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Nickel–palladium-catalyzed hydroamination/cyclization of sulfur-substituted 1,6-diynes with secondary amines

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ABSTRACT

Hydroamination/cyclizations of sulfur-substituted 1,6-diynes catalyzed by nickel or nickel–palladium in DMSO were examined. Pyrroles **2a**–**l** and furans **5a**–**i** bearing various secondary amines were obtained in high yields. The organosulfanylmethyl group on pyrroles was easily oxidized with ceric ammonium nitrate to produce the pyrrolecarboxaldehyde and corresponding acetal.

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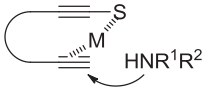
1. Introduction

Hydroamination (HA) of alkynes, defined as a simple and atom-economical process leading to enamines and imines, has been usually applied to the intramolecular cyclizations for the syntheses of a wide variety of nitrogen containing heterocycles such as pyrrolidines, pyrazoles, indoles, isoindoles, and imidazoles scaffolds.[1] Recently, considerable attention has been paid to HA-triggered cyclizations of alkynes for the synthesis of heterocyclic skeletons of greater structural complexity in a variety of biologically active natural products.[2] General and convenient methods for HA/cyclization processes consist of two common important strategies: i, activation of alkynes using transition metals[3–13] as well as lanthanides;[14–16] ii, nucleophilic attack of the intramolecular nitrogen atom, where, the possibility of successful construction of heterocycles is attributed to the nucleophilicity of nitrogen. Recently we investigated metal-free and metal-catalyzed cyclizations of sulfanyl 1,6-diynes triggered by some useful functionalization. Our concept is one of the useful approaches for the synthesis of heterocycles from 1,6-diynes bearing organosulfur substituents, which could activate their alkynes by their strong electron-donating effect. We previously reported that the alkoxylation- and aryloxylation-triggered cyclizations of oxygen-tethered 1,6-diynes afforded alkoxymethyl- and aryloxymethyl-furans and anti-cancer tanshinone derivatives.[17] Furthermore, the organosulfur functional group on the 1,6-diynes could be coordinated with some transition metals.[18] Therefore, the transition metal-catalyzed functionalization-cyclizations of the sulfanyl 1,6-diynes are expected to proceed with high regioselectivities. During the course of our study on the functionalization-cyclizations, we explored the HA-triggered cyclizations of 1,6-diynes, as shown in Fig. 1. To date, the only example of amine functionalization-cyclizations of 1,6-diynes is cobalt-mediated reactions using carboxamides,[19] which have very low nucleophilicities. However, the development the clinical drugs requires the preparation of heterocycles bearing a wide variety of highly nucleophilic amines, rather than amides (Fig. 2). A metal-free or metal-catalyzed amine functionalization-cyclization of 1,6-diynes leading to the amine-functionalized heterocycles will be an important tool in drug-discovery processes.

Here we report the first catalytic HA/cyclization of 1,6-diynes leading to functionalized heterocycles as shown in Eq. 1. Furthermore, we demonstrate that the organosulfanylmethyl group on the



Amine functionalization-cyclizations (This work)

Fig. 1. Intermolecular hydroaminations/cyclizations.

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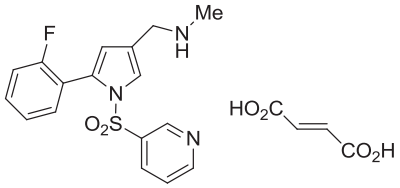
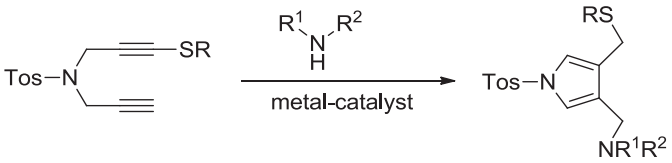


Fig. 2. Representative aminomethylpyrrole, TAK-438.

heterocycles is successively transformed to the formyl group, which is potentially useful for further transformations.



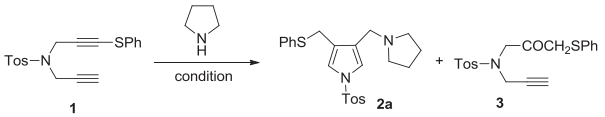
2. Results and discussion

First, we screened the suitable reaction condition for HA/cyclization of a simple *N*-tosyl 1,6-diyne **1**, which were simply prepared by Mitsunobu reaction from *N*-tosylpropyne and phenylsulfanylpropargyl alcohol, using pyrrolidine. We attempted the metal-free amination/cyclization of **1**; however, the reaction did not proceed. According to our alkynylation condition of 1,6-diynes, we examined the Cu(I)-catalyzed reactions and obtained the 4-pyrrolidinylmethylpyrrole **2a** in low yields (entry 1). Next, we performed the copper-catalyzed amination/cyclizations under the similar conditions. The results were not satisfied (entries 2 and 3), however, we continued to perform the HA/cyclizations catalyzed by transition metals such as palladium, nickel, and other lanthanides. Lanthanide metals were not effective. Nickel and palladium dramatically improved the yields of **2a** (entries 4 and 5), however, ynone **3** was obtained as a side product.

We attempted the palladium-catalyzed HA/cyclizations in the presence of some ligands and bases, however, the yields of the products did not dramatically change (entries 5 and 6). Then, we next performed the nickel-catalyzed amination/cyclizations as shown in entries 7–22. The inert ligands like chloride, triflate and diphenylphophinoethane (dppe), diethyl dithiocarbamate (dedt) were not effective (entries 7–9, 12). The reaction of **1** in DMSO/H_2O gave rise to increasing the yield of **3** (entry 10). The molecular sieves (MS) were not effective for the formation of **2a** (entry 11). The reaction using Ni(0), nickelocene, of which reactions would usually provide the nickellacycle intermediates, also afforded the pyrrolidinylmethyl **2a** in moderate yield (entry 13). DBU also accelerated the HA/cyclization reaction at room temperature (entry 14). Bis(hexafluoroacetylacetonato)nickel mono hydrate in DMSO was found to give superior results by comparing the examinations of both the solvent effects and the additives (entries 15–20). When the nickel-catalyzed HA/cyclizations were examined, the diyne **1** was not disappeared in the reaction mixture (entries 20 and 22). Since the reaction under the nickel–palladium mixed catalyst condition was complete without the formations of any side products (entry 21), we selected the suitable reaction condition (method B): Ni(hfa)$_2$ (0.1 equiv)/Pd(PPh$_3$)$_2$Cl$_2$ (0.1 equiv), DBU (1 equiv) in DMSO. We next performed amination/cyclizations using various amines. The results are shown in Table 2.

For a series of cyclic amines, two kinds of experiments were performed to investigate HA/cyclizations of 1,6-diynes **1**. The reaction with piperidine using Ni-catalyst at room temperature gave 4-(1-piperidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole **2b** in 79% yield (entry 1) (method A). The Ni/Pd-catalyzed reaction quantitatively afforded

Table 1
Screening for HA of 1,6-diyne **1** with pyrrolidine



Entry	Condition: catalyst (mol %), amine (equiv), solv, time	Yield[a] (%)	
		2a	**3**
1	CuOTf (10), DBU (1.5), DMF, rt, 0.5 h	32	0
2	CuI (3), DBU (1), DMF/H_2O, 0 °C, 1 h	19	0
3	CuBr SMe$_2$, DBU (1.5), DMSO, rt, 0.5 h	36	0
4	NiCl$_2$(PPh$_3$)$_2$ (10), DMSO, rt, 3 h	70	16
5	PdCl$_2$(PPh$_3$)$_2$ (10), DMSO, rt, 4 h	55	16
6	PdCl$_2$(PPh$_3$)$_2$ (10), DBU (1), DMSO, rt, 4 h	59	5
7	NiCl$_2$ (10), DMSO, rt, 2.5 h	64	15
8	Ni(OTf)$_2$ (10), DMSO, rt, 2 h	57	10
9	NiCl$_2$(dppe) (10), DMSO, rt, 1.5 h[b]	64	16
10	NiCl$_2$(dppe) (10), DMSO/H_2O, TBA,[c] rt, 4 h	39	19
11	NiCl$_2$(dppe) (10), MS,[d] DMSO, rt, 3.5 h	59	13
12	Ni(dedt) (10), DMSO, rt, 2 h[e]	62	15
13	Nickelocene (10), DMSO, rt, 2 h	52	23
14	NiCl$_2$(PPh$_3$)$_2$ (10), DMSO, DBU (1), rt, 1 h	88[f]	0
15	NiCl$_2$(PPh$_3$)$_2$ (10), THF, rt, 4 h	15[f]	8
16	Ni(hfa)$_2$ (10), DMSO, rt, 3.5 h[g]	78	9
17	Ni(hfa)$_2$ (10),[g] MeNO$_2$, rt, 3 h	18[f]	11
18	Ni(hfa)$_2$ (10), DMSO, rt, 1.2 h	72	13
19	Ni(hfa)$_2$ (10), DMF, rt, 2.5 h	60	19
20	Ni(hfa)$_2$ (10),[g] DBU (1), DMSO, rt, 4 h	89[f]	
21	Ni(hfa)$_2$ (10),[g] PdCl$_2$(PPh$_3$)$_2$ (10), DBU (1), DMSO, rt, 4 h	Quant.	0
22	Ni(hfa)$_2$ (10),[g] PPh$_3$ (10), DBU (1), DMSO, rt, 4 h	91[f]	

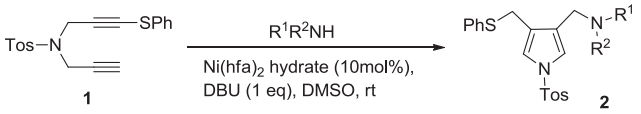
[a] Yield of isolated product.
[b] dppe: diphenylphosphinoethane.
[c] Tetrabutylammonium hydrogensulfate (0.2 equiv) was added.
[d] MS: molecular sieves.
[e] dedt: diethyl dithiocarbamate. Ni(dedt) were used as mono hydrate.
[f] The diyne **1** was recovered in 8% (entry 14), 70% (entry 16), 70% (entry 17), 4% (entry 20) and 3% (entry 22) yields.
[g] hfa: hexafluoroacetylacetone. Ni(hfa)$_2$ was used as mono hydrate.

2b (entry 2) (method B). A similar tendency was observed in the reactions with morpholine and *N*-methylpiperadine (entries 3–6). As shown in the entries 7 and 8, piperadine bearing further functionalized amines provided the aminomethylated product **2e**; however, the reaction with thiazolidine gave a ring-opening product **2f** in low yield (entry 9). Next we performed aminations using the linear amines and obtained diethylaminomethyl-, hydroxyethylmethylaminomethyl-, and 2-(*N*,*N*-dimethylamino) ethylmethylaminomethylpyrrole presented as **2g**, **2h**, and **2i**, respectively (entries 10–14). N-containing heterocycles also afforded the hetarylmethylpyrroles **2j**–**2l** in moderate-to-good yields (entries 15–20).

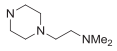
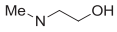
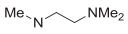
We also examined the HA/cyclizations of 3-aryl-4-oxahepta-1,6-diynes **4**, which were easily prepared by our usual method[20] from sulfur-substituted propargyl alcohol and prop-2-yn-1-ol, using the similar cyclic amines. The results are shown in Table 3. The cyclizations of 4-oxahepta-1,6-diynes provided 2-aryl-4-aminomethylfurans **5a**–**i** in good yields. Piperidinylmethyl-, 4-methylpiperadinylmethyl, benzimidazolylmethyl, and 3-oxo-1,4-benzthiazin-4-ylmethyl 2-arylfuran presented as **5a**–**d**, respectively, are shown in entries 1–4. 2-*p*-Bromophenyl- and *p*-chlorophenyl, and 1-naphthyl-1,6-diynes also afforded furans **4e**–**i** (entries 5–9).

Although the details of the mechanism of this HA/cyclization reaction are not completely understood, a speculative pathway is shown in Scheme 1. According to our previous reports,[17a,b] the sulfanyl 1,6-diynes isomerized to the alkyne–allene **8** or allene–allene intermediates **9** via a carbanion **7**. The nickel catalyst binds to give the sulfur-coordinated intermediate **10**, which would activate the alkyne toward intermolecular attack by the amine, and

Table 2
HA/cyclization of 1,6-diyne **1**

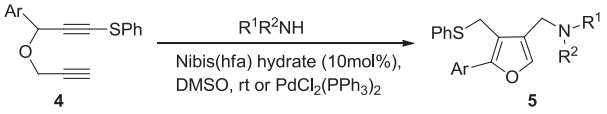


1 2

Entry	NR^1R^2	Method A or B,[a,b] reaction time (h)	Yield of **2**[c] (%)
1		A, 4 h	**2b** (79)
2		B, 8 h	**2b** (quant.)
3		A, 6 h	**2c** (77)
4		B, 8 h	**2c** (88)
5		A, 8 h	**2d** (75)
6		B, 8 h	**2d** (quant.)
7		A, 8 h	**2e** (50)
8		B, 8 h	**2e** (76)
9		B, 8 h	**2f** (43)
10	Et_2N	A, 8 h	**2g** (49)
11		B, 8 h	**2g** (82)
12		A, 8 h	**2h** (71)
13		B, 72 h	**2h** (84)
14		B, 72 h	**2i** (66)
15		A, 4 h	**2j** (70)
16		B, 4 h	**2j** (43)
17		A, 7 h	**2k** (74)
18		B, 1 h	**2k** (92)
19		A, 4 h	**2l** (48)
20		B, 2 h	**2l** (53)

[a] Method A: $Ni(hfa)_2$ hydrate (10 mol %), amine (2–5 equiv), and DBU (1 equiv) were added to the substrate in DMSO at rt.
[b] Method B: $Ni(hfa)_2$ hydrate (10 mol %), bis(triphenylphosphinie)palladium dichloride (0.1 equiv), DBU (1 equiv), and amine (2–5 equiv) were added to the substrate in DMSO at rt.
[c] Yield of isolated product.

Table 3
HA/cyclization of aryl-1,6-diyne **4**



4 5

Entry	Ar	R^1R^2N	Method A or B,[b,c] Time (h)	Yield[a] of **5** (%)
1	p-$MeOC_6H_4$		A, 6 h	**5a** (63)
2	p-$MeOC_6H_4$		A, 8 h	**5b** (71)
3	p-$MeOC_6H_4$		B, 8 h	**5c** (71)
4	p-$MeOC_6H_4$		B, 8 h	**5d** (70)
5	4-BrC_6H_4		B, 8 h	**5e** (61)
6	4-BrC_6H_4		B, 72 h	**5f** (39)[d]
7	4-ClC_6H_4		B, 72 h	**5g** (61)
8	4-ClC_6H_4		A, 4 h	**5h** (65)
9	1-Naphthyl		B, 1 h	**5i** (69)

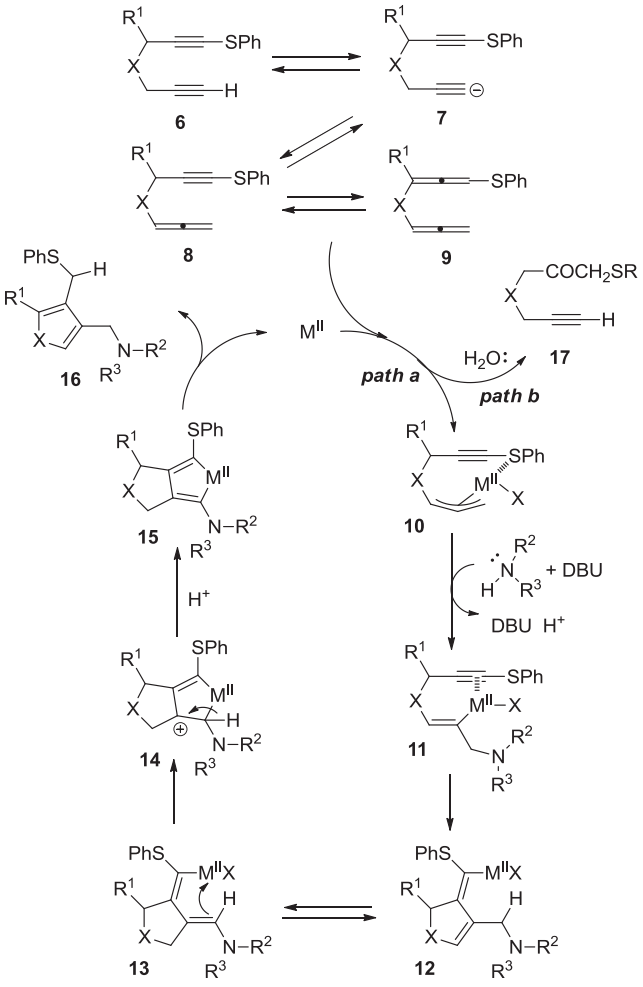
[a] Yield of isolated product.
[b] Method A: $Ni(hfa)_2$ hydrate (10 mol %), amine (2–5 equiv), and DBU (1 equiv) were added to the substrate in DMSO at rt.
[c] Method B: $Ni(hfa)_2$ hydrate (10 mol %), bis(triphenylphosphinie)palladium dichloride (10 mol %), DBU (1 equiv), and amine (2–5 equiv) were added to the substrate in DMSO at rt.
[d] Another isomer was obtained, however, it could not be isolated.

generating dienamino metal intermediate **13** through the 5-*exo*-cyclization of **11** and the subsequent isomerization of **12** (path a).[21] Then, the second intramolecular cyclization of **13** would proceed to produce a metalacycles **15** after the β-elimination of cationic intermediate **14**. Protonolysis and isomerization of **15** afford product **16** along with metal(II). When the amines are less nucleophilic, H_2O molecules attack the sulfur-substituted alkynyl carbon to yield a side product **17** via path b. Because the reaction of 4-methyl-*N*-[3-phenyl-2-propyn-1-yl]-*N*-2-propyn-1-ylbenzenesulfonamide (which bears no-sulfanyl group) with pyrrolidine yielded a complex mixture rather than a product such as **16**, it appears that the organosulfanyl group is highly effective for the selective formation and reaction of the key intermediate **10**.

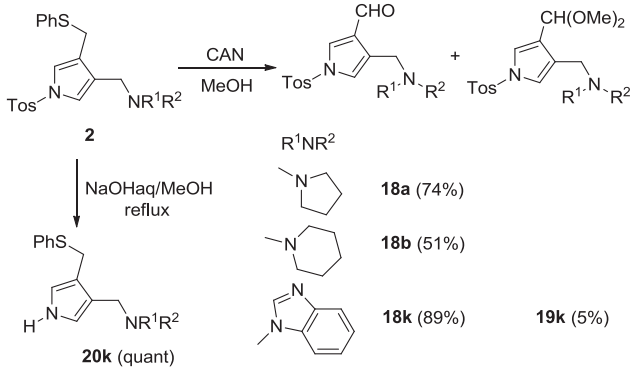
As we found a process that proved to be the most powerful tool for the direct synthesis of aminomethylpyrroles and aminomethylfurans through nickel or nickel–palladium–catalyzed HA–cyclizations of 1,6-diynes, which can be used to access compounds like TAK-438, we attempted the unique transformation of the 3-organosulfanylmethyl-4-aminomethylpyrroles **2** to other useful compounds (Scheme 2). Then we found the excellent transformation of the organosulfanylmethyl functional group of pyrrole **2** easily changed to the formyl and/or acetal moiety **18a**,**b**,**k** and **19k** by oxidations of the representative pyrroles with ceric ammonium nitrate (CAN). These results show that the organosulfanyl group would activate 1,6-diynes in the HA/cyclization. Then, the organosulfanylmethyl group of the product, pyrroles and furans, could easily be converted to the formyl group, which could explore further transformations. The reaction of **2k** with NaOH/MeOH underwent desulfonylation of pyrrole to give 1*H*-pyrrole **20k**, exclusively.[22]

3. Conclusion

In summary, we have discovered a powerful tool for synthesizing 3- or 4-aminomethylpyrroles and aminomethylfurans through nickel- or nickel–palladium-catalyzed HA/cyclizations of nitrogen- or oxygen-tethered 1,6-diynes bearing a sulfur substituent. The methodology is considered to be useful for drug-discovery processes because a wide variety of secondary amines



Scheme 1. Speculative mechanism for HA/cyclization of **6**.



Scheme 2. Transformation of aminomethylpyrroles **2**.

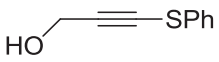
are applicable to this HA/cyclization process. While currently limited to sulfur-substituted 1,6-diynes, it would be solved by elucidating oxidation with CAN to produce pyrrolecarboxaldehydes, which could be utilized for further transformations.

4. Experimental section

4.1. General

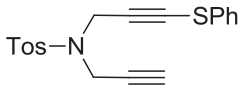
Melting points were determined on a J-Science Lab. Micro melting point apparatus and uncorrected. Elemental analyses were performed at the Center of Instrumentation of Gifu University. ^{1}H and ^{13}C NMR spectra were determined with JEOL ECA600 (600 MHz) spectrometer at Gifu University. Chemical shifts are expressed in parts per million (ppm) with respect to tetramethylsilane as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet. IR spectra were determined on a JASCO FT-IR 460-Plus infrared spectrometer and are expressed in reciprocal centimeters. EI mass spectra (MS) were obtained using JEOL MS-700 spectrometer with direct-insertion probe at 70 eV. All high-resolution mass determinations were obtained on the JMSD300 JMS 2000 on line system. *O*-Tetrahydropyranyl propargyl alcohol,[23] phenylsulfanyl chloride,[24] and the phenylsulfanyl 4-oxahepta-1,6-diynes **3a**–**j** were prepared according to the previous report.[20] *N*-Propargyl *p*-toluenesulfonamide was prepared according to the almost same method for the previous report.[25]

4.2. Preparation of 3-(phenylsulfanyl)prop-2-yn-1-ol



To a THF (100 mL) solution of *O*-tetrahydropyranylpropargyl alcohol[23] (20.0 g, 0.14 mol) was added *n*-butyllithium (2.6 M, 53.8 mL, 0.14 mol) at 0 °C under an Ar atmosphere. After stirring for 10 min, phenylsulfanyl chloride[24] (20.2 g, 0.14 mol) in THF (30.0 mL) was added dropwise to the mixture. The whole was stirred for 0.5 h and poured into water (500 mL). The organic layer was separated and the aqueous layer was extracted with ether (100 mL×2). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was used for the deprotection of tetrahydropyranyl group without further purification. To a mixed solution of both isopropyl alcohol (140 mL) and diethyl ether (35 mL) of the residue was added *p*-toluenesulfonic acid (1.30 g, 7.00 mol) at room temperature. The reaction mixture was stirred for 12 h. A small amount of triethylamine (0.8 ml) was added to the mixture. The solvent was removed under reduced pressure. The residue was poured into water (300 mL). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with AcOEt/*n*-hexane (1:10 to 1:5) to give the title compound[26] (15.2 g, 66%) as a pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (1H, br s, OH), 4.47 (2H, s, CH_2), 7.20–7.22 (1H, m, ArH), 7.31–7.33 (2H, m, ArH), 7.42 (2H, d, J=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.7 (t), 72.8 (s), 97.3 (s), 126.3 (d×2), 126.6 (d), 129.2 (d×2), 132.2 (s).

4.3. Preparation of 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-2-propyn-1-ylbenzenesulfonamide (1)

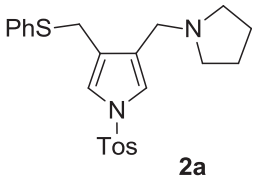


1

Diethyl azodicarboxylate (2.80 ml, 6.09 mmol) was added dropwise to a THF (8.0 mL) solution of 4-methyl-*N*-2-propyn-1-ylbenzensulfonamide (1.2 g, 6.09 mmol), 3-(phenylthio)prop-2-yn-1-ol (1.0 g, 6.09 mmol) and triphenyl phosphine (1.6 g, 6.09 mmol) under an Ar atmosphere. The reaction mixture was stirred for 45 min at room temperature. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with AcOEt/*n*-hexane (1:40 then 1:20) to give 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-2-propyn-1-ylbenzenesulfonamide (**1**) (1.82 g, 85%) as white powders.

Mp 38–42 °C; IR (KBr, cm^{-1}) 3437, 3291, 3061, 2923, 2189, 1598, 1583, 1479, 1442, 1352, 1165, 1094, 893, 815, 743, 666, 580, 558, 541; ^1H NMR (600 MHz, $CDCl_3$) δ 2.20 (1H, t, J=2.1 Hz, acetylenic H), 2.35 (3H, s, Me), 4.16–4.17 (2H, d, J=2.7 Hz, CH_2), 4.43 (2H, s, CH_2), 7.23–7.33 (7H, m, ArH), 7.70–7.71 (2H, d, J=9.0 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 36.5 (t), 37.7 (t), 73.0 (s), 74.2 (s), 76.2 (d), 91.2 (s), 126.2 (d×2), 126.7 (d), 127.8 (d×2), 129.2 (d×2), 129.6 (d×2), 131.9 (s), 134.9 (s), 144.1 (s); MS (70 eV): m/z: 355 (M^+), 200 (M^+–Tos); elemental analysis calcd (%) for $C_{19}H_{17}NO_2S_2$: C, 64.20; H, 4.82; N, 3.94. Found: C, 64.50; H, 4.89; N, 3.90.

4.4. Synthesis of 4-(1-pyrrolidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2a), typical Procedure for Ni–Pd-catalyzed amination/cyclizations (method B)



2a

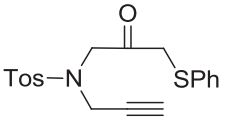
Bis(hexafluoroacetylacetonato)nickel(II) hydrate (66.5 mg, 0.14 mmol), bis(triphenylphosphine)palladium(II) dichloride (98.7 mg, 0.14 mmol), and DBU (0.21 g, 1.40 mmol) were added to a DMSO (5.0 ml) solution of 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-2-propyn-1-ylbenzenesulfonamide (**1**) (0.50 g, 1.41 mmol), pyrrolidine (0.50 g, 7.03 mmol) at room temperature. The mixture was stirred for 1 h and then poured into water (50 ml). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was washed with water and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with $CHCl_3$/MeOH (10:1) to give 4-(1-pyrrolidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (**2a**) (0.60 g, quant.) as a yellow oil.

4.5. Synthesis of 4-(1-pyrrolidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole, typical procedure for Ni-catalyzed HA/cyclizations (method A, Table 1, entry 20)

Bis(hexafluoroacetylacetonato)nickel(II) hydrate (6.7 mg, 0.0141 mmol) was added to a DMSO (0.50 mL) solution of 4-methyl-*N*-[3-(phenylthio)-2-propyn-1-yl]-*N*-2-propyn-1-ylbenzene-sulfonamide (**1**) (50 mg, 0.14 mmol), pyrrolidine (50 mg, 0.70 mmol), and DBU (21 mg, 0.14 mmol) at room temperature. The mixture was stirred for 4 h and poured into water (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with AcOEt/*n*-hexane (1:2) to give 4-(1-pyrrolidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (**2a**) (53 mg, 89%) as a yellow oil.

IR (KBr, cm^{-1}) 3428, 3133, 3059, 2959, 2926, 2795, 1661, 1542, 1371, 1298, 1255, 1191, 1173, 1146, 1092, 1067, 969, 946, 877, 792, 742, 674, 662, 586, 540; ^1H NMR (600 MHz, $CDCl_3$) δ 1.74 (4H, br s, CH_2×2), 2.40 (3H, s, Me), 2.45 (4H, br s, CH_2×2), 3.47 (2H, s, NCH_2), 3.96 (2H, s, SCH_2), 6.89 (1H, br s, ArH), 6.98 (1H, br s, ArH), 7.14–7.19 (3H, m, ArH), 7.22–7.26 (4H, m, ArH), 7.59–7.61 (2H, d, J=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 23.5 (t×2), 29.4 (t), 50.9 (t), 54.2 (t×2), 119.2 (d), 119.6 (d), 124.3 (s), 126.2 (d), 126.3 (s), 126.7 (d×2), 128.7 (d×2), 129.8 (d×2), 130.1 (d×2), 136.0 (s), 144.6 (s); MS (70 eV): m/z: 426 (M^+), 355 (M^+–C_4H_8N), 271 (M^+–Tos); elemental analysis calcd (%) for $C_{23}H_{26}N_2O_2S_2$: C, 64.76; H, 6.14; N, 6.57. Found: C, 64.71; H, 6.38; N, 6.28.

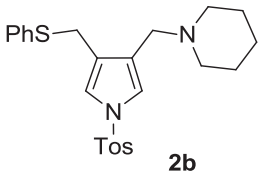
4.5.1. 3-[N-(Prop-2-ynyl)-N-(4-methylphenylsulfonyl)amino]-1-(phenylsulfanyl)propan-2-one (3).



3

Yield 9%, a yellow oil; IR (KBr, cm^{-1}) 3282, 2923, 2121, 1729, 1598, 1482, 1440, 1403, 1349, 1261, 1162, 1092, 1060, 912, 815, 743, 691, 663, 580, 547; ^1H NMR (600 MHz, $CDCl_3$): δ 1.59 (1H, br s, acetylenic H), 2.42 (3H, s, Me), 3.81 (2H, s, CH_2), 4.14 (2H, d, J=2.1 Hz, CH_2), 4.21 (2H, s, CH_2), 7.23–7.32 (5H, m, ArH), 7.37 (2H, d, J=6.9 Hz, ArH), 7.66 (2H, d, J=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 38.1 (t), 41.2 (t), 53.3 (t), 74.5 (d), 76.2 (s), 127.3 (d), 127.7 (d×2), 129.2 (d×2), 129.7 (d×2), 130.1 (d×2), 133.9 (s), 135.1 (s), 144.1 (s), 200.0 (s); MS (70 eV): m/z: 373 (M^+), 264 (M^+–SPh). High-resolution mass calcd for $C_{19}H_{19}NO_3S_2$: 373.0806, found m/z 373.0837.

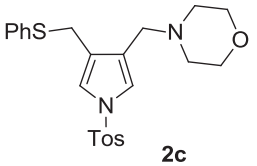
4.6. 4-(1-Piperidinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2b) (Table 2, entries 1 and 2)



2b

Yield quant, a yellow oil; IR (KBr, cm^{-1}) 3135, 3058, 2929, 2856, 2796, 2761, 1596, 1519, 1481, 1440, 1371, 1300, 1255, 1188, 1173, 1093, 1065, 1039, 993, 966, 861, 813; ^1H NMR (600 MHz, $CDCl_3$) δ 1.39 (2H, br s, CH_2), 1.50–1.52 (4H, m, CH_2), 2.28 (4H, br s, CH_2), 2.39 (3H, s, Me), 3.28 (2H, s, NCH_2), 4.01 (2H, s, SCH_2), 6.90 (1H, br s, ArH), 6.93 (1H, br s, ArH), 7.13–7.25 (7H, m, ArH), 7.59–7.60 (2H, d, J=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 24.4 (t), 26.0 (t×2), 29.4 (t), 54.3 (t), 54.4 (t×2), 119.7 (d), 119.8 (d), 124.9 (s), 125.5 (s), 126.1 (d), 126.6 (d×2), 128.6 (d×2), 129.7 (d×2), 129.8 (d×2), 136.0 (s), 136.2 (s), 144.6 (s); MS (70 eV): m/z: 440 (M^+), 355 (M^+–$C_5H_{10}N$), 285 (M^+–Tos); elemental analysis calcd (%) for $C_{24}H_{28}N_2O_2S_2$: C, 65.42; H, 6.41; N, 6.36. Found: C, 65.23; H, 6.39; N, 6.18.

4.7. 4-(4-Morpholinylmethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2c) (entries 3 and 4)

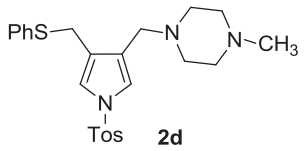


2c

Yield 88%, a yellow oil; IR (KBr, cm^{-1}) 2925, 2853, 2809, 1596, 1518, 1481, 1453, 1371, 1303, 1171, 1118, 1092, 1062, 1005, 865, 809, 747, 670, 585, 540, 428; ^1H NMR (600 MHz, $CDCl_3$) δ 2.34 (4H, br s, CH_2), 2.40 (3H, s, Me), 3.33 (2H, s, NCH_2), 3.63–3.64 (4H, m, CH_2), 4.00 (2H, s, SCH_2), 6.90 (1H, br s, ArH), 6.95 (1H, br s, ArH), 7.14–7.20 (2H, m, ArH), 7.21–7.26 (5H, m, ArH), 7.60–7.61 (2H, d, J=9.0 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.6 (t), 53.5 (t×2), 54.0 (t), 67.0 (t×2), 119.9 (d×2), 124.4 (s), 124.6(s), 126.3 (d),

126.7 (d×2), 128.7 (d×2), 129.8 (d×2), 130.0 (d×2), 135.9 (s), 136.1 (s), 144.7 (s); MS (70 eV): *m/z*: 442 (M^+), 355 ($M^+-C_4H_8ON$), 333 (M^+–SPh), 287 (M^+–Tos); elemental analysis calcd (%) for $C_{23}H_{26}N_2O_3S_2$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.16; H, 5.91; N, 6.21.

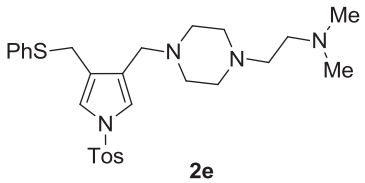
4.8. 4-[(4-Methyl-1-piperazinyl)methyl]-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2d) (entries 5 and 6)



2d

Yield quant, a yellow oil; IR (KBr, cm^{-1}) 3131, 3058, 2933, 2796, 1737, 1596, 1519, 1480, 1456, 1370, 1301, 1172, 1092, 1065, 1011, 967, 925, 881, 813, 741, 703, 673, 588, 540; ^1H NMR (600 MHz, $CDCl_3$) δ 2.25 (3H, s, Me), 2.37 (8H, br s, NCH_2), 2.40 (3H, s, NMe), 3.33 (2H, s, NCH_2), 4.00 (2H, s, SCH_2), 6.90 (1H, d, *J*=2.8 Hz, ArH), 6.94 (1H, d, *J*=2.8 Hz, ArH), 7.14–7.19 (3H, m, ArH), 7.21–7.27 (4H, m, ArH), 7.59–7.61 (2H, d, *J*=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (q), 29.5 (t), 45.9 (q), 52.9 (t×2), 53.5 (t), 55.1 (t×2), 119.8 (d×2), 124.7 (s), 125.0 (s), 126.1 (d), 126.6 (d×2), 128.6 (d×2), 129.8 (d×2), 129.9 (d×2), 135.9 (s), 136.1 (s), 144.6 (s); MS (70 eV): *m/z*: 455 (M^+), 355 ($M^+-C_5H_{11}N_2$), 300 (M^+–Tos); elemental analysis calcd (%) for $C_{24}H_{29}N_3O_2S_2$: C, 63.27; H, 6.42; N, 9.22. Found: C, 62.98; H, 6.45; N, 8.99.

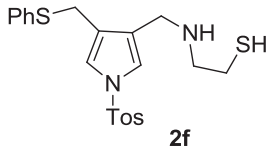
4.9. 4-[4-(*N*,*N*-Dimethylaminoethyl)-1-piperadinyl]methyl-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2e) (entry 7)



2e

Yield 76%, a yellow oil; IR (KBr, cm^{-1}) 2949, 2935, 2811, 1597, 1519, 1458, 1371, 1303, 1188, 1173, 1133, 1093, 1065, 1010, 968, 813; ^1H NMR (600 MHz, $CDCl_3$) δ 2.24 (6H, s, Me×2), 2.41 (3H, s, Me), 2.42–2.45 (12H, m, CH_2), 3.33 (2H, s, NCH_2), 4.00 (2H, s, SCH_2), 6.90 (1H, br s, ArH), 6.94 (1H, br s, ArH), 7.14–7.24 (7H, m, ArH), 7.60–7.61 (2H, d, *J*=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.5 (t), 45.8 (q×2), 52.9 (t×2), 53.6 (t), 53.7 (t×2), 56.6 (t), 56.9 (t), 119.8 (d×2), 124.7 (s), 125.0 (s), 126.2 (d), 126.7 (d×2), 128.6 (d×2), 129.8 (d×2), 130.0 (d×2), 136.0 (s), 136.1 (s), 144.7 (s); MS (70 eV): *m/z*: 512 (M^+), 403 (M^+–SPh); elemental analysis calcd (%) for $C_{27}H_{36}N_4O_2S_2$: C, 63.25; H, 7.08; N, 10.93. Found: C, 63.20; H, 7.09; N, 10.77.

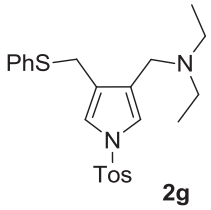
4.10. 4-(2-Mercaptoethylaminomethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2f) (entry 8)



2f

A yellow oil; IR (KBr, cm^{-1}) 3365, 3131, 3058, 2922, 1711, 1661, 1595, 1583, 1517, 1480, 1439, 1369, 1369, 1306, 1237, 1170, 1092, 1063, 967, 890, 812; ^1H NMR (600 MHz, $CDCl_3$) δ 1.51 (1H, br s, SH), 2.41 (3H, s, Me), 2.45 (2H, t, *J*=6.8 Hz, CH_2), 2.76–2.78 (2H, t, *J*=6.2 Hz, CH_2), 3.57 (2H, s, NCH_2), 3.99 (2H, s, SCH_2), 6.91 (1H, br s, ArH), 6.98 (1H, d, *J*=2.1 Hz, ArH), 7.16–7.26 (7H, m, ArH), 7.61–7.62 (2H, d, *J*=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 26.1 (t), 29.5 (t), 35.3 (t), 40.7 (t), 119.6 (d), 120.4 (d), 123.8 (s), 124.1 (s), 126.5 (d), 126.7 (d×2), 128.8 (d×2), 129.9(d×2), 130.4 (d×2), 135.6 (s), 135.8 (s), 144.9 (s) (s); MS (70 eV): *m/z*: 432 (M^+), 356 ($M^+-C_2H_6NS$), 323 (M^+–Tos); elemental analysis calcd (%) for $C_{21}H_{24}N_2O_2S_3$: C, 58.30; H, 5.59; N, 6.48. Found: C, 58.00; H, 5.61; N, 6.30.

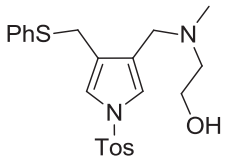
4.11. 4-(Diethylaminomethyl)-3-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrole (2g) (entry 9)



2g

Yield 82%, a yellow oil; IR (KBr, cm^{-1}) 3135, 3055, 2972, 2928, 2871, 2797, 1915, 1731, 1596, 1519, 1480, 1439, 1376, 1304, 1189, 1091, 967, 909, 810, 741, 703, 692, 589, 540, 487, 476, 408; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (6H, t, *J*=7.3 Hz, Me×2), 2.39 (3H, s, CH_3), 2.43 (4H, q, *J*=7.5 Hz, NCH_2×2), 3.38 (2H, s, NCH_2), 4.00 (2H, s, SCH_2), 6.89 (1H, d, *J*=2.1 Hz, ArH), 6.95 (1H, d, *J*=2.1 Hz, ArH), 7.15–7.23 (7H, m, ArH), 7.58–7.60 (2H, d, *J*=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 11.7 (q×2), 21.6 (q), 29.3 (t), 46.6 (t×2), 48.6 (t), 119.8 (d), 119.9 (d), 124.9 (s), 126.1 (d), 126.6 (s, d×2), 128.6 (d×2), 129.8 (d×2), 129.9 (d×2), 136.1 (s×2), 144.6 (s); MS (70 eV): *m/z*: 428 (M^+), 355 ($M^+-C_4H_{10}N$), 273 (M^+–Tos); elemental analysis calcd (%) for $C_{23}H_{28}N_2O_2S_2$: C, 64.45; H, 6.58; N, 6.54. Found: C, 64.36; H, 6.57; N, 6.52.

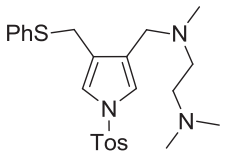
4.12. *N*-[3-(Phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrol-4-ylmethyl]-*N*-methylaminoethanol (2h) (entry 10)



2h

Yield 84%, a yellow oil; IR (KBr, cm^{-1}) 3132, 3060, 2950, 2925, 2876, 2848, 2794, 1596, 1584, 1519, 1480, 1456, 1439, 1369, 1302, 1172, 1121, 1092, 1067, 1025, 968, 876, 813; ^1H NMR (600 MHz, $CDCl_3$) δ 2.15 (3H, s, Me), 2.47 (3H, s, Me), 2.51–2.53 (2H, t, *J*=5.5 Hz, CH_2), 3.39 (2H, s, NCH_2), 3.58–3.60 (2H, t, *J*=5.5 Hz, CH_2), 3.92 (2H, s, SCH_2), 6.89 (1H, d, *J*=2.1 Hz, ArH), 6.97–6.98 (1H, d, *J*=2.0 Hz, ArH), 7.16–7.26 (7H, m, ArH), 7.61–7.63 (2H, d, *J*=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.8 (t), 41.5 (q), 53.2 (t), 58.7 (t), 58.8 (t), 120.0 (d), 120.1 (d), 124.2 (s), 125.2 (s), 126.6 (d), 126.7 (d×2), 128.8 (d×2), 129.9 (d×2), 130.4 (d×2), 135.7 (s), 135.9 (s), 144.8 (s); MS (70 eV): *m/z*: 430 (M^+), 356 ($M^+-C_3H_8ON$), 275 (M^+–Tos); elemental analysis calcd (%) for $C_{22}H_{26}N_2O_3S_2$: C, 61.37; H, 6.09; N, 6.51. Found: C, 61.08; H, 6.07; N, 6.35.

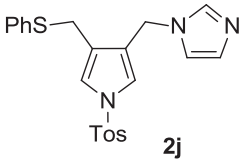
4.13. 4-[2-(*N*,*N*-Dimethylaminoethyl)-*N*-methylamino] methyl-4-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl) pyrrole (2i) (entry 11)



2i

Yield 66%, a yellow oil; IR (KBr, cm^{-1}) 3132, 3059, 2943, 2815, 2770, 2360, 2342, 1713, 1596, 1584, 1519, 1480, 1457, 1440, 1370, 1300, 1219, 1188, 1171, 1121, 1093, 1064, 1026, 967, 879, 812; ^1H NMR (600 MHz, $CDCl_3$) δ 2.13 (3H, s, NMe), 2.16 (6H, s, $NCH_3\times2$), 2.36–2.43 (4H, m, $NCH_2\times2$), 2.40 (3H, s, Me), 3.33 (2H, s, NCH_2), 3.99 (2H, s, SCH_2), 6.89 (1H, br s, ArH), 6.96 (1H, d, J=2.1 Hz, ArH), 7.14–7.27 (7H, m, ArH), 7.59–7.61 (2H, d, J=8.9 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.3 (t), 42.4 (q), 45.6 (q×2), 53.4 (t), 55.4 (t), 57.4 (t), 119.8 (d×2), 124.6 (s), 125.8 (s), 126.2 (d), 126.6 (d×2), 128.6 (d×2), 129.8 (d×2), 130.0 (d×2), 136.0 (s×2), 144.6 (s); MS (70 eV): m/z: 457 (M^+), 356 ($M^+-C_5H_{13}N_2$), 302 (M^+–Tos); elemental analysis calcd (%) for $C_{24}H_{31}N_3O_2S_2$: C, 62.99; H, 6.83; N, 9.18. Found: C, 62.78; H, 6.84; N, 9.03.

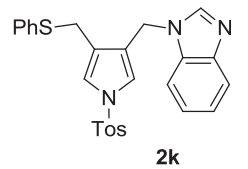
4.14. 1-[3-(Phenylsulfanylmethyl)-1-(4-methylphenylsulfonylpyrrol-4-yl)methyl]imidazole (2j) (entry 12)



2j

Yield 43%, a yellow oil; IR (KBr, cm^{-1}) 3130, 2927, 1710, 1671, 1596, 1506, 1481, 1440, 1372, 1301, 1225, 1189, 1171, 1092, 1065, 1027, 969, 815; ^1H NMR (600 MHz, $CDCl_3$) δ 2.36 (3H, s, Me), 3.56 (2H, s, NCH_2), 4.91 (2H, s, SCH_2), 6.76 (1H, br s, NArH), 6.83 (1H, br s, NArH), 6.89 (1H, br s, ArH), 6.97 (1H, br s, ArH), 7.11 (5H, br s, ArH), 7.21 (2H, d, J=7.8 Hz, ArH), 7.37 (1H, br s, NArH), 7.55 (2H, d, J=8.2 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.7 (t), 42.2 (t), 119.0 (d), 119.9 (d), 120.6 (d), 122.6 (s), 123.0 (s), 126.8 (d×2), 127.0 (d), 128.9 (d×2), 129.5 (d), 130.1 (d×2), 130.8 (d×2), 134.8 (s), 135.5 (s), 137.1 (d), 145.3 (s); MS (70 eV): m/z: 355 ($M^+-C_3H_3N_2$); elemental analysis calcd (%) for $C_{22}H_{21}N_3O_2S_2$: C, 62.39; H, 5.00; N, 9.92. Found: C, 62.17; H, 5.01; N, 9.72.

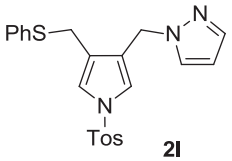
4.15. 1-[4-(Phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)-pyrrol-3-ylmethyl]benzimidazole (2k) (entry 13)



2k

Yield 92%, white prisms, mp 143–150 °C; IR (KBr, cm^{-1}) 3132, 3059, 2923, 2568, 1711, 1669, 1615, 1596, 1520, 1496, 1458, 1439, 1371, 1301, 1254, 1170, 1144, 1092, 1065, 1025, 968, 812; ^1H NMR (600 MHz, $CDCl_3$) δ 2.34 (3H, s, Me), 3.54 (2H, s, NCH_2), 5.12 (2H, s, SCH_2), 6.81 (1H, s, ArH), 6.87 (1H, s, ArH), 7.05–7.12 (6H, m, ArH), 7.14–7.20 (4H, m, ArH), 7.48–7.50 (2H, d, J=8.2 Hz, ArH), 7.70–7.72 (1H, d, J=7.8 Hz, ArH), 7.75 (1H, s, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.7 (t), 40.6 (t), 109.9 (d), 120.1 (d), 120.3 (d), 120.8 (d), 122.3 (d, s), 122.7 (s), 123.0 (d), 126.7 (d×2), 126.9 (d), 128.8 (d×2), 130.0 (d×2), 130.8 (d×2), 133.6 (s), 134.6 (s), 135.4 (s), 142.8 (d), 143.7 (s), 145.2 (s); MS (70 eV): m/z: 473 (M^+); elemental analysis calcd (%) for $C_{26}H_{23}N_3O_2S_2$: C, 65.94; H, 4.89; N, 8.87. Found: C, 65.75; H, 4.84; N, 8.86.

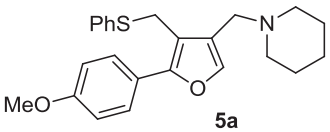
4.16. 1-[4-(Phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)-pyrrol-3-ylmethyl]pyrazole (2l) (entry 14)



2l

Yield 53%, a yellow oil; IR (KBr, cm^{-1}) 3132, 3060, 2924, 2854, 1711, 1596, 1584, 1514, 1481, 1439, 1371, 1300, 1172, 1092, 1068, 968, 918, 881, 814; ^1H NMR (600 MHz, $CDCl_3$) δ 2.35 (3H, s, Me), 3.63 (2H, s, NCH_2), 5.12 (2H, s, SCH_2), 6.16 (1H, d, J=2.0 Hz, ArH), 6.82 (1H, d, J=2.8 Hz, ArH), 6.94 (1H, d, J=2.7 Hz, ArH), 7.10 (5H, br s, ArH), 7.18–7.20 (2H, m, ArH), 7.24 (1H, d, J=2.8 Hz, ArH), 7.43 (1H, d, J=1.4 Hz, ArH), 7.54 (2H, d, J=8.3 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6 (q), 29.4 (t), 47.2 (t), 105.8 (d), 120.1 (d), 120.3 (d), 123.2 (s), 123.3 (s), 126.7 (d), 126.8 (d×2), 128.8 (d×2), 128.9 (d), 130.0 (d×2), 130.6 (d×2), 135.2 (s), 135.7 (s), 139.4 (d), 145.1 (s); MS (70 eV): m/z: 423 (M^+), 355 ($M^+-C_3H_3N_2$), 314 (M^+–SPh), 268 (M^+–Tos); elemental analysis calcd (%) for $C_{22}H_{21}N_3O_2S_2$: C, 62.39; H, 5.00; N, 9.92. Found: C, 62.19; H, 5.03; N, 9.71.

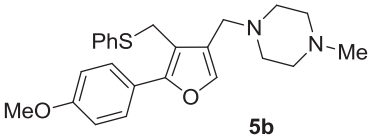
4.17. 1-[2-(*p*-Methoxyphenyl)-3-(phenylsulfanylmethyl)-4-(furanylmethyl)]piperidine (5a) (entry 1)



5a

Yield 63%, a yellow oil; IR (KBr, cm^{-1}) 3432, 2934, 1713, 1607, 1577, 1506, 1440, 1362, 1301, 1253, 1179, 1145, 1107, 1065, 1032, 992, 951, 908, 861, 835, 795, 741, 691, 599, 533, 410; ^1H NMR (600 MHz, $CDCl_3$) δ 1.41 (2H, br s, CH_2), 1.51–1.55 (4H, m, CH_2), 2.36 (4H, br s, CH_2), 3.34 (2H, s, CH_2), 3.82 (3H, s, Me), 4.30 (2H, s, CH_2), 6.92–6.94 (2H, d, J=8.9 Hz, ArH), 7.18–7.20 (1H, m, ArH), 7.25–7.28 (3H, m, ArH), 7.38 (2H, d, J=7.6 Hz, ArH), 7.56 (2H, d, J=9.0 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.5 (t), 26.1 (t×2), 29.1 (t), 52.8 (t), 54.5 (t×2), 55.3 (q), 114.0 (d×2), 115.0 (s), 123.8 (s), 126.2 (d), 127.5 (d×2), 128.8 (d×2), 129.9 (d×2), 137.0 (s), 139.3 (d), 144.8 (s), 151.4 (s), 159.0 (s); MS (70 eV): m/z: 393 (M^+), 284 (M^+–SPh); elemental analysis calcd (%) for $C_{24}H_{27}NO_2S$: C, 73.25; H, 6.92; N, 3.56. Found: C, 73.11; H, 6.89; N, 3.35.

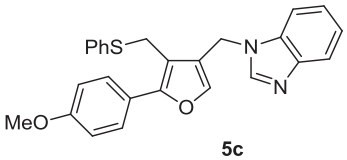
4.18. 1-[2-(*p*-Methoxyphenyl)-3-(phenylsulfanylmethyl)-4-(furanylmethyl)]-4-methylpiperazine (5b) (entry 2)



5b

Yield 71%, a yellow oil; IR (KBr, cm^{-1}) 3435, 2934, 2836, 2795, 1606, 1581, 1506, 1480, 1456, 1440, 1350, 1294, 1253, 1178, 1147, 1112, 1089, 1065, 1032, 1011, 952, 925, 834; ^1H NMR (600 MHz, $CDCl_3$) δ 2.26 (3H, s, Me), 2.41 (8H, br s, NCH_2), 3.39 (2H, s, NCH_2), 3.81 (3H, s, OMe), 4.29 (2H, s, SCH_2), 6.91–6.93 (2H, d, J=8.7 Hz, ArH), 7.17–7.20 (1H, t, J=7.3 Hz, ArH), 7.24–7.28 (3H, m, ArH), 7.37 (2H, d, J=7.4 Hz, ArH), 7.55 (2H, d, J=8.7 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.1 (t), 46.0 (q), 52.0 (t), 53.0 (t×2), 55.2 (t×2, q), 114.0 (d×2), 114.9 (s), 123.3 (s), 123.6 (s), 126.2 (d), 127.5 (d×2), 128.8 (d×2), 129.9 (d×2), 136.9 (s), 139.4 (d), 151.5 (s), 159.1 (s); MS (70 eV): m/z: 408 (M^+), 299 (M^+–SPh); elemental analysis calcd (%) for $C_{24}H_{28}N_2O_2S$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.36; H, 6.89; N, 6.73.

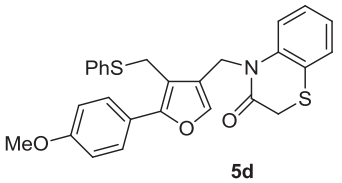
4.19. 1-[2-(*p*-Methoxyphenyl)-3-(phenylsulfanylmethyl)furan-4-methyl]-1*H*-benzimidazole (5c) (entry 3)



5c

Yield 71%, a yellow oil; IR (KBr, cm^{-1}) 3434, 3058, 2925, 2853, 2361, 1615, 1506, 1459, 1440, 1287, 1253, 1179, 1065, 1027, 950, 836, 745, 691; ^1H NMR (600 MHz, $CDCl_3$) δ 3.82 (3H, s, Me), 3.90 (2H, s, CH_2), 5.24 (2H, s, CH_2), 6.91 (2H, d, J=9.1 Hz, CH_2), 7.25–7.26 (8H, m, ArH), 7.40–7.42 (1H, m, ArH), 7.46 (2H, d, J=8.9–Hz, ArH), 7.81 (1H, dd, J=1.8 and 6.9 Hz, ArH), 7.93 (1H, s, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.2 (t), 39.5 (t), 55.4 (q), 102.2 (s), 110.1(d), 113.3 (s), 114.3 (d×2), 120.5 (d), 121.3 (s), 121.7 (s), 122.4 (d), 122.9 (s), 123.2 (d), 127.1 (d×2), 128.1 (d×2), 129.1 (d×2), 130.6 (d×2), 135.4 (s), 140.0 (d), 153.0 (s), 159.7 (s); MS (70 eV): m/z: 426 (M^+), 317 (M^+–SPh); elemental analysis calcd (%) for $C_{26}H_{22}N_2O_2S_2$: C, 68.10; H, 4.84; N, 6.11. Found: C, 68.26; H, 4.83; N, 6.10.

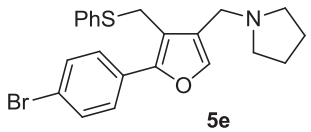
4.20. 1-[2-(*p*-Methoxyphenyl)-3-(phenylsulfanylmethyl)-4-furanylmethyl]-2*H*-1,4-benzothiazin-3(4*H*)one (5d) (entry 4)



5d

Yield 70%, a yellow oil; IR (KBr, cm^{-1}) 3446, 2926, 2854, 1759, 1711, 1672, 1608, 1584, 1506, 1479, 1447, 1376, 1308, 1285, 1253, 1179, 1151, 1091, 1067, 1029, 962, 897, 836, 755, 690, 529; ^1H NMR (600 MHz, $CDCl_3$) δ 3.45 (2H, s, CH_2), 3.82 (3H, s, CH_3), 4.14 (2H, s, CH_2), 5.11 (2H, s, $COCH_2$), 6.91 (2H, d, J=8.9 Hz, ArH), 6.97–7.02 (1H, m, ArH), 7.12 (1H, s, ArH), 7.17–7.23 (3H, m, ArH), 7.25–7.28 (2H, m, ArH), 7.35–7.37 (3H, dd, J=1.1 and 9.6 Hz, ArH), 7.48 (2H, d, J=8.9 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.2 (t), 31.6 (t), 39.8 (t), 55.3 (q), 113.0 (s), 114.1 (d×2), 118.3 (d), 122.8 (s), 123.2 (s), 123.7 (d), 123.8 (s), 126.6 (d), 127.3 (d), 127.8 (d×2), 128.3 (d), 128.9 (d×2), 130.1 (d×2), 135.9 (s), 138.6 (d), 139.3 (s), 152.1 (s), 159.3 (s), 165.1 (s); MS (70 eV): m/z: 473 (M^+), 364 (M^+–SPh); high-resolution mass calcd for $C_{27}H_{23}NO_3S_2$: 473.1119, found m/z 473.1092.

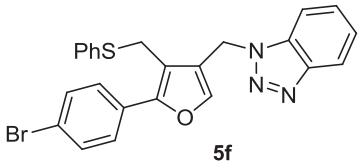
4.21. 1-[2-(*p*-Bromophenyl)-3-(phenylsulfanylmethyl)-4-(furanylmethyl)]pyrrolidine (5e) (entry 5)



5e

Yield 61%, a yellow oil; IR (KBr, cm^{-1}) 3058, 2959, 2926, 2873, 2790, 2360, 1714, 1654, 1483, 1584, 1559, 1542, 1507, 1483, 1458, 1439, 1395, 1376, 1349, 1322, 1293, 1221, 1025, 1009, 944, 877, 829, 691; ^1H NMR (600 MHz, $CDCl_3$) δ 1.77 (4H, br s, CH_2), 2.51 (4H, br s, CH_2), 3.50 (2H, s, CH_2), 4.23 (2H, s, CH_2), 7.20–7.22 (1H, m, ArH), 7.25–7.28 (2H, m, ArH), 7.35–7.37 (3H, m, ArH), 7.46–7.50 (4H, m, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.5 (t×2), 29.1 (t), 49.4 (t), 54.3 (t×2), 116.5 (s), 124.1 (s), 125.0 (s), 126.6 (d), 127.4 (d×2), 128.9 (d×2), 129.7 (s), 130.3 (d×2), 131.7 (d×2), 136.2 (s), 139.7 (d), 150.0 (s); MS (70 eV): m/z: 427 (M^+), 356 (M^+–C_4H_9N); elemental analysis calcd (%) for $C_{22}H_{22}BrNOS$: C, 61.68; H, 5.18; N, 3.27. Found: C, 61.45; H, 5.13; N, 3.16.

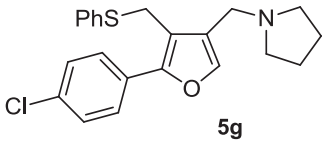
4.22. 1-[2-(*p*-Bromophenyl)-3-(phenylsulfanylmethyl)-4-furanylmethyl]-1*H*-benzotriazole (5f) (entry 6)



5f

Yield 39%, white prisms, 85–88 °C; IR (KBr, cm^{-1}) 3438, 3059, 2927, 1567, 1483, 1439, 1394, 1324, 1275, 1146, 1075, 1009, 948, 851, 829, 747, 690; ^1H NMR (600 MHz, $CDCl_3$) δ 4.18 (2H, s, CH_2), 5.80 (2H, s, CH_2), 7.23–7.28 (4H, m, ArH), 7.34–7.40 (7H, m, ArH), 7.48 (1H, dd, J=2.1 and 6.9 Hz, ArH), 7.63 (1H, s, ArH), 7.83 (1H, dd, J=2.1 and 6.9 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.9 (t), 49.9 (t), 116.0 (s), 118.1 (d×2), 121.1 (s), 122.1 (s), 126.4 (s), 126.5 (d×2), 127.1 (d), 127.8 (d×2), 129.0 (d×2), 129.1 (s), 131.1 (d×2), 131.8 (d×2), 135.1 (s), 141.5 (d), 144.5 (s), 151.2 (s); MS (70 eV): m/z: 477 (M^+), 369 (M^+–SPh); elemental analysis calcd (%) for $C_{24}H_{18}BrN_3OS$: C, 60.51; H, 3.81; N, 8.82. Found: C, 60.33; H, 3.78; N, 8.75.

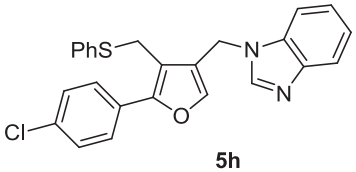
4.23. 1-[2-(*p*-Chlorophenyl)-3-(phenylsulfanylmethyl)-4-(furanylmethyl)]pyrrolidine (5g) (entry 7)



5g

Yield 61%, a yellow oil; IR (KBr, cm^{-1}) 2962, 2926, 2789, 2364, 1714, 1653, 1559, 1542, 1488, 1458, 1438, 1362, 1221, 1120, 1093, 1062, 1026, 1012, 944, 909, 876, 832, 741, 690, 531, 511, 444, 412; ^1H NMR (600 MHz, $CDCl_3$) δ 1.77–1.78 (4H, m, CH_2), 2.52 (4H, br s, CH_2), 3.50 (2H, s, CH_2), 4.23 (2H, s, CH_2), 7.20–7.22 (1H, m, ArH), 7.25–7.28 (2H, m, ArH), 7.33–7.37 (5H, m, ArH), 7.53–7.54 (2H, d, J=8.9 Hz, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.6 (t×2), 29.1 (t), 49.4 (t), 54.3 (t×2), 116.5 (s), 124.9 (s), 126.6 (d), 127.2 (d×2), 128.8 (d×2), 128.9 (d×2), 129.3 (s), 130.4 (d×2), 133.3 (s), 136.3 (s), 139.7 (d), 150.1 (s); MS (70 eV): m/z: 383 (M^+), 311 (M^+–C_4H_9N); high-resolution mass calcd for $C_{22}H_{22}ClONS$: 383.1110, found m/z 383.1104.

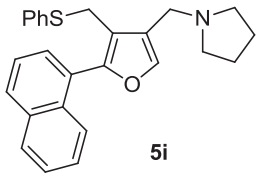
4.24. 1-[2-(*p*-Chlorophenyl)-3-(phenylsulfanylmethyl)-4-furanylmethyl]-1*H*-benzimidazole (5h) (entry 8)



5h

Yield 65%, a yellow oil; IR (KBr, cm^{-1}) 3057, 2925, 2855, 2359, 1710, 1615, 1583, 1489, 1458, 1439, 1364, 1331, 1286, 1268, 1202, 1150, 1093, 1062, 1011, 949, 833, 742, 691, 618, 507, 473, 426; ^1H NMR (600 MHz, $CDCl_3$) δ 3.89 (2H, s, CH_2), 5.24 (2H, s, CH_2), 7.24–7.32 (10H, m, ArH), 7.34 (1H, d, J=9.0 Hz, ArH), 7.44 (2H, d, J=8.2 Hz, ArH), 7.82 (1H, d, J=6.9 Hz, ArH), 7.93 (1H, s, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.1 (t), 39.1 (t), 109.9 (d), 115.1 (s), 120.5 (d), 122.0 (s), 122.4 (d), 123.1 (d), 127.3 (d), 127.6 (d×2), 128.4 (s), 128.9 (d×2), 129.1 (d×2), 131.0 (d×2), 133.7 (s), 134.2 (s), 134.7 (s), 140.3 (d), 142.8 (d), 143.9 (s), 151.7 (s); MS (70 eV): m/z: 430 (M^+), 321 (M^+−SPh); elemental analysis calcd (%) for $C_{25}H_{19}Cl\ N_2OS$: C, 69.68; H, 4.44; N, 6.50. Found: C, 69.34; H, 4.42; N, 6.25.

4.25. 1-[2-(Naphthyl)-3-(phenylsulfanylmethyl)-4-(furanylmethyl)]pyrrolidine (5i) (entry 9)

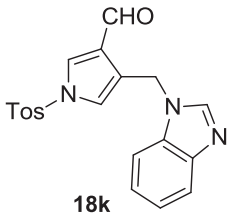


5i

Yield 69%, a yellow oil; IR (KBr, cm^{-1}) 3450, 3055, 2963, 2926, 2873, 2790, 1584, 1558, 1507, 1480, 1460, 1438, 1412, 1389, 1376, 1347, 1322, 1292, 1251, 1199, 1123, 1104, 1068, 1024, 935, 877, 864, 802, 777, 740, 691, 568; ^1H NMR (600 MHz, $CDCl_3$) δ 1.81 (4H, br s, CH_2), 2.60 (4H, br s, CH_2), 3.68 (2H, s, CH_2), 4.09 (2H, s, CH_2), 7.04–7.05 (3H, m, ArH), 7.16–7.17 (2H, m, ArH), 7.41–7.47 (4H, m, ArH), 7.49 (1H, s, ArH), 7.83–7.86 (3H, m, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 23.6 (t×2), 29.0 (t), 49.9 (t), 54.4 (t×2), 118.2 (s), 124.2 (s), 125.1 (s), 125.9 (d), 126.0 (d), 126.1 (d), 126.4 (d), 127.8 (s), 128.1 (d), 128.1 (d), 128.6 (d×2), 129.2 (d), 130.0 (d×2), 132.1 (s), 133.7 (s), 136.3 (s), 140.1 (d), 151.2 (s); MS (70 eV): m/z: 399 (M^+), 328 (M^+−C_4H_9N); elemental analysis calcd (%) for $C_{26}H_{25}NOS$: C, 78.16; H, 6.31; N, 3.51. Found: C, 77.93; H, 6.30; N, 3.46.

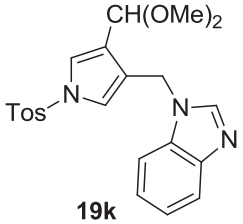
4.26. Oxidation of 1-[4-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrol-4-ylmethyl]benzimidazole (2k) with ceric ammonium nitrate (CAN) (Scheme 2)

CAN (0.17 g, 0.31 mmol) was added to a MeOH (1.0 mL) solution of **2k** (50 mg, 0.10 mmol) at room temperature. The reaction mixture was stirred for 1 h and poured into water (50 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with $CHCl_3$/MeOH (40:1) to give 4-(1-benzimidazolylmethyl)-*N*-(4-methylphenylsulfonyl)-*1H*-pyrrole-3-carboxaldehyde (**18k**) (36 mg, 89%) and 4-(1-benzimidazolylmethyl)-*N*-(4-methylphenylsulfonyl)-*1H*-pyrrole-3-carboxaldehyde dimethyl acetal (**19k**) (2.0 mg, 5%).



18k

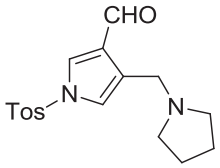
White plates, mp 147–149 °C; IR (KBr, cm^{-1}) 3124, 2924, 2853, 1735, 1681, 1596, 1512, 1496, 1459, 1381, 1310, 1287, 1191, 1175, 1901, 1066, 968, 887, 817, 754, 703, 674, 887, 817, 754, 703, 674, 590, 539; ^1H NMR (600 MHz, $CDCl_3$) δ 2.42 (3H, s, Me), 5.46 (2H, s, CH_2), 6.81 (1H, s, ArH), 7.23–7.28 (3H, m, ArH), 7.31 (2H, d, J=7.6 Hz, ArH), 7.70 (2H, d, J=8.2 Hz, ArH), 7.76 (1H, d, J=2.7 Hz, ArH), 7.81 (1H, d, J=8.2 Hz, ArH), 8.01 (1H, s, ArH), 9.85 (1H, s, CHO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.8 (q), 40.8 (t), 109.8 (d), 120.6 (d), 120.8 (d), 122.3 (d), 123.1 (d), 126.6 (s), 127.4 (d×2), 130.6 (d×2), 130.8 (d), 133.6 (s), 134.3 (s), 143.4 (d), 143.4 (s), 146.6 (s), 185.6 (d); MS (70 eV): m/z: 379 (small M^+); elemental analysis calcd (%) for $C_{20}H_{17}N_3O_3S$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.25; H, 4.46; N, 11.02.



19k

A pale yellow oil; IR (KBr, cm^{-1}) 2931, 1615, 1596, 1496, 1459, 1373, 1331, 1287, 1266, 1190, 1173, 1093, 1066, 983, 814, 746, 703, 676; ^1H NMR (600 MHz, $CDCl_3$) δ 2.41 (3H, s, Me), 3.21 (6H, s, OMe×2), 5.06 (1H, s, CH), 5.18 (2H, s, CH_2), 6.97 (1H, br s, ArH), 7.18 (1H, br s, ArH), 7.20–7.28 (5H, m, ArH), 7.68 (2H, d, J=8.3 Hz, ArH), 7.79 (1H, d, J=8.2 Hz, ArH), 7.89 (1H, br s, ArH); MS 308 (M^+−imidazole).

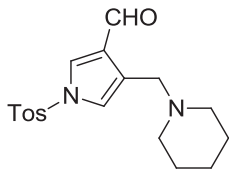
4.27. Oxidation of 1-[4-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrol-4-ylmethyl]pyrrolidine (2a) with ceric ammonium nitrate (CAN) (Scheme 2)



18a

A yellow oil; IR (KBr, cm^{-1}) 2957, 2925, 2854, 1684, 1596, 1507, 1458, 1380, 1312, 1261, 1191, 1174, 1092, 1064, 814, 758, 703, 673, 592; ^1H NMR (600 MHz, $CDCl_3$) δ 1.76–1.78 (4H, m, CH_2), 2.43 (3H, s, Me), 2.55 (4H, br s, CH_2), 3.75 (2H, s, CH_2), 7.13 (1H, br s, ArH), 7.34 (2H, d, J=8.2 Hz, ArH), 7.71 (1H, d, J=2.7 Hz, ArH), 7.80 (2H, d, J=8.2 Hz, ArH), 9.89 (1H, s, CHO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7 (q), 23.5 (t×2), 51.0 (t), 54.2 (t×2), 120.3 (d), 126.5 (s), 127.3 (d×2), 127.5 (s), 128.8 (d), 130.3 (d×2), 134.9 (s), 146.0 (s), 186.1 (d); MS (70 eV): m/z: 332 (M^+). High-resolution mass calcd for $C_{17}H_{20}N_2O_3S$: 332.1194, found m/z 332.1176.

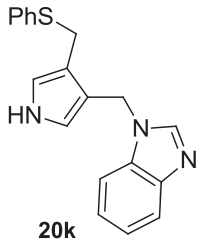
4.28. Oxidation of 1-[4-(phenylsulfanylmethyl)-1-(4-methylphenylsulfonyl)pyrrol-4-ylmethyl]piperidine (2b) with ceric ammonium nitrate (CAN) (Scheme 2)



18b

Colorless prisms, mp 128–129 °C; IR (KBr, cm^{-1}) 3129, 2934, 2348, 1685, 1596, 1508, 1455, 1380, 1313, 1175, 1091, 1063, 968, 815, 756, 673, 592, 539; ^1H NMR (600 MHz, $CDCl_3$) δ 1.41 (2H, br s, CH_2), 1.53–1.55 (4H, m, CH_2), 2.39 (4H, br s, CH_2), 2.43 (3H, s, Me), 3.57 (2H, s, CH_2), 7.09 (1H, br s, ArH), 7.34 (2H, d, J=8.2 Hz, ArH), 7.71 (1H, d, J=2.8 Hz, ArH), 7.79 (2H, d, J=8.2 Hz, ArH), 9.92 (1H, s, CHO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.7 (q), 24.2 (t), 25.9 (t×2), 53.9 (t), 54.5 (t×2), 120.4 (d), 125.7 (s), 127.3 (d×2), 128.9 (s), 128.3 (d), 130.3 (d×2), 135.0 (s), 146.0 (s), 186.4 (d); MS (70 eV): m/z: 346 (M^+); elemental analysis calcd (%) for $C_{18}H_{22}N_2O_3S$: C, 62.40; H, 6.40; N, 8.09. Found: C, 62.19; H, 6.38; N, 7.88.

4.29. Desulfonylation of *N*-tosylpyrrole 4k[22]



20k

The 5 M NaOH solution (1.0 mL) was added to **2k** (30 mg, 0.06 mmol) in isopropanol (1.0 mL). The mixture was refluxed for 8 h. The cooled mixture was poured into water (50 mL). The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by preparative TLC on silica gel eluting with AcOEt/*n*-hexane (1:2) to give **20k** (16 mg, 80%).

Colorless needles, mp 156–157 °C; IR (KBr, cm^{-1}) 3419, 2924, 1853, 1716, 1615, 1583, 1496, 1480, 1459, 1439, 1381, 1332, 1287, 1267, 1197, 1121, 1072, 1025, 744, 692; ^1H NMR (600 MHz, $CDCl_3$) δ 3.86 (2H, s, CH_2), 5.35 (2H, s, CH_2), 6.65 (1H, br s, ArH), 6.76 (1H, br s, ArH), 7.14–7.28 (7H, m, ArH), 7.51 (1H, brd, J=8.2 Hz, ArH), 7.62–7.68 (1H, m, ArH), 7.96 ppm (1H, s, ArH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 29.1 (t), 40.3 (t), 109.9 (d), 114.9 (s), 115.8 (s), 117.9 (d), 118.1 (d), 118.3 (d), 121.6 (d), 122.2 (d), 125.4 (d), 127.9 (d×2), 129.0 (d×2), 133.2 (s), 136.0 (s), 142.3 (s×2); MS (70 eV): m/z: 319 (M^+); elemental analysis calcd (%) for $C_{19}H_{17}N_3S$: C, 71.44; H, 5.36; N, 13.15. Found: C, 71.25; H, 5.35; N, 12.93.

References and notes

1. (a) Review on HA/cyclization: Patil, N. T.; Singh, V. *J. Organomet. Chem.* **2011**, *696*, 419–432; (b) Review on HA: Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703; (c) Doye, S. *Synlett* **2004**, 1653–1672; (d) Nobis, M.; Drießen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983–3985; (e) Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C. G.; Seayad, J.; Thiel, O. R.; Tillack, A.; Trauthwein, H. *Synlett* **2002**, 1579–1594; (f) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935–946; (g) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686; (h) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398; (i) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563; (j) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420; (k) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105–5118; (l) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892; (m) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009–3019; (n) Andrea, T.; Eisen, M. S. *Chem. Soc. Rev.* **2008**, *37*, 550–567.
2. (a) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2002**, *124*, 14542–14543; (b) Nagle, A.; Wu, T.; Kuhen, K.; Gagaring, K.; Borboa, R.; Francek, C.; Chen, Z.; Plouffe, D.; Lin, X.; Caldwell, C.; Ek, J.; Skolnik, S.; Liu, F.; Wang, J.; Chang, J.; Li, B.; Hollenbeck, T.; Tuntland, T.; Isbell, J.; Chuan, T.; Alper, P. B.; Fischli, C.; Brun, R.; Lakshminaeayana, S. B.; Rottmann, M.; Diagana, T. T.; Winzeler, E. A.; Glynne, R.; Tully, D. C.; Chatterjee, A. K. *J. Med. Chem.* **2012**, *55*, 4244–4273; (c) Ko, E.; Burgess, K. *Org. Lett.* **2011**, *13*, 980–983; (d) Samala, S.; Saifuddin, M.; Mandadapu, A. K.; Kundu, B. *Eur. J. Org. Chem.* **2013**, 3797–3806; (e) Xu, M.; Xu, K.; Wang, S.; Yao, Z.-J. *Tetrahedron Lett.* **2013**, *54*, 4675–4678; (f) Wang, Y.; Chen, C.; Zhang, S.; Lou, Z.; Su, X.; Wen, L.; Li, M. *Org. Lett.* **2013**, *15*, 4794–4797; (g) Bhonde, V. R.; Looper, R. E. *J. Am. Chem. Soc.* **2011**, *133*, 20172–20174; (h) Nolan, S. P. PCT Int. Appl. WO 2011107736 A1 20110909, 2011; (i) Perl, N. R.; Ide, N. D.; Prajapati, S.; Perfect, H. H.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2010**, *132*, 1802–1803; (j) Enomoto, T.; Girard, A.-L.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 9158–9164; (k) Ackermann, L.; Barfuesser, S.; Potukuchi, H. K. *Adv. Synth. Catal.* **2009**, *351*, 1064–1072; (l) Bertrand, G.; Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleihavoup, M. PCT Int. Appl. WO 2009137810 A2 20091112, 2009.
3. Au or Ag: (a) Wong, V. H. L.; Hor, T. S. A.; Hii, K. K. *Chem. Commun.* **2013**, 9272–9274; (b) Xu, M.; Samala, S.; Krishna, D. G. V.; Kundu, B. *Synthesis* **2013**, *45*, 1553–1563; (c) Suzuki, Y.; Naoe, S.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2012**, *14*, 326–329; (d) Demir, A. S.; Emrullahoglu, M.; Buran, K. *Chem. Commun.* **2010**, 8032–8034; (e) Hirano, K.; Inaba, Y.; Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Adv. Synth. Catal.* **2010**, *352*, 368–372; (f) Zoh, Y.; Feng, E.; Liu, G.; Ye, D.; Li, J.; Jiang, H.; Liu, H. *J. Org. Chem.* **2009**, *74*, 7344–7348; (g) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537–3540; (h) Robinson, R. S.; Dovey, M. C.; Gravestock, D. *Eur. J. Org. Chem.* **2005**, 505–511.
4. Ti: (a) Shen, H.; Xie, Z. *J. Am. Chem. Soc.* **2010**, *132*, 11473–11480; (b) Facotti, D.; Abbiati, G.; d'Avolio, L.; Ackermann, L.; Rossi, E. *Synlett* **2009**, 2273–2276; (c) Lian, B.; Spaniol, T. P.; Horrillo-Martinez, P.; Hultzsch, K. C.; Okuda, J. *Eur. J. Inorg. Chem.* **2009**, 429–434; (d) Zhan, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Schafer, L. L. *Chem.—Eur. J.* **2007**, *13*, 2012–2022; (e) Abbianti, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839–4842; (f) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Commun.* **2004**, 2824–2825; (g) Ramanathan, B.; Keith, A. J.; Armstrong, D.; Odom, A. L. *Org. Lett.* **2004**, *6*, 2957–2960; (h) Ackermann, L. *Organometallics* **2003**, *22*, 4367–4368; (i) Li, C.; Thompson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2462–2463; (j) Bytschkov, I.; Doye, S. *Tetrahedron Lett.* **2002**, *43*, 3715–3718.
5. Zn: (a) Biyikal, M.; Loehnwitz, K.; Meyer, N.; Dochnahl, M.; Roesky, P. W.; Blechert, S. *Eur. J. Inorg. Chem.* **2010**, 1070–1081; (b) Yin, Y.; Chai, Z.; Ma, W.-Y.; Zhao, G. *Synthesis* **2008**, 4036–4040.
6. Pt: (a) Patil, N. T.; Kavthe, R. D.; Shinde, V. S.; Sridhar, B. *J. Org. Chem.* **2010**, *75*, 3371–3380; (b) Krogstad, D. A.; Cho, J.; DeBoer, A. J.; Klitzke, J. A.; Sanow, W. R.; Williams, H. A.; Halfen, J. A. *Inorg. Chim. Acta* **2006**, *359*, 136–148.
7. Ir: Wong, C. M.; Vuong, K. Q.; Gatus, M. R. D.; Hua, C.; Bhadbhade, M.; Messerle, B. A. *Organometallics* **2012**, *31*, 7500–7510.
8. Rh: (a) Hua, C.; Vuong, K. Q.; Bhadbhade, M.; Messerle, B. A. *Organometallics* **2012**, *31*, 1790–1800; (b) Clentsmith, G. K. B.; Field, L. D.; Messerle, B. A.; Barbara, A.; Shasha, A.; Turner, P. *Tetrahedron Lett.* **2009**, *50*, 1469–1471; (c) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 6149–6167; (d) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P.; Failes, T. *Organometallics* **2007**, *26*, 2058–2069.
9. Ca: Datta, S.; Roesky, P. W.; Blechert, S. *Organometallics* **2007**, *26*, 4392–4394; Fe: Majumdar, K. C.; De, N.; Roy, B. *Synthesis* **2010**, 4207–4212.
10. (a) Patil, N.; Lutete, L. M.; Wu, H.; Pahadi, N. K.; Gridnev, I. D.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 4270–4279; (b) Müller, T. E.; Berger, M.; Grosche, M.; Herdtweck, E.; Schmidtchen, F. P. *Organometallics* **2001**, *20*, 4384–4393; (c) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170–183; (d) Kadota, I.; Shibuya, A.; Lutete, L. M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4570–4571.
11. Ru: (a) Ackermann, L.; Althammer, A. *Synlett* **2006**, 3125–3129; (b) Kuninobu, Y.; Nishina, Y.; Takai, K. *Org. Lett.* **2006**, *8*, 2891–2893; (c) Yi, C. S.; Yun, S. Y. *J. Am. Chem. Soc.* **2005**, *127*, 17000–17006; (d) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *J. Am. Chem. Soc.* **2005**, *127*, 5782–5783.
12. Y: Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *Chem.—Eur. J.* **2003**, *9*, 4796–4810.
13. In: Chanda, T.; Verma, R. K.; Singh, M. S. *Chem. Asian J.* **2012**, *7*, 778–787.
14. Lanthanides: (a) Seo, S.-Y.; Marks, T. J. *Chem.—Eur. J.* **2010**, *16*, 5148–5162; (b) Yuen, H.; Marks, T. J. *Organometallics* **2009**, *28*, 2423–2440; (c) Seo, S.-Y.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263–276; (d) Motta, A.; Fragala, I.; Marks, T. J. *Organometallics* **2006**, *25*, 5533–5539; (e) Rastaetter, M.; Zulys, A.; Roesky, P. W. *Chem. Commun.* **2006**, 874–876; (f) Kim, H.; Livinghouse, T.; Shim, J.-H.; Lee, S. G.; Lee, P. H. *Adv. Synth. Catal.* **2006**, *348*, 701–704; (g) Panda, T. K.; Zulys, A.; Gamer, M. T.; Roesky, P. W. *J. Organomet. Chem.* **2005**, *690*, 5078–5089; (h) Zulys, A.; Panda, T. K.; Gamer, M. T.; Roesky, P. W. *Chem. Commun.* **2004**, 2584–2585; (i) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584–12605; (j) Burgstein, M. R.; Berberich, H.; Roesky, P. W. *Chem.—Eur. J.* **2001**, *7*, 3078–3085; (k) Ki, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295–9306; (l) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439–440.
15. Actinides: (a) Stubbert, B. D.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 4253–4271; (b) Stubbert, B. D.; Stern, C. L.; Marks, T. J. *Organometallics* **2003**, *22*, 4836–4838.

16. Base: Llauger, L.; Bergami, C.; Kinzel, O. D.; Lilleni, S.; Pescatore, G.; Torrisi, C.; Jones, P. *Tetrahedron Lett.* **2009**, *50*, 172–177; Ca: Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 2193–2207.
17. (a) Yoshimatsu, M.; Watanabe, H.; Koketsu, E. *Org. Lett.* **2010**, *12*, 4192–4194; (b) Takahashi, N.; Nagase, Y.; Tanabe, G.; Muraoka, O.; Yoshimatsu, M. *Tetrahedron* **2012**, *68*, 1566–1580.
18. Yoshimatsu, M.; Sasaki, H.; Sugimoto, Y.; Nagase, Y.; Tanabe, G.; Muraoka, O. *Org. Lett.* **2012**, *14*, 3190–3193.
19. Co-Mediated HA/cyclization: Gandon, V.; Aubert, C.; Malacria, M.; Vollhardt, K. P. C. *Chem. Commun.* **2008**, 1599–1601.
20. Ohta, K.; Koketsu, E.; Nagase, Y.; Takahashi, N.; Watanabe, H.; Yoshimatsu, M. *Chem. Pharm. Bull.* **2011**, *59*, 1133–1140.
21. Nickel-catalyzed hydrocyanative allenyne cyclization: Arai, S.; Amako, Y.; Yang, X.; Nishida, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 8147–8150.
22. Settambolo, R.; Lazzaroni, R.; Messeri, T.; Mazzetti, M.; Salvadori, P. *J. Org. Chem.* **1993**, *58*, 7899–7902.
23. Earl, R. A.; Townsend, L. B. *Organic. Syntheses*; John Wiley & Sons: New York, 1990, Collect. Vol. 7, pp 334–338.
24. Barrett, A. G. M.; Dhanak, D.; Graboski, G. G.; Taylor, S. J. *Organic. Syntheses*; John Wiley & Sons: New York, 1993, Collect. Vol. 8, pp 550–556.
25. Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274–3277.
26. Carson, S.; Kocienski, P.; Reid, G.; Smith, N.; Street, J. M.; Webster, M. *Synthesis* **1994**, 1301–1309.