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PAPER

Direct preparation of thiazoles, imidazoles, imidazopyridines and thiazolidines from alkenes†

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A range of heterocycles, namely thiazoles, imidazoles, imidazopyridines, thiazolidines and dimethoxyindoles, have been synthesised directly from alkenes *via* a two-step ketoidoination/cyclisation protocol. The alkene starting materials are themselves readily accessible using many different and well-established approaches, and allow access to a variety of heterocycles with excellent yields and regioselectivity.

Introduction

A large proportion of modern pharmaceutical chemistry involves aromatic and non-aromatic heterocyclic compounds which makes general methods for their rapid and efficient synthesis extremely valuable. To build heterocyclic compounds α-halo- and tosyloxy-ketones have proved to be important precursors. For example, the Hantzsch thiazole synthesis from α-haloketones and thioamides has been known since the late nineteenth century,[1] and alcohols[2] as well as ketones,[3] have been converted through α-tosyloxyketones into a series of thiazoles, imidazoles and imidazopyridines. Similarly, by employing the condensation between α-haloketones and amidines,[4] imidazoles can be obtained. Also, dimethoxyindoles can be accessed from α-haloketones using Bischler and modified Bischler methododologies.[5]

Despite the fact that heterocyclic syntheses employing iodoketones would be expected to occur under mild reaction conditions, compared to their chloro- and bromo-analogues, they have been seldom employed as electrophilic partners in aromatic heterocyclic synthesis.[6] Iodoketones can be prepared from ketones[7] or their enolates[8] by iodination. Alternatively, iodoketones can be prepared directly from alkenes; this is perhaps a more powerful and versatile method due to the ready accessibility of alkenes *via* a wide variety of well established synthetic methodologies. The direct ketoiodination of alkenes was first described by Cardillo *et al.*[9] who used silver(I) chromate and iodine. Later, *bis*(sym-collidine)iodine(I) tetrafluoroborate in DMSO was used as a reagent,[10] and latterly IBX has been introduced as an oxidant for the ketoiodination of alkenes in conjunction with iodine[11a,12] or NIS.[11b]

Recently we reported an efficient and succinct method for the synthesis of various heterocycles directly from alkenes using a ketoiodination protocol.[13] Herein we describe further applications of the alkene ketoiodination reaction towards the efficient synthesis of a wider range of heterocyclic compounds such as thiazoles, imidazoles, imidazopyridines and thiazolidines.

Results and discussion

In our initial experiments, we carried out the ketoiodination of 2-methylstyrene using a procedure described by Moorthy *et al.*[11b] (1.1 eqv. NIS, 2 eqv. IBX, r.t., DMSO). The reaction proceeded smoothly with $\tau_{1/2} = 10$ min[14] and full consumption of the starting material in 40 min. After the excesses of NIS and IBX were washed out with aqueous $NaHCO_3$-$Na_2S_2O_3$, the intermediate iodoketone **2a**[15] was treated with thiourea **4a** (3 eqv., 25 °C, DMSO-DMF) to afford 5-methyl-4-phenyl-1,3-thiazol-2-amine **3a** as the only detectable product in 71% isolated yield and as a single regioisomer. We subsequently found that replacement of NIS with I_2 (1.1 eqv.) led to a substantial increase of the reaction rate: ($\tau_{1/2} = 2$ min) with full consumption of the starting material within 10 min. After condensation of the iodoketone with thiourea, the corresponding aminothiazole product was isolated in a similar yield of 74% (Table 1, entry 1). However, when the pyridyl-substituted alkene **1b** was ketoiodinated using the original conditions (NIS-IBX, in DMSO at 25 °C) a markedly slower reaction was observed with $\tau_{1/2}$ = 6 h.[14] Consumption of the starting alkene reached 90% after 20 h, however only traces of iodoketone were detected by LCMS at this point due to competing Kornblum oxidation of **2b** by DMSO.[16] When the ketoiodination reaction was stopped after 6 h, the subsequent condensation with thiourea afforded the corresponding thiazole **3b** in only 25% yield. As expected from our earlier results, replacing NIS with I_2 (1.1 eqv.) led to a substantial increase in the reaction rate, reducing $\tau_{1/2}$ from 6 h to 50 min and consequently we managed to obtain the desired thiazole **3b** in 62% yield (Table 1, entry 2). The

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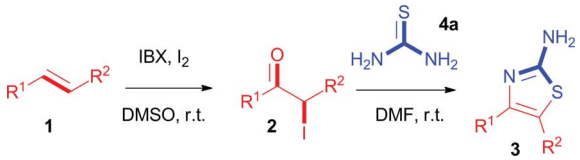
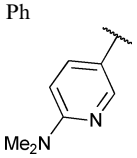
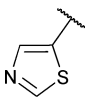
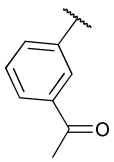
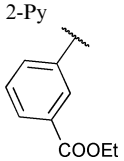
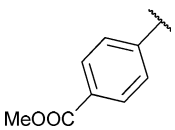
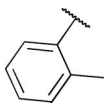
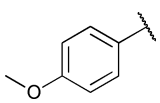
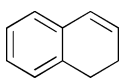
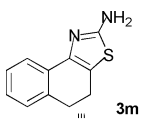
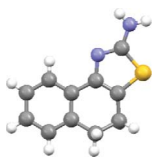
[b]*GlaxoSmithKline Research and Development Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, UK, SG1 2NY. E-mail: ian.e.smith@gsk.com; Fax: +44 1438764502; Tel: +44 1438762631*

† Electronic supplementary information (ESI) available: CCDC reference numbers 845133–845135. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06587d

‡ The author to whom correspondence regarding the X-ray structures should be addressed

Table 1 Synthesis of 2-aminothizoles[a]



Entry	Alkene	R^1	R^2	Product	Yield,%[b]
1	**1a**	Ph	Me	**3a**	74
2	**1b**	3-Py	*n*-Pr	**3b**	62
3	**1c**	Ph	H	**3c**	77
4	**1d**		*n*-Pr	**3d**	67
5	**1e**		*n*-Pr	**3e**	76
6	**1f**	Ph	$-CH_2OCH_3$	**3f**	83
7	**1g**		H	**3g**	73
8	**1h**	2-Py	H	**3h**	55
9	**1i**		H	**3i**	62
10	**1j**		H	**3j**	65
11	**1k**		H	**3k**	67
12	**1l**		H	**3l**	46
13	**1m**			 **3m** 	54

[a] See experimental for conditions. [b] Isolated yield.

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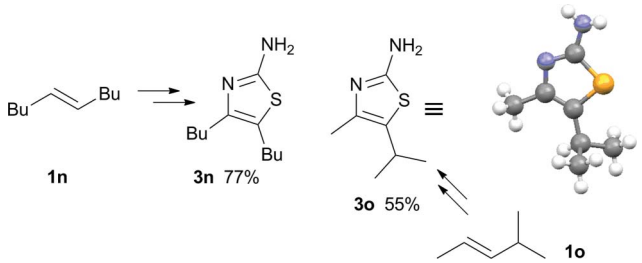
regiochemistry of the ketoiodination and subsequent heteroarene formation is that to be expected on mechanistic grounds, *vide infra*. A range of solvents other than DMSO (THF, dioxane, water, DMF, DCM) were trialled in the ketoiodination step but found to be unsuitable for the ketoiodination reaction.

Our method for heterocycle synthesis was then applied to access various 2-aminothiazoles (**3a–3m**, Table 1) utilising a range of mono- and disubstituted alkenes **1** as starting materials.

The ketoiodination reaction was found to be faster for aromatic alkenes bearing neutral or electron-rich substituents. However, the reaction is also tolerant of the presence of a wide range of functionalities and there was no detrimental effect on the reaction yield when 2- and 3-substituted pyridines (**1b**, **1d**, **1h**), thiazole (**1e**), α-methoxymethyl (**1f**) or a substituted benzene (**1i–1m**) were structural parts of the starting alkene **1** (Table 1).[17] The same methodology is also applicable to disubstituted alkenes without any aryl substituents (Scheme 1).[18]



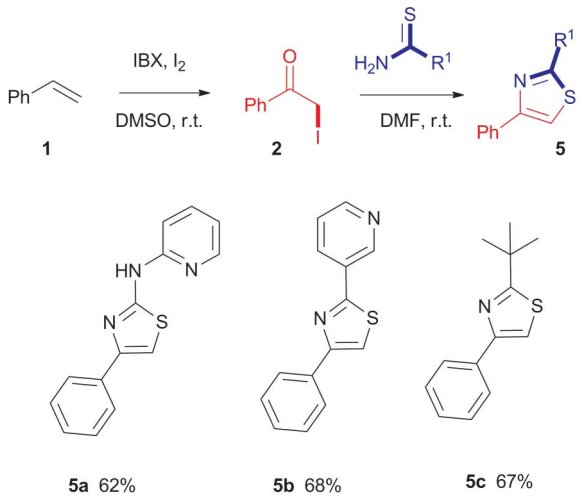
Scheme 1 Dialkyl-2-aminothiazoles (IBX/I_2 then thiourea, see Experimental).

Both symmetrical and unsymmetrical dialkyl alkenes were converted to the corresponding 2-aminothiazoles (**3n** and **3o**, Scheme 1). The aminothiazole **3o** was isolated as a single regioisomer,[19] probably due to steric effects (see mechanism in Scheme 7 and discussion). The structures of the thiazole products were supported by correlation with literature data for **3a**, **3c**, **3h**, **3j**, **3k**, **3l**, **3m**, **3o**. In addition, HMBC experiments were undertaken to prove the structure of **3o**, and X-ray diffraction data has been collected for compounds **3m** and **3o** (see Table 1 and Scheme 1). We have previously reported X-ray diffraction data for compounds **3b** and **3f**.[13] The remaining compounds were assigned by analogy.

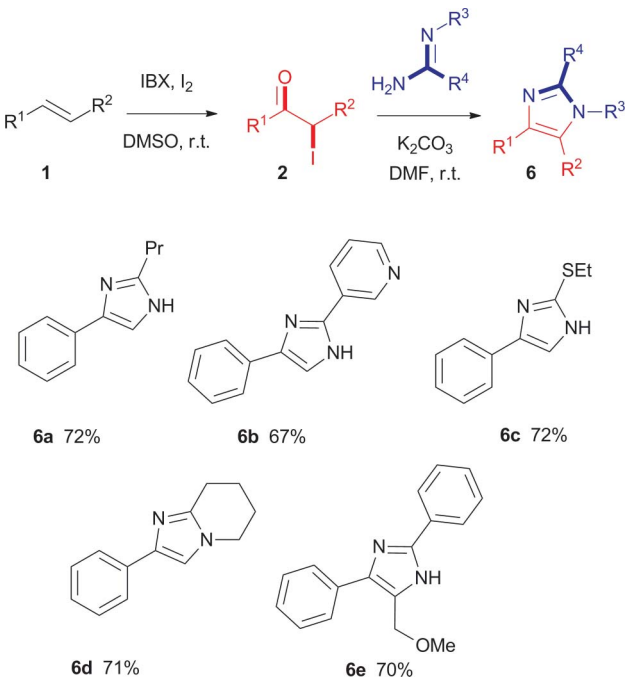
In addition to thiourea, we showed that *N*-substituted thioureas (R^1 = NHPy, **5a**, Scheme 2), alkyl thioamides (R^1 = *t*-Bu, **5c**, Scheme 2) or aryl thioamides (R^1 = 3-Py, **5b**, Scheme 2) can also be used as nucleophiles in this sequence, in so doing extending the scope of the product substitution. The structures of products **5b** and **5c** were assigned by correlation with literature data.[13]

By employing amidines, or their salts, as nucleophiles, one can access the corresponding imidazoles **6a–6e** (Scheme 3). Thus, the method is applicable to the use of alkyl amidines (**6a**, **6d**), aryl amidines (**6b**, **6e**), mono *N*-substituted amidines (**6d**) and *S*-alkylated pseudothioureas (**6c**), in partnership with mono- (**6a–d**) or disubstituted (**6e**) alkenes. The structures of products **6a**, **6b**, **6c**, **6d** were proven by correlation with literature data and, additionally, HMBC experiments supported the structure of **6d**.

In a manner similar to that shown above for imidazoles, imidazopyridines **7a**, **7b**, **7c** can be synthesised from the corresponding alkene **1** and a substituted 2-aminopyridine. The more nucleophilic 2-aminopyridine precursors would be expected to react faster with



Scheme 2 Synthesis of 2-substituted thiazoles.



Scheme 3 Synthesis of imidazoles.

the corresponding iodoketones which in turn could explain the trend in isolated yields of the final products (compare **7b** and **7c**, Scheme 4). The structure of **7a** was proven by correlation with literature data, and X-ray diffraction data has been collected for compound **7c** (Scheme 4); the structure of compound **7b** was assigned by analogy.

When *N*,*N*′-disubstituted thioureas were used as nucleophiles, thiazolidines (**8a**, **8b**) were synthesised from the corresponding alkene (Scheme 5) with good yields. It is interesting to note that compound **8b** was obtained as a single regioisomer as determined by HMBC NMR.

Finally, the dimethoxyindole (**9**) was synthesised using 3,5-dimethoxyaniline as the nucleophile by a Bischler-type method (Scheme 6).[5] Unfortunately, the scope of this reaction is limited because the use of a symmetrical and electron-rich aniline is

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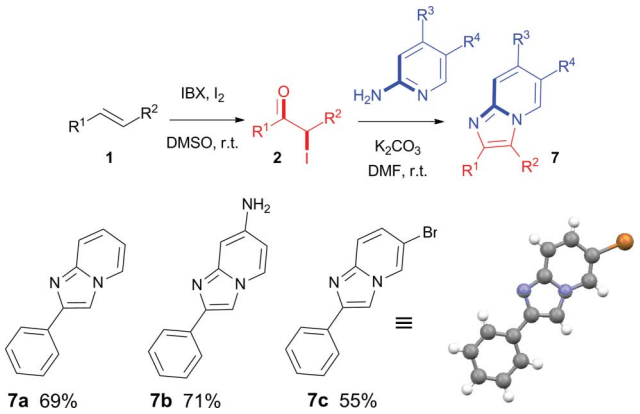
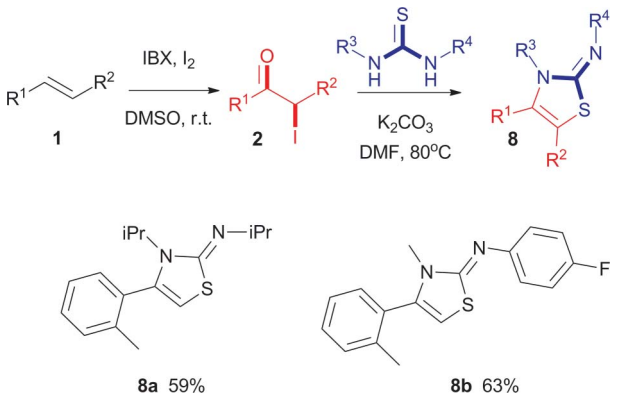
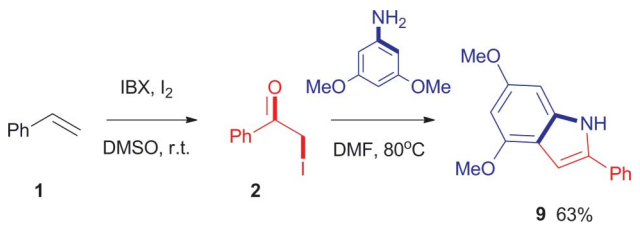


Scheme 4 Synthesis of imidazopyridines.



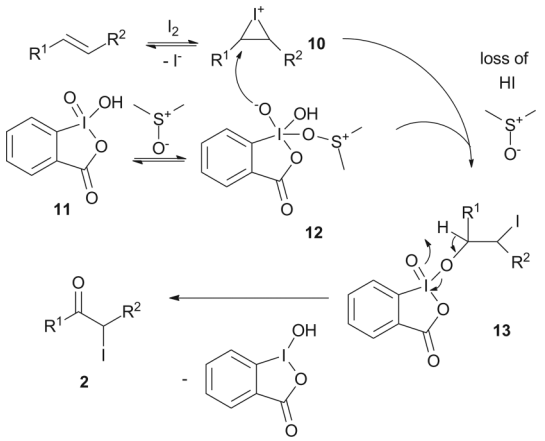
Scheme 5 Synthesis of thiazolidines.



Scheme 6 Synthesis of dimethoxyindole **9**.

required. Thus, only traces of the corresponding indole products were detected when *p*-methylaniline or *p*-bromoaniline were used as nucleophiles. The structure of **9** was proven by correlation with literature data.

The following mechanism of the ketoiodination has been proposed (Scheme 7).[11b] The alkene **1** reacts reversibly with I_2 to form the iodonium ion **10**,[20] which can be attacked by IBX **11** acting as a nucleophile. However, it has been demonstrated[21] that IBX (**11**) forms a complex **12** with DMSO which enhances its nucleophilicity, and formation of this activated IBX-DMSO complex **12** may explain why ketoiodination proceeds significantly better in DMSO than in other solvents.[22] The regioselectivity of the nucleophilic substitution reaction between intermediates **10** and **12**, which ultimately leads to that of the iodoketone (**2**) when R^1 = aryl and R^2 = H or alkyl, can be easily explained by a faster S_N2 reaction at a benzylic centre. When both R^1 and R^2 are alkyl groups, complex **12** would be expected to react preferentially with the least hindered end of the iodonium ion



Scheme 7 The proposed mechanism of ketoiodination.

10 giving the corresponding regioisomer of the iodoketone **2** (see **3o**, Scheme 1). Finally, the corresponding iodoketone **2** is formed from the intermediate **13** *via* an elimination step. In the second step to form the aromatic heterocycle, the regiochemistry of the iodoketone is translated into the regiochemistry of the heteroarene product. Thus, during this step the most nucleophilic atom of the corresponding reagent (*e.g.*, thiourea, thioamide, amidine, aminopyridine) initially substitutes iodide and then a cyclisation-dehydration step follows.

Conclusions

In summary, we have demonstrated that a series of aromatic heterocycles, here thiazoles, imidazoles, imidazopyridines, thiazolidines and indoles, can be synthesised directly from the corresponding alkenes using an efficient and succinct method. This methodology enables the preparation of heterocycles having multiple points of diversity whilst controlling the regiochemistry of many unsymmetrical heterocyclic products especially those derived from aryl/alkyl alkenes. The method should become a useful tool for medicinal chemistry enabling the synthesis of suitable heterocyclic compounds either individually or in parallel as multidimensional arrays.

Experimental

General

All solvents and reagents were used as received from commercial sources. Alkenes **1b**, **1d**, **1e**, **1f** were prepared employing standard methods for Suzuki coupling[23] from commercially available precursors. Proton nuclear magnetic resonance spectra (NMR) were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. The LCMS analysis was conducted on an Acquity UPLC BEH C18 column (50 mm × 2.1 mm internal diameter 1.7 μm packing diameter) at 40 °C employing gradient CH_3CN–H_2O with 0.1% formic acid or on an XBridge C18 column (50 mm × 4.6 mm internal diameter 3.5 μm packing diameter) at 30 °C employing gradient CH_3CN-H_2O with 10 mM NH_4HCO_3. Mass-Directed Autopreparative HPLC analysis (MDAP) was conducted on an XBridge C18 column (150 mm × 30 mm internal diameter, 5 μm packing diameter) at ambient temperature employing

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gradient $CH_3CN–H_2O$ with 10 mM NH_4HCO_3. Accurate mass spectra under the conditions of electrospray ionisation (ESI) were recorded on Bruker Apex IV. Infrared spectra (IR) were recorded as evaporated films. Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

General procedure A

To a solution of IBX (2 eqv., 45% stabilized with benzoic and isophthalic acids) and iodine (1.1 eqv.) in dry dimethyl sulfoxide (0.25 M) stirred at room temperature was added the corresponding alkene (1 eqv.) in one charge. The reaction mixture was stirred at room temperature until full consumption of the starting alkene (monitored by LCMS). Then it was diluted with DCM (30 mL for ~0.5 mmol scale) and washed with saturated aqueous $NaHCO_3$–$Na_2S_2O_3$. The aqueous layer was extracted with DCM (2 × 20 mL for ~0.5 mmol scale); the combined organic layers were dried over Na_2SO_4 and filtered. The corresponding nucleophile (3 eqv.) and dry *N*,*N*-dimethylformamide (0.15 M) were added to the DCM solution and its volume was reduced down to ~2 mL (for ~0.5 mmol scale) under vacuum. The reaction mixture was stirred at room temperature for 12 h. The corresponding product was isolated by MDAP using a gradient CH_3CN-H_2O solvent mixture unless otherwise stated.

5-Methyl-4-phenyl-1,3-thiazole-2-amine (3a)

Using β-methylstyrene (**1a**, 0.055 mL, 0.42 mmol) and thiourea (**4a**, 97 mg, 1.3 mmol) as the nucleophile, the product was obtained as a yellow solid (60 mg, 74% yield). M.p. 118–121 °C [$CHCl_3$; lit.[24] 115–116 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.39 (s, 3 H, CH_3), 5.28 (br. s., 2 H, NH_2), 7.32 (t, *J* = 7.5 Hz, 1 H, Ph), 7.40 (t, *J* = 7.5 Hz, 2 H, Ph), 7.56 (d, *J* = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 12.3 (*C*H_3), 117.4 (*C*-S), 127.1 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 135.1 (*C*), 146.0 (*C*-N), 164.0 (*C*-NH_2). NMR data matched that reported in the literature.[25]

5-Propyl-4-(3-pyridinyl)-1,3-thiazol-2-amine (3b)

Using 3-[(1*E*)-1-penten-1-yl]pyridine (**1b**, 60 mg, 0.41 mmol) and thiourea (**4a**, 93 mg, 1.2 mmol) as the nucleophile, the product was obtained as a pale yellow solid (55 mg, 62% yield). M.p. 61–62 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.97 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.66 (sxt, *J* = 7.5 Hz, 2 H, CH_2), 2.75 (t, *J* = 7.5 Hz, 2 H, CH_2), 5.02 (br. s, 2 H, NH_2), 7.33 (dd, *J* = 8.0, 5.0 Hz, 1 H, Ar), 7.86 (d, *J* = 8.0 Hz, 1 H, Ar), 8.55 (d, *J* = 5.0 Hz, 1 H, Ar), 8.78 (s, 1 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 13.7 (*C*H_3), 25.4 (*C*H_2), 29.0 (*C*H_2), 123.2 (*C*H), 126.1 (*C*), 131.3 (*C*), 135.8 (*C*H), 142.7 (*C*-N), 148.3 (*C*H), 149.3 (*C*H), 164.5 (N = *C*-S); IR υ cm^{-1} 3290, 3130, 2959, 2930, 1628, 1535, 1340, 1320, 1180, 1100, 1024, 813, 710; HRMS (ES+) *m*/*z* 220.0905 (M+H; $C_{11}H_{14}N_3S$ requires 220.0908).

4-Phenyl-1,3-thiazol-2-amine (3c)

Using styrene (**1c**, 0.055 mL, 0.48 mmol) and thiourea (**4a**, 110 mg, 1.44 mmol) as the nucleophile, the product was obtained as a pale yellow solid (65 mg, 77% yield). M.p. 146–150 °C [$CHCl_3$; lit.[24] 150–151 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.24 (br. s, 2 H, NH_2), 6.73 (s, 1 H, C*H*-S), 7.31 (t, *J* = 7.0 Hz, 1 H, Ph), 7.39 (t, *J* = 7.0 Hz, 2 H, Ph), 7.78 (d, *J* = 7.0 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 102.9 (*C*H-S), 126.0 (*C*H), 127.7 (*C*H), 128.6 (*C*H), 134.6 (*C*), 151.3 (*C*-N), 167.1 (N = *C*-S). NMR data matched that reported in the literature.[25]

5-(2-Amino-5-propyl-1,3-thiazol-4-yl)-*N*,*N*-dimethyl-2-pyridinamine (3d)

Using *N*,*N*-dimethyl-5-[(1*E*)-1-penten-1-yl]-2-pyridinamine (**1d**, 60 mg, 0.32 mmol) and thiourea (**4a**, 72 mg, 0.95 mmol) as the nucleophile, the product was obtained as a yellow solid (55 mg, 67% yield). M.p. > 110 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.96 (t, *J* = 7.5 Hz, 3 H, CH_3CH$_2$), 1.63 (sxt, *J* = 7.5 Hz, 2 H, CH_2), 2.71 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.12 (s, 6 H, CH_3N), 4.96 (br. s, 2 H, NH_2), 6.56 (d, *J* = 8.5 Hz, 1 H, Ar), 7.68 (dd, *J* = 8.5, 2.5 Hz, 1 H, Ar), 8.30 (d, *J* = 2.5 Hz, 1 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 13.8 (*C*H_3), 25.5 (*C*H_2), 29.1 (*C*H_2), 38.2 (*C*H_3N), 105.4 (*C*H), 119.3 (*C*), 123.1 (*C*), 137.5 (*C*H), 143.6 (*C*); 147.2 (*C*H), 158.2 (*C*), 164.0 (*C*); IR υ cm^{-1} 3178, 2958, 2928, 1610, 1567, 1542, 1512, 1392, 1317, 1215, 956, 813; HRMS (ES+) *m*/*z* 263.1324 (M+H; $C_{13}H_{19}N_4S$ requires 263.1330).

5-Propyl-4,5′-bi-1,3-thiazol-2-amine (3e)

Using 5-propyl-4,5′-bi-1,3-thiazol-2-amine (**1e**, 70 mg, 0.46 mmol) and thiourea (**4a**, 104 mg, 1.37 mmol) as the nucleophile, the product was obtained as a pale yellow solid (78 mg, 76% yield). M.p. 133–134 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.01 (t, *J* = 7.4 Hz, 3 H, CH_3), 1.67 (sxt, *J* = 7.4 Hz, 2 H, CH_2), 2.79 (t, *J* = 7.4 Hz, 2 H, CH_2), 5.37 (br. s, 2 H, NH_2), 8.01 (s, 1 H, Ar), 8.73 (s, 1 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 13.8 (*C*H_3), 24.5 (*C*H_2), 29.1 (*C*H_2), 125.5 (*C*), 133.3 (*C*), 136.4 (*C*), 140.1 (*C*H), 151.8 (*C*H), 164.5 (N = *C*-S); IR υ cm^{-1} 3300, 3134, 2957, 2905, 1640, 1559, 1537, 1501, 1318, 1262, 1105, 1016, 884, 804, 775, 674; HRMS (ES+) *m*/*z* 226.0466 (M+H; $C_9H_{12}N_3S_2$ requires 226.0473).

5-[(Methoxy)methyl]-4-phenyl-1,3-thiazol-2-amine (3f)

Using methyl (2*E*)-3-phenyl-2-propen-1-yl ether (**1f**, 50 mg, 0.34 mmol) and thiourea (**4a**, 77 mg, 1.0 mmol) as the nucleophile, the product was obtained as a pale yellow solid (62 mg, 83% yield). M.p. 127–128 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.39 (s, 3 H, CH_3), 4.49 (s, 2 H, CH_2), 5.31 (br. s, 2 H, NH_2), 7.32–7.38 (m, 1 H, Ph), 7.39–7.45 (m, 2 H, Ph), 7.58 (d, *J* = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 57.7 (*C*H_3), 66.4 (*C*H_2), 119.0 (*C*-S), 127.9 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 134.5 (*C*), 149.6 (*C*–N), 166.2 (N = *C*–S); IR υ cm^{-1} 3330, 3297, 3123, 2928, 2867, 1625, 1527, 1487, 1336, 1190, 1071, 775, 701; HRMS (ES+) *m*/*z* 221.0741 (M+H; $C_{11}H_{13}N_2OS$ requires 221.0749).

1-(3-(2-Aminothiazol-4-yl)phenyl)ethanone (3g)

Using 1-(3-vinylphenyl)ethanone (**1g**, 80 mg, 0.55 mmol) and thiourea (**4a**, 125 mg, 1.64 mmol) as the nucleophile, the product was obtained as a pale yellow solid (87 mg, 73% yield). M.p. 148–150 °C [CH_3CN]; ^{1}H NMR (400 MHz, $CDCl_3$ + MeOH-*d4* (1 : 1)) δ (ppm) 2.67 (s, 3 H, CH_3), 6.84 (s, 1 H, C*H*), 7.50 (t, *J* = 8.0 Hz, 1 H, C*H*), 7.86–7.92 (m, 1 H, C*H*), 7.95–7.99 (m, 1 H, C*H*), 8.35 (t, *J* = 1.5 Hz, 1 H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$ + MeOH-*d4*

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(1 : 1)) 27.0 (*C*H$_3$), 103.8 (*C*H), 126.6 (*C*H), 128.1 (*C*H), 129.6 (*C*H), 131.3 (*C*H), 136.0 (*C*), 138.0 (*C*), 150.1 (*C*), 170.6 (*C*), 200.2 (*C*O); IR υ cm^{-1} 3345, 1677, 1540, 1418, 1358, 1254, 714; HRMS (ES+) *m*/*z* 219.0588 (M+H; $C_{11}H_{11}N_2OS$ requires 219.0592).

4-(2-Pyridinyl)-1,3-thiazol-2-amine (3h)

Using 2-vinylpyridine (**1h**, 60 mg, 0.57 mmol) and thiourea (**4a**, 130 mg, 1.71 mmol) as the nucleophile, the product was obtained as a pale yellow solid (56 mg, 55% yield). M.p. 170–172 °C [$CHCl_3$; lit.[26] 173–175 °C]; ^{1}H NMR (400 MHz, MeOH-*d4*) δ (ppm) 7.23 (s, 1 H, C*H*-S), 7.24–7.30 (m, 2 H, C*H*), 7.78–7.90 (m, 2 H, C*H*), 8.50–8.52 (m, 1 H, C*H*); ^{13}C NMR (101 MHz, MeOH-*d4*) 106.3 (*C*H), 121.3 (*C*H), 122.7 (*C*H), 137.8 (*C*H), 148.9 (*C*H), 149.9 (*C*), 152.8 (*C*), 170.2 (*C*); IR υ cm^{-1} 3291, 3128, 1590, 1535, 1423, 1344, 1056, 793, 746, 710; HRMS (ES+) *m*/*z* 178.0436 (M+H; $C_8H_8N_3S$ requires 178.0439). ^{1}H NMR data matched that reported in the literature.[27]

Ethyl 3-(2-amino-1,3-thiazol-4-yl)benzoate (3i)

Using 3-vinylbenzoic acid ethyl ester (**1i**, 70 mg, 0.40 mmol) and thiourea (**4a**, 91 mg, 1.2 mmol) as the nucleophile, the product was obtained as a pale yellow solid (61 mg, 62% yield). M.p. 112–114 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.41 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$), 4.40 (q, *J* = 7.0 Hz, 2 H, C*H*$_2$), 5.20 (br. s, 2 H, N*H*$_2$), 6.82 (s, 1 H, C*H*), 7.45 (t, *J* = 8.0 Hz, 1 H, C*H*), 7.94–8.00 (m, 2 H, C*H*), 8.42 (t, *J* = 2.0 Hz, 1 H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) 14.4 (*C*H$_3$), 61.1 (*C*H$_2$), 103.7 (*C*H), 127.0 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 130.3 (*C*H), 130.9 (*C*), 134.9 (*C*), 150.3 (*C*), 166.6 (*C*), 167.4 (*C*); IR υ cm^{-1} 3344, 3119, 2981, 1706, 1609, 1534, 1338, 1256, 1197, 1106, 1021, 762, 710; HRMS (ES+) *m*/*z* 249.0695 (M+H; $C_{12}H_{13}N_2O_2S$ requires 249.0698).

Methyl 4-(2-amino-1,3-thiazol-4-yl)benzoate (3j)

Using methyl 4-ethenylbenzoate (**1j**, 150 mg, 0.92 mmol) and thiourea (**4a**, 211 mg, 2.77 mmol) as the nucleophile, the product was obtained as a pale yellow solid (140 mg, 65% yield). M.p. 233–235 °C [CH_3CN]; ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm) 3.85 (s, 3 H, C*H*$_3$), 7.16 (br. s, 2 H, N*H*$_2$), 7.25 (s, 1 H, C*H*), 7.91–8.00 (m, 4 H, Ar); ^{13}C NMR (101 MHz, acetone-*d6*) δ (ppm) 51.3 (*C*H$_3$), 104.5 (*C*H), 125.6 (*C*H), 128.6 (*C*), 129.5 (*C*H), 139.5 (*C*), 149.7 (*C*), 166.1 (*C*), 168.2 (*C*); IR υ cm^{-1} 1694, 1606, 1556, 1282, 1112, 859, 718; HRMS (ES+) *m*/*z* 235.0541 (M+H; $C_{11}H_{11}N_2O_2S$ requires 235.0541). ^{1}H NMR data matched that reported in the literature.[28]

4-(2-Methylphenyl)-1,3-thiazol-2-amine (3k)

Using 2-methylstyrene (**1k**, 50 mg, 0.42 mmol) and thiourea (**4a**, 97 mg, 1.3 mmol) as the nucleophile, the product was obtained as a pale yellow solid (54 mg, 67% yield). M.p. 80–82 °C [$CHCl_3$; lit.[29] 81–82 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.44 (s, 3 H, C*H*$_3$), 5.18 (br. s, 2 H, N*H*$_2$), 6.45 (s, 1 H, C*H*), 7.18–7.26 (m, 3 H, C*H*), 7.51–7.54 (m, 1 H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) 21.0 (*C*H$_3$), 105.7 (*C*H), 125.7 (*C*H), 127.8 (*C*H), 129.5 (*C*H), 130.7 (*C*H), 134.9 (*C*), 136.0 (*C*), 151.3 (*C*), 166.4 (*C*); IR υ cm^{-1} 3285, 3119, 1622, 1523, 1329, 1032, 767, 730; HRMS (ES+) *m*/*z* 191.0638 (M+H; $C_{10}H_{11}N_2S$ requires 191.0643).

4-(4-Methoxyphenyl)thiazol-2-amine (3l)

Using 1-methoxy-4-vinylbenzene (**1l**, 50 mg, 0.37 mmol) and thiourea (**4a**, 85 mg, 1.1 mmol) as the nucleophile. The product was obtained as a pale yellow solid (35 mg, 46% yield). M.p. 205–207 °C [CH_3CN; lit.[29] 204–205 °C]; ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm) 3.76 (s, 3 H, C*H*$_3$), 6.83 (s, 1 H, C*H*), 6.92 (d, *J* = 8.5 Hz, 1 H, C*H*), 7.01 (br. s, 2 H, N*H*$_2$), 7.72 (d, *J* = 8.5 Hz, 1 H, C*H*); ^{13}C NMR (101 MHz, DMSO-*d6*) 55.1 (*C*H$_3$), 99.3 (*C*H), 113.8 (*C*H), 126.8 (*C*H), 127.8 (*C*), 149.7 (*C*), 158.5 (*C*), 168.0 (*C*); IR υ cm^{-1} 3440, 3270, 3117, 1626, 1538, 1493, 1246, 1179, 1037, 836, 738; HRMS (ES+) *m*/*z* 207.0591 (M+H; $C_{10}H_{11}N_2OS$ requires 207.0592). NMR data matched that reported in the literature.[30]

4,5-Dihydronaphtho[1,2-d]thiazol-2-amine (3m)

Using 1,2-dihydronaphthalene (**1m**, 50 mg, 0.38 mmol) and thiourea (**4a**, 88 mg, 1.2 mmol) as the nucleophile, the product was obtained as a pale yellow solid (42 mg, 54% yield). M.p. 132–134 °C [CH_3CN; lit.[29] 133–134 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.82–2.90 (m, 2 H, C*H*$_2$), 2.97–3.07 (m, 2 H, C*H*$_2$), 5.01 (br. s, 2 H, N*H*$_2$), 7.12–7.27 (m, 3 H, C*H*), 7.68 (d, *J* = 7.5 Hz, 1 H, C*H*); ^{13}C NMR (101 MHz, $CDCl_3$) 21.7 (*C*H$_2$), 29.1 (*C*H$_2$), 120.3 (*C*), 122.7 (*C*H), 126.2 (*C*H), 126.7 (*C*H), 127.7 (*C*H), 131.5 (*C*), 134.4 (*C*), 145.2, (*C*), 165.5 (*C*); IR υ cm^{-1} 3283, 3124, 2934, 1606, 1527, 1364, 1293, 1062, 766. 718; HRMS (ES+) *m*/*z* 203.0643 (M+H; $C_{11}H_{11}N_2S$ requires 203.0643). NMR data matched that reported in the literature.[31]

4,5-Dibutyl-1,3-thiazol-2-amine (3n)

Using 5-decene (**1n**, 0.095 mL, 0.50 mmol) and thiourea (**4a**, 77 mg, 1.0 mmol) as the nucleophile, the product was obtained as a colorless oil (82 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.92 (t, *J* = 7.3 Hz, 6 H, C*H*$_3$), 1.25–1.40 (m, 4 H, C*H*$_2$), 1.44–1.63 (m, 4 H, C*H*$_2$), 2.36–2.48 (m, 2 H, C*H*$_2$), 2.56 (t, *J* = 7.5 Hz, 2 H, C*H*$_2$), 4.90 (br. s, 2 H, N*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 13.8 (*C*H$_3$), 14.0 (*C*H$_3$), 22.1 (*C*H$_2$), 22.5 (*C*H$_2$), 25.8 (*C*H$_2$), 28.7 (*C*H$_2$), 31.8 (*C*H$_2$), 34.1 (*C*H$_2$), 121.9 (*C*-S), 147.1 (*C*-N), 164.0 (S-*C* = N); IR υ cm^{-1} 3283, 3122, 2954, 2927, 2857, 1609, 1523, 1461, 1317, 1127, 1064, 748, 705; HRMS (ES+) *m*/*z* 213.1423 (M+H; $C_{11}H_{21}N_2S$ requires 213.1425).

5-Isopropyl-4-methylthiazol-2-amine (3o)

Using 4-methylpent-2-ene (**1o**, 0.073 mL, 0.60 mmol) and thiourea (**4a**, 136 mg, 1.78 mmol) as the nucleophile, the product was obtained as a colorless oil (51 mg, 55% yield). M.p. 64–66 °C [$CHCl_3$; lit.[32] 65–67 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.20 (d, *J* = 7.0 Hz, 6 H, C*H*$_3$CH), 2.13 (s, 3 H, C*H*$_3$), 3.07 (sept, *J* = 7.0 Hz, 1 H, CH$_3$C*H*), 4.65 (br. s, 2 H, N*H*$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) 14.6 (*C*H$_3$), 24.8 (*C*H$_3$CH), 27.1 (CH$_3$*C*H), 129.6 (*C*), 140.3 (*C*), 163.7 (*C*); IR υ cm^{-1} 3292, 3176, 2959, 1610, 1521, 1460, 1382, 1310, 1108; HRMS (ES+) *m*/*z* 157.0806 (M+H; $C_7H_{13}N_2S$ requires 157.0799). ^{1}H NMR data matched that reported in the literature.[33]

N-(4-Phenyl-1,3-thiazol-2-yl)-2-pyridinamine (5a)

Using styrene (**1c**, 0.055 mL, 0.48 mmol) and 2-pyridylthiourea (**4b**, 221 mg, 1.44 mmol) as the nucleophile, the product was

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obtained as a colorless oil (75 mg, 62% yield). M.p. 164–166 °C [CH_3CN]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.42 (d, J = 8.0 Hz, 1 H, C*H*), 6.73 (dd, J = 7.0 Hz, J = 5.0 Hz, 1 H, C*H*), 6.98 (s, 1 H, C*H*), 7.15–7.35 (m, 4 H, C*H*), 7.81–7.84 (m, 2 H, Ph), 8.25 (d, J = 5.0 Hz, 1 H, C*H*), 10.15 (br. s, 1 H, N*H*); ^{13}C NMR (101 MHz, $CDCl_3$) 105.7 (*C*H), 110.6 (*C*H), 116.2 (*C*H), 126.1 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 134.7 (*C*), 137.4 (*C*H), 146.6 (*C*H), 149.3 (*C*), 151.3 (*C*), 161.1 (*C*); IR υ cm^{-1} 3176, 3053, 2950, 1605, 1542, 1478, 1408, 1328, 770, 715; HRMS (ES+) *m/z* 254.0752 (M+H; $C_{14}H_{12}N_3S$ requires 254.0752).

3-(4-Phenyl-1,3-thiazol-2-yl)pyridine (5b)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and thionicotinamide (**4c**, 175 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (71 mg, 68% yield). M.p. 64–65 °C [$CHCl_3$; lit[34] 67–68 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35–7.52 (m, 4 H, Ar), 7.55 (s, 1 H, C*H*-S), 8.01 (d, J = 7.5 Hz, 2 H, Ar), 8.34 (br. d, J = 8.0 Hz, 1 H, Ar), 8.68 (br. d, J = 3.5 Hz, 1 H, Ar), 9.26 (br. s, 1 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 113.2 (*C*H-S), 123.7 (*C*H), 126.4 (*C*H), 128.4 (*C*H), 128.8 (*C*H), 129.7 (*C*), 133.6 (*C*H), 134.0 (*C*), 147.7 (*C*H), 150.8 (*C*H), 156.7 (*C*), 164.3 (*C*); IR υ cm^{-1} 3062, 2987, 1569, 1495, 1474, 1444, 1417, 1408, 1330, 1254, 1189, 1072, 1024, 976, 808, 730, 702, 679; HRMS (ES+) *m/z* 239.0638 (M+H; $C_{14}H_{11}N_2S$ requires 239.0643).

2-(1,1-Dimethylethyl)-4-phenyl-1,3-thiazole (5c)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and 2,2-dimethylthiopropioamide (**4d**, 149 mg, 1.27 mmol) as the nucleophile, the product was obtained as a yellow oil (62 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51 (s, 9 H, CH_3), 7.29–7.37 (m, 2 H, Ph + C*H*-S), 7.43 (t, J = 7.5 Hz, 2 H, Ph), 7.94 (d, J = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, DMSO-*d6*) δ (ppm) 30.6 (CH_3), 37.3 (CH_3C), 112.9 (*C*H-S), 126.0 (*C*H), 127.8 (*C*H), 128.7 (*C*H), 134.3 (*C*), 153.5 (*C*-N), 180.2 (S-*C* = N); IR υ cm^{-1} 2962, 2927, 1494, 1475, 1460, 1445, 1363, 1223, 1066, 1015, 727, 689; HRMS (ES+) *m/z* 218.1000 (M+H; $C_{13}H_{16}NS$ requires 218.1003). ^{13}C NMR data matched that reported in the literature.[35]

General procedure B

To a solution of IBX (2 eqv., 45% stabilized with benzoic and isophthalic acids) and iodine (1.1 mmol) in dry dimethyl sulfoxide (0.25 M) stirred at room temperature was added the corresponding alkene (1 eqv.) in one charge. The reaction mixture was stirred at room temperature until full consumption of the starting alkene (monitored by LCMS). Then it was diluted with DCM (30 mL for ~0.5 mmol scale) and washed with saturated aqueous $NaHCO_3$–$Na_2S_2O_3$. The aqueous layer was extracted with DCM (2 × 20 mL for ~0.5 mmol scale); the combined organic layers were dried over Na_2SO_4 and filtered. The corresponding nucleophile (3 eqv.), potassium carbonate (2 eqv.) and dry *N*,*N*-dimethylformamide (0.15 M) were added to the DCM solution and the volume was reduced down to ~2 mL (for ~0.5 mmol scale) under vacuum. The reaction mixture was stirred at room temperature for 12 h. The corresponding product was isolated by MDAP using gradient CH_3CN–H_2O solvent mixture unless otherwise stated.

4(5)-Phenyl-2-propyl-1*H*-imidazole (6a)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and butyramidine hydrochloride (**4e**, 156 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (57 mg, 72% yield). M.p. 130–132 °C [aq. EtOH; lit[36] 136 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.95 (t, J = 7.5 Hz, 3 H, CH_3), 1.75 (sxt, J = 7.5 Hz, 2 H, CH_2), 2.72 (t, J = 7.5 Hz, 2 H, CH_2), 7.18–7.26 (m, 2 H, Ph + C*H*-NH), 7.36 (t, J = 7.5 Hz, 2 H, Ph), 7.69 (d, J = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 13.7 (CH_3), 22.0 (CH_2), 30.3 (CH_2), 115.1 (*C*H-N), 124.8 (*C*H), 126.8 (*C*H), 128.7 (*C*H), 132.6 (*C*), 137.4 (*C*-N), 149.4 (N = *C*-NH); IR υ cm^{-1} 3033, 2961, 2930, 2871, 1607, 1539, 1514, 1455, 1426, 1260, 1134, 1094, 1069, 1014, 801, 748, 692; HRMS (ES+) *m/z* 187.1232 (M+H; $C_{12}H_{15}N_2$ requires 187.1235).

3-(4(5)-Phenyl-1*H*-imidazol-2-yl)pyridine (6b)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and 3-amidinopyridine hydrochloride (**4f**, 200 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (62 mg, 67% yield). M.p. 192–194 °C [aq. EtOH; lit.[37] 201–203 °C]. ^{1}H NMR (400 MHz, MeOD) δ (ppm) 7.26 (t, J = 7.5 Hz, 1 H, Ar), 7.40 (t, J = 7.5 Hz, 2 H, Ar), 7.49–7.60 (m, 2 H, Ar + C*H*NH), 7.78 (d, J = 7.5 Hz, 2 H, Ar), 8.35 (d, J = 8.5 Hz, 1 H, Ar), 8.54 (d, J = 3.5 Hz, 1 H, Ar), 9.12 (s, 1 H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$ + 5% MeOD) δ (ppm) 118.4 (*C*H-NH), 124.2 (*C*H), 125.0 (*C*H), 126.6 (*C*), 127.4 (*C*H), 128.7 (*C*H), 131.8 (*C*), 134.0 (*C*H), 139.4 (*C*), 143.7 (*C*), 145.6 (CH), 148.4 (CH); IR υ cm^{-1} 3100, 3056, 2980, 2950, 1660, 1606, 1576, 1484, 1464, 1436, 1148, 1087, 1026, 950, 811, 757, 695; HRMS (ES+) *m/z* 222.1028 (M+H; $C_{14}H_{12}N_3$ requires 222.1031). ^{1}H NMR of **6b**·2HCl (400 MHz, DMSO-d6) δ (ppm) 7.45 (t, J = 7.5 Hz, 1 H), 7.55 (t, J = 7.5 Hz, 2H), 7.81 (dd, J = 8.5 Hz, J = 5.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 2H), 8.29 (s, 1H), 8.75 (d, J = 8.5 Hz, 1H), 8.83 (dd, J = 5.5 Hz, J = 1.5 Hz, 1H), 9.42 (d, J = 1.5 Hz, 1H) identical to that reported in the literature.[38]

2-(Ethylthio)-4(5)-phenyl-1*H*-imidazole (6c)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and 2-ethylisothiourea, hydrobromide (**4g**, 235 mg, 1.27 mmol) as the nucleophile, the product was obtained as a white solid (62 mg, 72% yield). M.p. 130–132 °C [aq. EtOH; lit.[39] 129–130 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (t, J = 7.2 Hz, 3 H, CH_3), 3.04 (q, J = 7.2 Hz, 2 H, CH_2), 7.23–7.29 (m, 1 H, Ph), 7.33–7.42 (m, 3 H, Ph + C*H*-N), 7.70 (d, J = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 15.3 (CH_3), 29.5 (CH_2), 117.6 (*C*H-N), 124.8 (*C*H), 127.1 (*C*H), 128.7 (*C*H), 132.3 (*C*), 139.9 (*C*-N), 140.6 (*N*-*C*-S); IR υ cm^{-1} 3059, 2965, 2925, 2867, 1606, 1495, 1449, 1389, 1261, 1129, 1082, 986, 801, 756, 692; HRMS (ES+) *m/z* 205.0797 (M+H; $C_{11}H_{13}N_2S$ requires 205.0799).

2-Phenyl-5,6,7,8-tetrahydroimidazo[1,2a]pyridine (6d)

Using styrene (**1c**, 0.050 mL, 0.42 mmol) and 2-iminopiperidine hydrochloride (**4h**, 171 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (60 mg, 71% yield). M.p. 93–95 °C [$CHCl_3$; lit[40] 98–100 °C]. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.92–2.04 (m, 4 H, CH_2), 2.94 (t, J = 6.0 Hz, 2 H, CH_2), 3.98 (t, J = 6.0 Hz, 2 H, CH_2N), 7.07 (s, 1 H, C*H*-N), 7.21

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(t, J = 7.5 Hz, 1 H, Ph), 7.35 (t, J = 7.5 Hz, 2 H, Ph), 7.75 (d, J = 7.5 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 21.1 (CH_2), 23.0 (CH_2), 24.6 (CH_2), 44.8 (CH_2N), 113.8 (*C*H-N), 124.6 (*C*H), 126.4 (*C*H), 128.4 (*C*H), 134.4 (*C*), 140.5 (*C*), 145.2 (*N*-*C* = N); IR υ cm^{-1} 2947, 2862, 1604, 1516, 1446, 1425, 1377, 1319, 1193, 1076, 951, 744, 696; HRMS (ES+) m/z 199.1234 (M+H; $C_{13}H_{15}N_2$ requires 199.1235).

3-{4(5)-[(Methoxy)methyl]-5(4)-phenyl-1*H*-imidazol-2-yl}pyridine (6e)

Using (2*E*)-3-phenyl-2-propen-1-yl ether (**1f**, 70 mg, 0.47 mmol) and benzamidine (**4i**, 170 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow oil (87 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.41 (s, 3 H, CH_3), 4.57 (s, 2 H, CH_2), 7.28–7.45 (m, 6 H, Ph), 7.61 (d, J = 7.0 Hz, 2 H, Ph), 7.87 (d, J = 7.0 Hz, 2 H, Ph); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 58.0 (CH_3), 66.0 (CH_2), 125.5 (*C*H), 127.3 (*C*H), 127.4 (*C*H), 128.6 (*C*H), 128.7 (*C*H), 128.8 (*C*H), 129.4 (*C*), 129.6 (*C*), 131.7 (*C*), 135.5 (*C*), 145.9 (N = *C*-N); IR υ cm^{-1} 3059, 2923, 1589, 1494, 1461, 1402, 1189, 1087, 912, 773, 696; HRMS (ES+) m/z 265.1346 (M+H; $C_{17}H_{17}N_2O$ requires 265.1341).

2-Phenylimidazo[1,2-a]pyridine (7a)

Using styrene (**1c**, 50 mg, 0.48 mmol) and 2-aminopyridine (**4j**, 136 mg, 1.44 mmol) as the nucleophile, the product was obtained as a pale yellow solid (64 mg, 69% yield). M.p. 132–134 °C [CH_3CN; lit.[41] 133–133.5 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.78 (t, J = 7.0 Hz, 1 H, *C*H), 7.15–7.22 (m, 1 H, *C*H), 7.33 (t, J = 7.0 Hz, 1 H, Ph), 7.44 (t, J = 7.0 Hz, 2 H, *C*H), 7.66 (d, J = 9.0 Hz, 1 H, *C*H), 7.86 (s, 1 H, *C*H), 7.94–7.98 (m, 2 H, Ph), 8.12 (d, J = 7.0 Hz, 1 H, *C*H); ^{13}C NMR (101 MHz, *C*DCl_3) δ (ppm) 108.1 (*C*H), 112.6 (*C*H), 117.4 (*C*H), 119.5 (*C*), 124.9 (*C*H), 125.6 (*C*H), 126.1 (*C*H), 128.1 (*C*H), 128.7 (*C*H), 133.4 (*C*), 145.5 (*C*); IR υ cm^{-1} 1561, 1476, 1371, 1229, 742, 722; HRMS (ES+) m/z 195.0919 (M+H; $C_{13}H_{11}N_2$ requires 195.0922). NMR data matched that reported in the literature.[42]

2-Phenylimidazo[1,2-a]pyridin-7-amine (7b)

Using styrene (**1c**, 50 mg, 0.48 mmol) and 2,4-diaminopyridine (**4k**, 157 mg, 1.44 mmol) as the nucleophile, the product was obtained as a pale yellow solid (71 mg, 71% yield). M.p. 215 °C [decomp., CH_3CN]; ^{1}H NMR (400 MHz, MeOH-d4) δ (ppm) 6.44 (dd, J = 7.0 Hz, J = 2.0 Hz, 1 H, C*H*), 6.53 (d, J = 2.0 Hz, 1 H, *C*H), 7.25–7.30 (m, 1 H, Ph), 7.35–7.42 (m, 2 H, Ph), 7.75–7.85 (m, 3 H, Ph + *CH*), 8.03 (d, J = 7.0 Hz, 1 H, *C*H); ^{13}C NMR (101 MHz, MeOH-*d4*) 93.7 (*C*H), 108.1 (*C*H), 108.4 (*C*H), 126.8 (*C*H), 127.9 (*C*H), 128.65 (*C*H), 129.8 (*C*H), 135.4 (*C*H), 145.0 (*C*H), 149.2 (*C*), 149.9 (*C*); IR υ cm^{-1} 3380, 3204, 1657, 1484, 1373, 1227, 710; HRMS (ES+) m/z 210.1029 (M+H; $C_{13}H_{12}N_3$ requires 210.1031).

6-Bromo-2-phenylimidazo[1,2-a]pyridine (7c)

Using styrene (**1c**, 50 mg, 0.48 mmol) and 5-bromo-2-aminopyridine (**4l**, 249 mg, 1.44 mmol) as the nucleophile, the product was obtained as a pale yellow solid (72 mg, 55% yield). M.p. 193–196 °C [CH_3CN]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24 (dd, J = 9.5 Hz, J = 2.0 Hz, 1 H, *C*H), 7.33–7.38 (m, 1 H, Ph), 7.42–7.48 (m, 2 H, Ph), 7.54 (d, J = 9.5 Hz, 1 H, *C*H), 7.84 (br. s, 1 H, *C*H-N), 7.92–7.96 (m, 2 H, Ph), 8.28 (dd, J = 2.0 Hz, J = 1.0 Hz, 1 H, *C*H); ^{13}C NMR (101 MHz, $CDCl_3$) 107.0 (*C*), 108.3 (*C*H), 118.1 (*C*H), 125.5 (*C*H), 126.1 (*C*H), 128.1 (*C*H), 128.3 (*C*H), 128.8 (*C*H), 133.2 (*C*), 144.1 (*C*), 146.7 (*C*); IR υ cm^{-1} 1565, 1481, 1380, 1230, 808, 774, 718, 689; HRMS (ES+) m/z 273.0030 (M+H; $C_{13}H_{10}N_2Br$ requires 273.0027).

General procedure C

To a solution of IBX (2 eqv., 45% stabilized with benzoic and isophthalic acids) and iodine (1.1 mmol) in dry dimethyl sulfoxide (0.25 M) stirred at room temperature was added the corresponding alkene (1 eqv.) in one charge. The reaction mixture was stirred at room temperature until full consumption of the starting alkene (monitored by LCMS). Then it was diluted with DCM (30 mL for ~0.5 mmol scale) and washed with saturated aqueous $NaHCO_3$–$Na_2S_2O_3$. The aqueous layer was extracted with DCM (2 × 20 mL for ~0.5 mmol scale); the combined organic layers were dried over Na_2SO_4 and filtered. The corresponding nucleophile (3 eqv.) and dry *N*,*N*-dimethylformamide (0.15 M) were added to the DCM solution and the volume was reduced down to ~2 mL (for ~0.5 mmol scale) under vacuum. The reaction mixture was stirred at room temperature for 15 min and then at 80 °C for 2 h. The corresponding product was isolated by MDAP using gradient CH_3CN–H_2O solvent mixture unless otherwise stated.

N-(3-Isopropyl-4-(o-tolyl)thiazol-2(3H)-ylidene)propan-2-amine (8a)

Using 1-methyl-2-vinylbenzene (**1k**, 50 mg, 0.42 mmol) and 1,3-diisopropylthiourea (**4m**, 203 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (68 mg, 59% yield). M.p. 65–67 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.15–1.22 (m, 6 H, CH_3), 1.28 (d, J = 7.0 Hz, 3 H, CH_3), 1.46 (d, J = 7.0 Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3Ar), 3.06 (sept, J = 7.0 Hz, 1 H, *C*H), 3.73 (sept, J = 7.0 Hz, 1 H, *C*H), 5.50 (s, 1 H, *C*H), 7.18–7.35 (m, 4 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 18.7 (CH_3), 19.5 (CH_3), 19.8 (CH_3), 23.5 (CH_3), 23.5 (CH_3), 49.7 (*C*H-N), 56.6 (*C*H-N), 93.5 (*C*H), 125.6 (*C*H), 129.0 (*C*H), 130.1 (*C*H), 130.5 (*C*H), 133.1 (*C*), 138.1 (*C*), 139.5 (*C*), 154.2 (*C*); IR υ cm^{-1} 2965, 2928, 1622, 1377, 1338, 1251, 760, 693; HRMS (ES+) m/z 275.1573 (M+H; $C_{16}H_{23}N_2S$ requires 275.1582).

4-Fluoro-*N*-(3-methyl-4-(o-tolyl)thiazol-2(3H)-ylidene)aniline (8b)

Using 1-methyl-2-vinylbenzene (**1k**, 50 mg, 0.42 mmol) and 1-(4-fluorophenyl)-3-methylthiourea (**4n**, 234 mg, 1.27 mmol) as the nucleophile, the product was obtained as a pale yellow solid (79 mg, 63% yield). M.p. 104–106 °C [$CHCl_3$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.27 (s, 3 H, CH_3C), 3.13 (s, 3 H, CH_3N), 5.71 (s, 1 H, CH), 7.00–7.10 (m, 4 H, Ar), 7.20–7.40 (m, 4 H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) 19.6 (CH_3C), 32.1 (CH_3N), 94.6 (*C*H), 116.0 (d, J = 22.0 Hz, *C*H), 122.0 (d, J = 8.0 Hz, *C*H), 126.1 (*C*H), 129.6 (*C*H), 130.3 (*C*H), 130.4 (*C*H), 131.1 (*C*), 137.8 (*C*), 139.3 (*C*), 147.8 (d, J = 2.5 Hz, *C*), 157.4 (d, J = 241.0 Hz, *C*), 160.3 (d, J = 1.5 Hz, *C*); IR υ cm^{-1} 2917, 1601, 1578, 1500, 1363, 1204, 837, 766, 743; HRMS (ES+) m/z 299.1018 (M+H; $C_{17}H_{16}N_2F_S$ requires 299.1018).

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4,6-Bis(methoxy)-2-phenyl-1*H*-indole (9)

Using styrene (**1c**, 50 mg, 0.42 mmol) and 3.5-bis(methoxy)aniline (**4o**, 234 mg, 1.27 mmol) as the nucleophile, the product was obtained as a greenish oil (67 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.87 (s, 3 H, CH_3O), 3.95 (s, 3 H, CH_3O), 6.25 (s, 1 H, CO-*CH*-CO), 6.53 (s, 1 H, CO-*CH*-CN), 6.87 (s, 1 H, C*H* = C-NH), 7.24–7.32 (m, 1 H, Ph), 7.42 (t, J = 7.5 Hz, 2 H, Ph), 7.61 (d, J = 7.5 Hz, 2 H, Ph), 8.26 (br. s, 1 H, NH); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 55.4 (CH_3), 55.7 (CH_3), 86.7 (CO-*CH*-CN), 91.9 (CO-*CH*-CO), 97.1 (*CH*=C–NH), 114.5 (CO-*C*-C-NH), 124.4 (Ph, *C*H), 127.0 (Ph, *C*H), 129.0 (Ph, *C*H), 132.5 (Ph, *C*), 135.1 (*C*N), 138.1 (*C*-N), 153.7 (*C*-O), 157.8 (*C*-O); IR υ cm^{-1} 3419, 2935, 2838, 1624, 1600, 1511, 1453, 1373, 1345, 1277, 1216, 1199, 1148, 1127, 1043, 803, 761, 738, 692; HRMS (ES+) m/z 254.1171 (M+H; $C_{16}H_{16}NO_2$ requires 254.1181). ^{1}H NMR data was identical to that reported in the literature.[43]

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