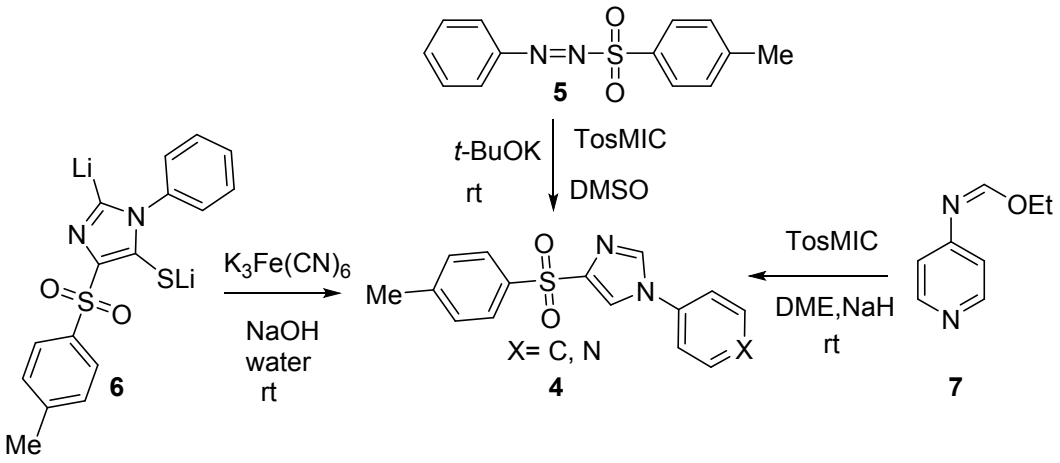
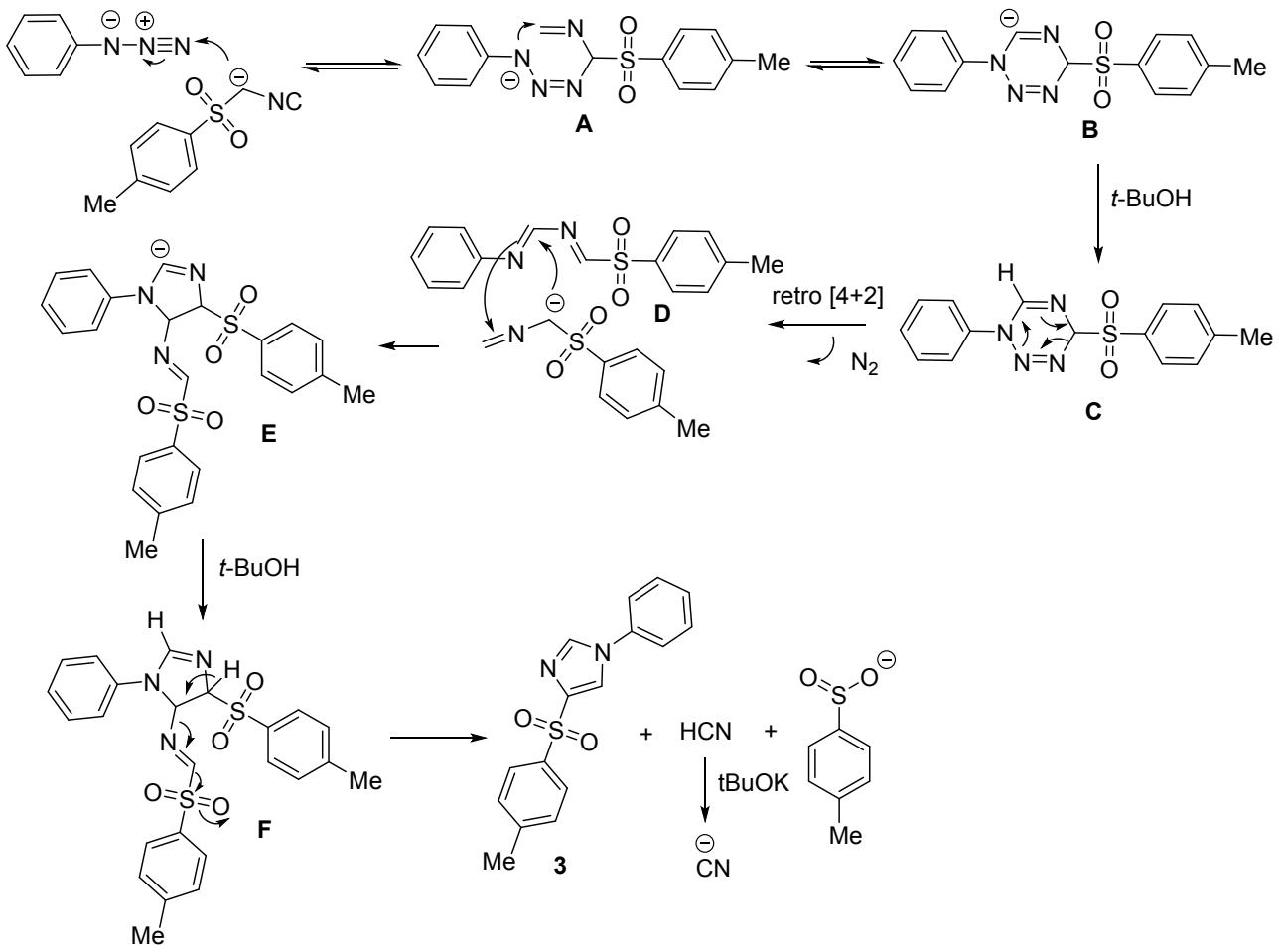


Figure 1. Reported methods for the synthesis of 4-tosyl-1-arylimidazoles.

While these methods can give access to 4-tosyl-1-arylimidazoles, there are evident limitations associated with them such as the use of strong base, problems of selectivity, reaction time, required synthesis of intermediates, and use of external oxidants which can restrict the versatility of these transformations.

As the preparation of aryl azides is an easy task which does not suffer limitations, thus allowing for the preparations of any aromatic azide, this novel transformation could give access to an increased number of functionalized 4-tosyl-1-arylimidazoles not attainable with the other reported methods. For this reason, we considered this novel transformation worthy of further studies and improvements. At first, reasoning on the possible reaction mechanism, it was clear that two equivalents of TosMIC participated actively in this transformation. A possible scenario for this

multicomponent reaction is represented in Scheme 2. To initiate the process, the TosMIC anion attacks N-3 of the azide to form intermediate **A**. Subsequently, N-1 intercepts the isocyanide in a 6 *endo*-*trig* cyclization to form anion **B,** which is quenched by a proton source (e.g. *tert*-butanol) to form **C**. Due to its instability, **C** undergoes a [4+2] cycloreversion to form **D** with loss of nitrogen. The imine of **D** then undergoes attack by a second molecules of TosMIC anion, followed by ring closure to form **E**. At this point, after protonation, intermediate **F** regains aromaticity through a base assisted mechanism with the expulsion of the most acidic proton and loss of hydrogen cyanide and sulfinate. Under strong basic conditions, excess of *t*-BuOK deprotonates the newly formed hydrogen cyanide, avoiding the release of toxic HCN. It is worth to note that the two molecules of TosMIC participate in the reaction mechanism in two different ways, with the second molecule in the scheme undergoing a fragmentation resulting in the incorporation of a C-H into the final molecule. To the best of our knowledge, this mechanistic feature has never been reported for the TosMIC reagent. HRMS infusion of the reaction mixture revealed the presence both intermediates **A** or **B** and *p*-toluensulfinic acid, while intermediate **D** was not detectable probably due to its instability (see supporting information).



Scheme 2. Plausible reaction pathway.

Relying on this mechanistic scenario, several reaction parameters were varied (solvent, base, temperature, reagent equivalents) in order to increase the yield and control the exothermicity of the reaction. The results are shown in the supporting information. As expected, increasing the number of TosMIC and base equivalents boosted the yield with *t*-BuOK still being the best base, since it has the possibility to exchange protons with intermediates **B** and **E**. Cooling the reaction to 0 °C before adding the base had the beneficial effect of increasing the yield. Interestingly, when a polar protic solvent (MeOH) was used, no reaction was observed after 30 minutes; aprotic solvents (DMSO, DMF) were the best choice to carry out the reaction. Best reaction conditions (DMF, 2.5 equiv. of TosMIC, 0 °C then rt, 30 minutes) increased the yield of **3** to 58%. With these optimal conditions in

hand, the substrate scope of the reaction using different aryl azides (**A**-**U**) and TosMIC analogues (**V**-**X**) (Figure 2) was evaluated, resulting in 23 additional successful examples (**8**-**30**) as shown in Figure 3.

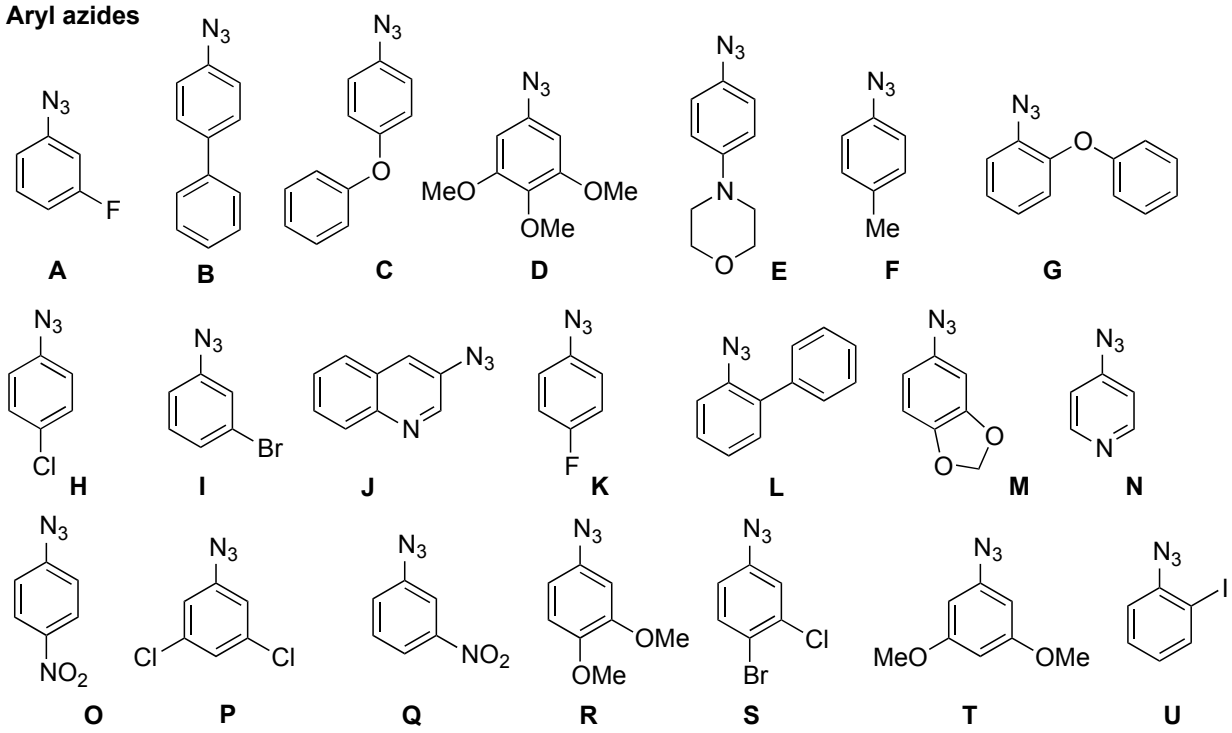


Figure 2. Building blocks used.

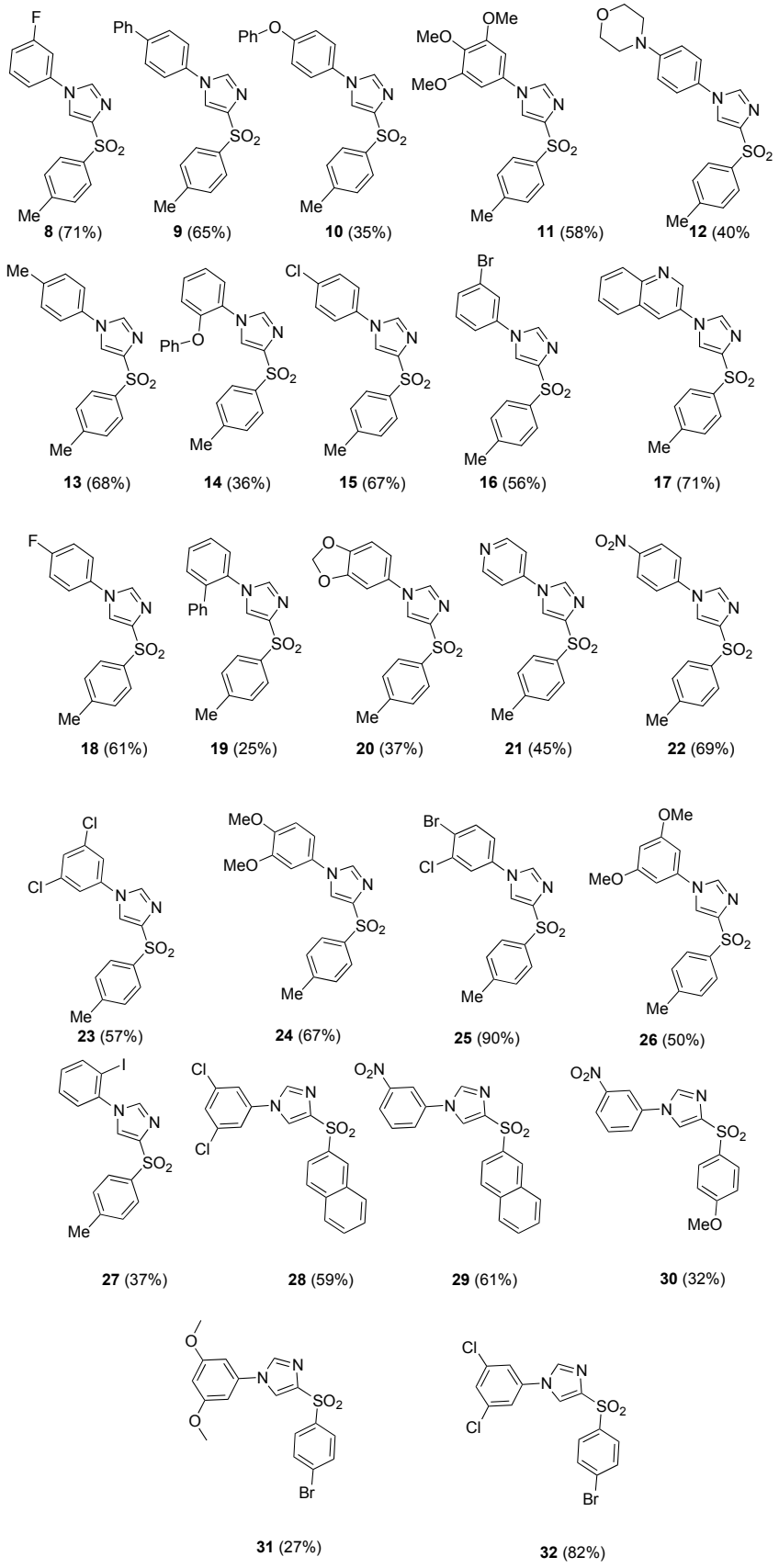
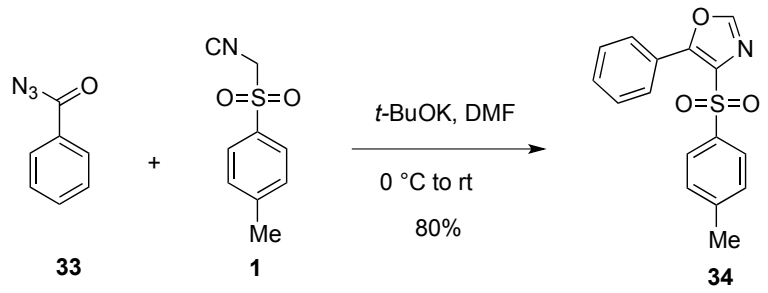


Figure 3. 4-arylsulfonyl-1-(hetero)arylimidazoles synthesized

When electron withdrawing groups (EWGs) were present on the aryl azides, the reaction afforded higher yields. This is in line with the same observation for the Dimroth reaction, as the presence of EWGs increase the electrophilic nature of the azide group.[23] However, the reaction was also successful with aryl azides containing electron donating groups, with only a slight reduction in yields, and even with sterically demanding substrates. Finally, the use of heteroaryl azides were well tolerated, together with the use of TosMIC analogues. When two different TosMIC analogues were used, the reaction led to both the two possible products in a 1:1 ratio. Moreover, a TosMIC analogue substituted at the alpha position with a phenyl ring was also tested, but unfortunately, no definite products were obtained. Notably, the reaction was very fast, with full conversion of starting materials in less than 30 minutes. Simple column chromatography and methanol recrystallization afforded the desired products.

The presented reaction does not work with aliphatic azides, vinyl azides, boronic azides, and toluene sulphonyl azide, as we detected an inseparable reaction mixture. When acyl azides were employed, we isolated 5-aryl-4-tosyloxazoles in high yield. This is exemplified by the reaction in Scheme 3. In this case, acyl azide **33** behaves like an acyl choride[4] towards the TosMIC anion and, after acylation of the α-carbon of TosMIC, enolization and ring closure of the isocyanide, the corresponding 4,5-disubstituted oxazole **34** is formed.



33 **1** **34**

Scheme 3. With acylazides, 5-aryl-4-tosyloxazoles are formed.

In conclusion, following the idea that aryl azides have never been considered as potential electrophilic partner in the Van Leusen reaction with the anion of TosMIC, we demonstrated the

feasibility of this strategy, enabling the formation of 4-arylsulfonyl-1-(hetero)arylimidazoles in good yields. In this novel multicomponent reaction, two molecules of TosMIC participate in the reaction mechanism displaying two distinct chemical behaviors, and sulfinic acid anion and hydrogen cyanide fragmentation of TosMIC was reported for the first time. The versatility of this reaction associated with the ready availability of aryl azides, operational simplicity, and reduced reaction times renders this methodology much more attractive with respect to previously reported routes.

EXPERIMENTAL SECTION

Solvents and Reagents. Commercially available reagents and solvents were used without further purification. When necessary the reactions were performed in oven-dried glassware under a positive pressure of dry nitrogen.

Chromatography. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254). When necessary they were developed with $KMnO_4$.

Spectra. Infrared spectra were recorded on a FT-IR Thermo-Nicolet Avatar spectrometer with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). ^{1}H and ^{13}C APT NMR were recorded on at 400 MHz. High-resolution ESI-MS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in part per million (ppm) relative to residual solvent peak. Melting points were determined using a Stuart Scientific SMP3 apparatus and remain uncorrected.

General preparation of phenyl azides (A-U). The aryl azides were readily synthesized in two steps starting from the corresponding anilines.

Preparation of aryl azides. The corresponding aniline (5 mmol) was suspended in water (1 M, 5 mL); hydrochloric acid (2M, 2.5 mL) was added dropwise and a solution of sodium nitrite (1.1 equiv., 5.5 mmol, 379 mg) in water (3M, 1.8 mL) was added at 0°C. The reaction was stirred at 0°C for 10 minutes. A solution of sodium azide (1.1 equiv., 5.5 mmol, 358 mg) in water (6M, 0.9 mL) was added at 0°C and the reaction mixture was stirred for additional 10 minutes.

The aryl azide was extracted with dichloromethane (x3), the organic phase was washed with brine, evaporated under reduced pressure, and used without further purification in the multicomponent reaction. Phenyl azides **A-U** matched the NMR data as reported in literature (see supporting information for references)[24-42], while the aryl azide **S** was newly synthesized.

4-azido-1-bromo-2-chlorobenzene (S). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 199:1) to give the product as yellowish solid (767 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.8 Hz, 1H), 7.12 (d, J_m = 2.4 Hz, 1H), 6.80 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 140.5, 135.6, 134.5, 120.8, 118.6, 117.8. Mp 46-47 °C.

Preparation of benzoyl azide (33). Benzoyl chloride (5 mmol) was dissolved in acetone (1.5 M, 3.3 mL) at 0°C; a 3M solution of sodium azide (1.5 equiv., 7.5 mmol, 0.49 g) in water was added dropwise at 0°C and the reaction mixture was stirred at room temperature until the complete formation of the product as judged by TLC (typically 10 minutes).

The benzoyl azide was extracted with ethyl acetate (x3), the organic phase was washed with brine, evaporated under reduced pressure, and the crude was purified by chromatographic column. Benzoyl azide **31** matched the NMR data as reported in literature.[43]

General preparation of 1-phenyl-4-(phenylsulfonyl)-1*H*-imidazoles (3, 8-32). The isocyanide (0.62 mmol, 2.5 equiv.) was dissolved in DMF (0.25 M), potassium *tert*-butoxide (0.62 mmol, 2.5 equiv., 70 mg) was added at 0 °C. After 2 minutes the aryl azide (0.25 mmol, 1 equiv.), was added

and the reaction mixture was stirred at 0 °C for 10 minutes and at room temperature for 20 minutes. The reaction mixture was diluted with ethyl acetate and water. The aqueous layer was extracted 3 times with ethyl acetate, and the collected organic phases were then washed one more time with brine. After evaporation of the solvent, the crude material was purified by column chromatography.

1-phenyl-4-tosyl-1*H*-imidazole (3). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 6:4) to give the product as yellowish solid (43 mg, 58% yield). The model reaction was then carried out at 1 mmol scale, referred to aryl azide, without noticing any reduction in yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.94 (m, 3H), 7.81 (s, 1H), 7.52-7.42 (m, 3H), 7.37-7.31 (m, 4H), 2.40 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 144.3, 143.6, 137.7, 135.9, 130.2, 129.8, 128.9, 128.0, 122.2, 121.9, 21.6. IR (KBr) 3146, 3126, 2923, 1595, 1514, 1316, 1179, 1144, 1086, 763 ν_{max}/cm^{-1}; Mp 144-146 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{15}N_2O_2S^+$: 299.0849; Found: 299.0844 $[M+H]^+$.

1-(3-fluorophenyl)-4-tosyl-1*H*-imidazole (8). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as a light brown solid (56 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 3H), 7.82 (s, 1H), 7.52-7.47 (m, 1H), 7.32 (d, J= 8.0 Hz, 2H), 7.20-7.10 (m, 3H), 2.41 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 163.1 (d, J_{ipso}= 248.7 Hz), 144.4, 144.0, 137.5, 137.1 (d, J_m= 9.8 Hz), 131.8 (d, J_m= 9.0 Hz), 129.8, 128.1, 122.0, 117.5 (d, J_p= 3.3 Hz), 115.9 (d, J_o= 20.9 Hz), 109.6 (d, J_o= 25.1 Hz), 21.6. IR (KBr) 3138, 3083, 2924, 1613, 1602, 1521, 1326, 1304, 1142, 857, 694 ν_{max}/cm^{-1}; Mp 157-159 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}FN_2O_2S^+$: 317.0755; Found: 317.0750 $[M+H]^+$.

1-([1,1'-biphenyl]-4-yl)-4-tosyl-1*H*-imidazole (9). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as an amorphous black solid (61 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 3H), 7.87 (s, 1H), 7.69 (d, *J*= 8.4 Hz, 2H), 7.57 (d, *J*= 7.6 Hz, 2H), 7.47-7.36 (m, 5H), 7.31 (d, *J*= 8.0 Hz, 2H), 2.39 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 144.3, 143.5, 141.9, 139.2, 137.7, 134.9, 129.8, 129.0, 128.7, 128.1, 128.0, 127.0, 122.2, 21.6. IR (KBr) 3120, 3057, 2918, 1595, 1525, 1488, 1319, 1183, 1145, 1086, 693, 602 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{19}N_2O_2S^+$: 375.1162; Found: 375.1158 $[M+H]^+$.

1-(4-phenoxyphenyl)-4-tosyl-1*H*-imidazole (10). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as an amorphous brown solid (51 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J*= 8.0 Hz, 2H), 7.89 (s, 1H), 7.76 (s, 1H), 7.40-7.29 (m, 6H), 7.20-7.16 (m, 1H), 7.10-7.03 (m, 4H), 2.41 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 158.1, 156.0, 144.3, 143.4, 137.6, 130.8 (2C), 130.0, 129.7, 128.0, 124.3, 123.7, 122.5, 119.5, 119.4, 21.6. IR (KBr) 3155, 3134, 3121, 3054, 2922, 1588, 1519, 1489, 1312, 1243, 1144, 1085, 694 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{19}N_2O_3S^+$: 391.1111; Found: 391.1105 $[M+H]^+$.

4-tosyl-1-(3,4,5-trimethoxyphenyl)-1*H*-imidazole (11). The crude material was purified by column chromatography (PE/EtOAc 7:3 and PE/EtOAc 6:4) to give the product as an amorphous black solid (59 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96-7.91 (m, 3H), 7.76 (s, 1H), 7.32 (d, *J*= 8.0 Hz, 2H), 6.54 (s, 2H), 3.87 (s, 6H), 3.85 (s, 3H), 2.40 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 154.1, 144.3, 143.3, 138.4, 137.6, 131.7, 129.8, 128.0, 122.7, 100.1, 61.0, 56.4, 21.6. IR

(KBr) 3125, 2963, 2849, 1600, 1514, 1465, 1262, 1095, 1028, 801 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{19}H_{20}N_2NaO_5S$: 411.0991; Found: 411.0967 $[M+Na]^+$.

4-(4-(4-tosyl-1*H*-imidazol-1-yl)phenyl)morpholine (12). The crude material was purified by column chromatography (PE/EtOAc 6:4 and PE/EtOAc 5:5) to give the product as a pink solid (38 mg, 40% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*= 7.2 Hz, 2H), 7.85 (s, 1H), 7.71 (s, 1H), 7.32 (d, *J*= 7.6 Hz, 2H), 7.25-7.22 (m, 2H), 6.95 (d, *J*= 8.0 Hz, 2H), 3.87-3.85 (m, 4H), 3.20-3.18 (m, 4H), 2.40 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 144.2, 143.1, 137.8, 129.7, 128.0, 127.9, 123.2, 116.0, 66.6, 48.7, 21.6. IR (KBr) 3148, 3128, 2954, 2813, 1528, 1450, 1303, 1237, 1137, 1116, 926, 830 ν_{max}/cm^{-1}; Mp 198-200 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{20}H_{22}N_3O_3S^+$: 384.1377; Found: 384.1371 $[M+H]^+$.

1-(*p*-tolyl)-4-tosyl-1*H*-imidazole (13). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as an amorphous reddish solid (53 mg, 68% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*= 8.0 Hz, 2H), 7.90 (s, 1H), 7.77 (s, 1H), 7.31-7.22 (m, 6H), 2.38 (s, 6H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 143.3, 139.0, 137.8, 137.4, 133.5, 130.7, 129.7, 128.0, 122.3, 121.8, 21.6, 21.0. IR (KBr) 3151, 3107, 3063, 2962, 2919, 1521, 1312, 1302, 1139, 1086, 816, 662 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{17}H_{17}N_2O_2S^+$: 313.1006; Found: 313.1000 $[M+H]^+$.

1-(2-phenoxyphenyl)-4-tosyl-1*H*-imidazole (14). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as an amorphous brown solid (35 mg, 36% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*= 8.0 Hz, 2H), 7.91 (s, 1H), 7.77 (s, 1H), 7.38-7.28 (m, 6H), 7.07-7.01 (m, 4H), 2.37 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ

158.0, 156.0, 144.3, 143.3, 137.7, 130.8, 130.1, 129.8, 128.0, 124.3, 123.7, 119.5, 21.6. IR (KBr) 3152, 3121, 3071, 1588, 1522, 1488, 1318, 1236, 1141, 1086, 693 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{19}N_2O_3S^+$: 391.1111; Found: 391.1106 $[M+H]^+$.

1-(4-chlorophenyl)-4-tosyl-1*H*-imidazole (15). The crude material was purified by column chromatography (PE/EtOAc 9:1 and PE/EtOAc 7:3) to give the product as a light brown solid (56 mg, 67% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.92 (m, 3H), 7.79 (s, 1H), 7.48 (d, *J*= 8.8 Hz, 2H), 7.34-7.31 (m, 4H), 2.41 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.4, 143.9, 137.5, 134.8, 134.4, 130.4, 129.8, 128.0, 123.2, 122.1, 21.6. IR (KBr) 3125, 3078, 2922, 1597, 1519, 1321, 1140, 1083, 706, 605 ν_{max}/cm^{-1}; Mp 173-175 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}ClN_2O_2S^+$: 333.0460; Found: 333.0448 $[M+H]^+$.

1-(3-bromophenyl)-4-tosyl-1*H*-imidazole (16). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 6:4) to give the product as an orange-pink solid (53 mg, 56% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97-7.93 (m, 3H), 7.81 (s, 1H), 7.58-7.54 (m, 2H), 7.41-7.26 (m, 4H), 2.41 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.4, 144.0, 137.5, 137.0, 132.0, 131.5, 129.8, 128.1, 125.1, 123.7, 120.6, 21.6. IR (KBr) 3153, 3113, 3063, 2922, 1594, 1516, 1490, 1315, 1303, 1142, 1087, 673, 601ν_{max}/cm^{-1}; Mp 190-192 °C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{16}H_{13}BrN_2NaO_2S$: 400.9758 (97.3%); Found: 400.9745 $[M+Na]^+$.

3-(4-tosyl-1*H*-imidazol-1-yl)quinoline (17). The crude material was purified by column chromatography (PE/EtOAc 6:4 and PE/EtOAc 5:5) to give the product as a light brown solid (67 mg, 71% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J_m= 2.4 Hz, 1H), 8.21-8.10 (m, 3H), 7.96-7.89 (m, 4H), 7.80-7.76 (m, 1H), 7.67-7.63 (m, 1H), 7.31-7.29 (m, 2H), 2.38 (s, 3H); $^{13}C\{1H\}$

NMR (100 MHz, $CDCl_3$) δ 147.6, 144.6, 144.2, 144.0, 137.3, 130.9, 129.8, 129.5, 129.3, 128.6, 128.3, 128.0 (2C), 127.2, 122.5, 21.6. IR (KBr) 3140, 3112, 3062, 2918, 1610, 1515, 1317, 1189, 1147, 1084, 693, 607 ν_{max}/cm^{-1}; Mp 189-191 °C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{19}H_{15}N_3NaO_2S$: 372.0783; Found: 372.0763 $[M+Na]^+$.

1-(4-fluorophenyl)-4-tosyl-1*H*-imidazole (18). The crude material was purified by column chromatography (PE/EtOAc 8:2 and PE/EtOAc 7:3) to give the product as an orange solid (48 mg, 61% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*= 8.4 Hz, 2H), 7.90 (s, 1H), 7.77 (s, 1H), 7.38-7.30 (m, 4H), 7.21-7.17 (m, 2H), 2.40 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6, 161.1, 144.4, 143.7, 137.6, 132.1 (d, J_o=3.2 Hz), 129.8, 128.0, 124.1 (d, J_m= 8.6 Hz), 122.5, 117.2 (d, J_o= 23.1 Hz), 21.6. IR (KBr) 3138, 3089, 3066, 2962, 2922, 1525, 1326, 1261, 1142, 1088, 1020, 807, 694 ν_{max}/cm^{-1}; Mp 163-165 °C dec; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}FN_2O_2S^+$: 317.0755; Found: 317.0750 $[M+H]^+$.

1-([1,1'-biphenyl]-2-yl)-4-tosyl-1*H*-imidazole (19). The crude material was purified by column chromatography (PE/EtOAc 9:1 and PE/EtOAc 7:3) to give the product as an orange solid (23 mg, 25% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*= 8.0 Hz, 2H), 7.57-7.47 (m, 3H), 7.43 (d, *J*= 5.6 Hz, 2H), 7.36-7.21 (m, 6H), 7.01 (d, *J*= 7.6 Hz, 2H), 2.42 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.0, 142.4, 137.9, 137.8, 136.9, 133.6, 131.5, 129.8, 129.6, 128.9, 128.8, 128.1, 127.9, 126.0, 124.7, 21.6. IR (KBr) 3146, 3117, 3055, 3029, 2917, 1595, 1514, 1482, 1315, 1177, 1141, 694, 660 ν_{max}/cm^{-1}; Mp 165-167 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{22}H_{19}N_2O_2S^+$: 375.1162; Found: 375.1149 $[M+H]^+$.

1-(benzo[*d*][1,3]dioxol-5-yl)-4-tosyl-1*H*-imidazole (20). The crude material was purified by column chromatography (PE/EtOAc 7:3 and PE/EtOAc 6:4) to give the product as an amorphous black solid (31 mg, 36% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*= 8.4 Hz, 2H), 7.83 (s, 1H), 7.70 (s, 1H), 7.32 (d, *J*= 8.0 Hz, 2H), 6.88-6.79 (m, 3H), 6.06 (s, 2H), 2.40 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 148.9, 148.2, 144.3, 143.2, 137.7, 130.1, 129.8, 128.0, 122.7, 115.9, 108.8, 103.9, 102.3, 21.6. IR (KBr) 3142, 2915, 1517, 1317, 1306, 1246, 1149, 1037, 691, 604 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{17}H_{14}N_2NaO_4S$: 365.0572; Found: 365.0556 $[M+Na]^+$.

4-(4-tosyl-1*H*-imidazol-1-yl)pyridine (21). The crude material was purified by column chromatography (PE/EtOAc 6:4 and PE/EtOAc 3:7) to give the product as a yellow solid (34 mg, 45% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76-8.75 (m, 2H), 8.06 (s, 1H), 7.98-7.94 (m, 3H), 7.35-7.33 (m, 4H), 2.41 (s, 3H); ^{13}C{1H} NMR (100 MHz, DMSO-d_6) δ 155.4, 150.8, 144.7, 143.5, 143.3, 138.0, 130.4, 127.9, 115.4, 22.3. IR (KBr) 3137, 2963, 2921, 1591, 1519, 1323, 1143, 1085, 819, 806 ν_{max}/cm^{-1}; Mp 195-197 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{14}N_3O_2S^+$: 300.0802; Found: 300.0794 $[M+H]^+$.

1-(4-nitrophenyl)-4-tosyl-1H-imidazole (22). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 6:4) to give the product as a yellowish solid (59 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J*= 9.2 Hz, 2H), 8.02 (d, J_m= 1.6 Hz, 1H), 7.98 (d, *J*= 8.4 Hz, 2H), 7.92 (d, J_m= 1.2 Hz, 1H), 7.59 (d, *J*= 9.2 Hz, 2H), 7.35 (d, *J*= 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 145.1, 144.7, 140.5, 137.1, 129.9, 128.2, 126.0, 122.0, 110.0, 21.6. IR (KBr) 3132, 2922, 2853, 1594, 1518, 1311, 1287, 1140, 1077, 853, 603, 534 ν_{max}/cm^{-1}; Mp 228-229 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}N_3O_4S^+$: 344.0700; Found: 344.0693 $[M+H]^+$.

1-(3,5-dichlorophenyl)-4-tosyl-1*H*-imidazole (23). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a yellowish solid (52 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34-8.32 (m, 1H), 8.28 (s, 1H), 8.01-7.98 (m, 2H), 7.90 (s, 1H), 7.76-7.75 (m, 2H), 7.35 (d, *J*= 8.4 Hz, 2H), 2.43 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 144.6, 144.5, 137.4, 137.3, 136.7, 129.8, 129.0, 128.1, 121.8, 120.5, 21.6. IR (KBr) 3070, 2920, 2851, 1589, 1573, 1432, 1303, 1141, 1084, 799, 665, 599, 532 ν_{max}/cm^{-1}; Mp 209-210 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{13}Cl_2N_2O_2S^+$: 367.0070; Found: 367.0064 $[M+H]^+$.

1-(3,4-dimethoxyphenyl)-4-tosyl-1*H*-imidazole (24). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a brownish solid (60 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J*= 8.0 Hz, 2H), 7.88 (d, J_m= 1.2 Hz, 1H), 7.74 (d, J_m= 1.2 Hz, 1H), 7.32 (d, *J*= 8.0 Hz, 2H), 6.94-6.89 (m, 2H), 6.82 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 2.40 (s, 3H); ^{13}C{1H} NMR (100 MHz, $CDCl_3$) δ 150.0, 149.5, 144.2, 143.1, 137.8, 129.7, 129.2, 128.0, 122.8, 114.5, 111.6, 106.2, 56.2, 21.6. IR (KBr) 3160, 2921, 2852, 1600, 1517, 1442, 1236, 1136, 1082, 1025, 662, 599, 536 ν_{max}/cm^{-1}; Mp 130-131 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{18}H_{19}N_2O_4S^+$: 359.1061; Found: 359.1057 $[M+H]^+$.

1-(4-bromo-3-chlorophenyl)-4-tosyl-1*H*-imidazole (25). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a brown to red solid (93mg, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.48 (s, 1H), 8.16 (d, J_m= 2.4 Hz, 1H), 7.92 (d, *J*= 8.8 Hz, 1H), 7.81 (d, *J*= 8.0 Hz, 2H), 7.70 (dd, J_a= 8.4 Hz, J_b= 2.4 Hz, 1H), 7.41 (d, *J*= 7.6 Hz, 2H), 2.36 (s, 3H); ^{13}C{1H} NMR (100 MHz, DMSO-d_6) δ 144.6, 142.6, 138.7, 138.3, 136.5, 135.2, 134.8, 130.3, 127.8, 123.5, 121.8, 121.1, 21.5. IR (KBr) 3111, 2922, 2852, 1592,

1513, 1463, 1313, 1138, 1084, 810, 634, 585, 532 ν_{max}/cm^{-1}; Mp 183-184 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{13}BrClN_2O_2S^+$: (97%) 412.9544; Found: 412.9536 $[M+H]^+$.

1-(3,5-dimethoxyphenyl)-4-tosyl-1*H*-imidazole (26). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as brownish oil (45 mg, 50% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J*= 7.6 Hz, 2H), 7.88 (s, 1H), 7.73 (s, 1H), 7.31 (d, *J*= 7.6 Hz, 2H), 6.91-6.83 (m, 3H), 3.90 (s, 6H), 2.39 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0, 149.5, 144.2, 143.1, 137.7, 129.7, 129.2, 128.0, 122.8, 114.5, 111.6, 106.2, 56.2, 21.6. IR (KBr) 3124, 2924, 2838, 1599, 1517, 1315, 1235, 1136, 1084, 1020, 660, 597, 534 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{18}H_{19}N_2O_4S^+$: 359.1061; Found: 359.1053 $[M+H]^+$.

1-(2-iodophenyl)-4-tosyl-1*H*-imidazole (27). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a yellow solid (39 mg, 37% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99-7.97 (m, 3H), 7.77 (d, J_m= 1.2 Hz, 1H), 7.61 (d, J_m= 1.2 Hz, 1H), 7.50-7.46 (m, 1H), 7.35-7.21 (m, 4H), 2.42 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 142.9, 140.4, 139.1, 138.7, 137.7, 131.4, 129.7, 129.6, 128.0, 127.6, 124.4, 95.1, 21.6. IR (KBr) 3159, 3106, 2921, 2851, 1511, 1312, 1139, 1084, 766, 688, 660, 602, 533 ν_{max}/cm^{-1}; Mp 180-181 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}IN_2O_2S^+$: 424.9816; Found: 424.9806 $[M+H]^+$.

1-(3,5-dichlorophenyl)-4-(naphthalen-2-ylsulfonyl)-1*H*-imidazole (28). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a yellowish solid (59 mg, 58.5% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.03-7.81 (m, 6H), 7.64-7.58 (m, 2H), 7.43 (s, 1H), 7.31 (s, 2H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.2, 137.4, 137.1, 136.7, 135.2, 132.2, 129.7, 129.5 (2C), 129.2, 129.1, 127.9, 127.5, 122.9, 122.1, 120.6. IR (KBr) 3127,

2922, 1583, 1518, 1311, 1144, 1124, 1072, 852, 751, 682, 665, 588 ν_{max}/cm^{-1}; Mp 212-213 °C; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{19}H_{13}Cl_2N_2O_2S^+$: 403.0070; Found: 403.0062 $[M+H]^+$.

4-(naphthalen-2-ylsulfonyl)-1-(3-nitrophenyl)-1*H*-imidazole (29). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 8:2) to give the product as a brownish solid (58 mg, 61% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.65-8.60 (m, 3H), 8.20-8.10 (m, 4H), 8.01-7.63 (m, 5H); $^{13}C\{1H\}$ NMR (100 MHz, DMSO-d_6) δ 148.9, 142.4, 139.1, 138.1, 137.0, 135.0, 132.1, 131.7, 130.0, 129.9, 129.7, 129.0, 128.3, 128.2, 128.1, 124.1, 123.1, 116.8. IR (KBr) 3152, 3121, 1535, 1518, 1346, 1318, 1143, 1125, 1070, 737, 662, 537 ν_{max}/cm^{-1}; Mp 163-164°C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{19}H_{13}N_3NaO_4S$: 402.0524; Found: 402.0516 $[M+Na]^+$.

4-((4-methoxyphenyl)sulfonyl)-1-(3-nitrophenyl)-1*H*-imidazole (30). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 6:4) to give the product as a yellow to orange solid (29 mg, 32% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.62 (s, 1H), 8.56 (s, 1H), 8.24-8.19 (m, 2H), 7.88-7.78 (m, 3H), 7.13-7.11 (m, 2H), 3.81 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 149.1, 145.1, 136.9, 131.6, 131.5, 130.4, 127.4, 123.4, 121.4, 117.0, 114.5, 55.7. IR (KBr) 3110, 2921, 2851, 1591, 1525, 1348, 1298, 1256, 1135, 737, 673, 600, 545 ν_{max}/cm^{-1}; Mp 180-181 °C; MS (ESI) *m/z* $(M+Na)^+$ Calcd for $C_{16}H_{13}N_3NaO_5S$: 382.0474; Found: 382.0459 $[M+Na]^+$.

4-((4-bromophenyl)sulfonyl)-1-(3,5-dimethoxyphenyl)-1*H*-imidazole (31). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 6:4) to give the product as a yellowish amorphous solid (29 mg, 27% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J= 8.8 Hz, 2H), 7.92 (d, J_m= 1.2 Hz, 1H), 7.78 (d, J_m= 1.6 Hz, 1H), 7.70 (d, J= 8.8 Hz, 2H), 6.95-6.94 (m, 2H), 6.85 (d,

J_m= 2.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0, 149.7, 142.4, 139.8, 138.0, 132.4, 129.6, 129.1, 128.6, 123.3, 114.6, 111.6, 106.3, 56.3, 56.2. IR (KBr) 3087, 2925, 2022, 1516, 1236, 1064, 1008, 856 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{17}H_{16}BrN_2O_4S^+$: 423.0009; Found: 423.0010 $[M+H]^+$.

4-((4-bromophenyl)sulfonyl)-1-(3,5-dichlorophenyl)-1*H*-imidazole (32). The crude material was purified by column chromatography (*n*-hexane/ EtOAc 9:1) to give the product as a yellowish amorphous solid (89 mg, 82% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 3H), 7.85 (s, 1H), 7.71 (d, *J*= 8.4 Hz, 2H), 7.49 (s, 1H), 7.34-7.37 (m, 2H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.8, 139.3, 137.3, 137.2, 136.8, 132.5, 129.6, 129.2, 128.9, 123.0, 122.3, 120.6. IR (KBr) 3135, 2922, 2230, 1571, 1432, 1313, 1140, 1064, 742, 628 ν_{max}/cm^{-1}; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{15}H_{10}BrCl_2N_2O_2S^+$: 430.9018; Found: 430.9026 $[M+H]^+$.

5-phenyl-4-tosyloxazole (34). The crude material was purified by column chromatography (PE/EtOAc 9.5:0.5 and PE/EtOAc 8:2) to give the product as a pink solid (61 mg, 75% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.85 (m, 5H), 7.51-7.50 (m, 3H), 7.31 (d, *J*=8.4 Hz, 2H), 2.41 (s, 3H); $^{13}C\{1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 149.2, 145.0, 137.1, 135.6, 130.9, 129.8, 129.0, 128.6, 128.2, 125.5, 21.7. IR (KBr) 3143, 2963, 2922, 1595, 1512, 1313, 1263, 1144, 1112, 1032, 812, 671 ν_{max}/cm^{-1}; Mp 133-135 °C dec.; MS (ESI) *m/z* $(M+H)^+$ Calcd for $C_{16}H_{14}NO_3S^+$: 300.0689; Found: 300.0688 $[M+H]^+$.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Table with the optimization reaction conditions, Spectroscopic data, HRMS spectra of reaction mixture, Crystallographic description of **3**, Copies of ^{1}H and ^{13}C spectra, (PDF)

Cif file of **3** (CCDC number: 1884065) (PDF)

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