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Tandem 1,2-sulfur migration and (aza)-Diels–Alder reaction of β-thio-α-diazoimines: rhodium catalyzed synthesis of (fused)-polyhydropyridines, and cyclohexenes†

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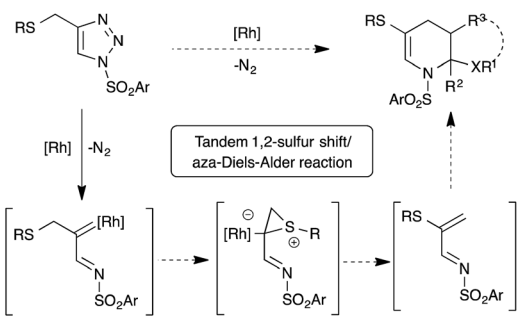
Rhodium catalyzed synthesis of substituted tetrahydropyridines was accomplished from readily accessible thio-tethered *N*-sulfonyl-1,2,3-triazoles. The reaction involves tandem rhodium catalyzed 1,2-sulfur migration in β-thio-α-diazoimines, generated from thio-tethered *N*-sulfonyl-1,2,3-triazoles, to thio-substituted 1-azadiene and subsequent self aza-Diels–Alder reaction. Interestingly, the methodology was effectively extended to the synthesis of fused tetrahydropyridines, dihydropyridines and cyclohexenes through the *in situ* trapping of the intermediate, 1-azadiene, with various dienophiles such as enol ether, enamine, ketene *S*,*S*-acetal, alkyne, alkene and diene. Furthermore, the direct conversion of propargyl sulfides to (fused)-tetrahydropyridines was also achieved through the successful integration of copper and rhodium catalysts in one-pot.

Introduction

1,2-Migration of atoms or groups is one of the fundamental reactions in organic synthesis. Particularly, 1,2-sulfur migration in various 1,2-functionalized thio-derivatives is an important tool for the construction of sulfur-containing building blocks and heterocycles.[1] For example, rhodium catalyzed 1,2-sulfur migrations in α-thio carbenes were documented for the synthesis of α-thio-α,β-unsaturated carbonyl compounds[2] and 3-alkoxycarbonyl β-lactam derivatives from β-thio-α-diazo carbonyl compounds.[3] Although 1,2-sulfur migrations in α-thio metalcarbenes have been reported, they are rather limited to only β-thio-α-diazo carbonyl compounds.

In the past few years, the use of readily accessible *N*-sulfonyl-1,2,3-triazoles[4] as a source of α-diazoimines has been greatly exploited in organic synthesis as a vital reactive intermediate.[5] Unlike traditional α-oxo metal carbenoids, metal carbenoids generated from α-diazoimines possess both an electrophilic carbon atom and nucleophilic nitrogen atom, which allows interesting inter/intramolecular reactions with various functional groups, like nitriles,[6] alkynes,[7] alkenes,[8] enol ethers[9]/enamines,[10] carbonyl compounds,[11] cumulenes,[12] C–H,[13] X–H[14] and C–X[15] bonds and other carbene induced transformations to functionalized carbo(hetero)cycles[16] and heteroatom-based building blocks.[17] Interestingly, 1,2-hydride or alkyl migrations onto the electrophilic carbenoid carbon of α-imino metal-carbenes were also reported.[18] Our contribution in this interesting field includes [2,3]-sigmatropic rearrangement with aryl allyl sulfides,[15a] chemo- and regioselective insertion into the *para* C–H bond of aniline derivatives[13c] and transannulation with enol ethers.[9b] Based on our continuous interest in the functionalization of *N*-sulfonyl-1,2,3-triazoles and potential 1,2-sulfur rearrangement, we envisioned rhodium catalyzed 1,2-sulfur migration in β-thio-α-diazoimines, generated from suitably substituted thio-tethered *N*-sulfonyl-1,2,3-triazoles, for the synthesis of thio-substituted 1-azadienes (Scheme 1).[19]

Thio-substituted 1-azadienes are potential building blocks for the synthesis of various polyhydropyridines[20] *via* (aza)-Diels–Alder reaction[21] (Scheme 1). These substituted polyhydropyridines are



Scheme 1 Rhodium catalyzed tandem 1,2-sulfur migration and aza-Diels–Alder reaction of β-thio-α-diazoimines derived from *N*-sulfonyl-1,2,3-triazoles.

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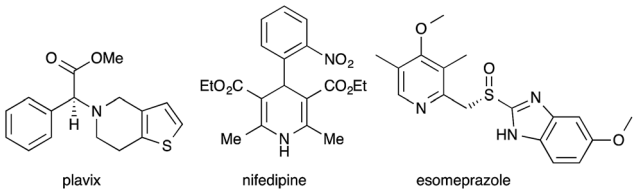


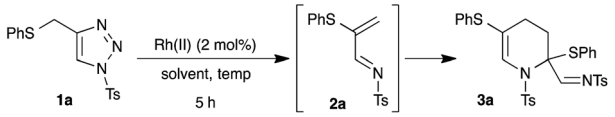
Fig. 1 Representative examples of commercialized polyhydropyridine and pyridine derivatives.

the most common heterocyclic scaffolds encountered in naturally occurring bioactive compounds and pharmaceutical drugs (Fig. 1).[22] In addition, they are also exploited as vital intermediates for the construction of piperidine and pyridine derivatives and organic hydride donors in biomimetic asymmetric transfer hydrogenation reactions.[23] Hence, development of new strategies to access these important scaffolds is of continued interest in contemporary organic and medicinal chemistry. We herein disclose the rhodium catalyzed synthesis of substituted polyhydropyridines from readily accessible thio-tethered *N*-sulfonyl-1,2,3-triazoles *via* tandem 1,2-sulfur migration and (aza)-Diels–Alder reaction.

Results and discussion

To test our hypothesis, we synthesized thio-tethered *N*-sulfonyl-1,2,3-triazole **1a** from phenyl propargyl sulfide and tosyl azide under CuAAC conditions[4a,4b] and **1a** was used as a suitable model substrate. The initial reaction of **1a** with 2 mol% of rhodium acetate at 75 °C in $CHCl_3$ for 5 h directly afforded the tetrahydropyridine **3a** in 43% yield (Table 1, entry 1). The structure of **3a** was unambiguously confirmed by X-ray analysis (Fig. 2).[24] The formation of **3a** can be explained through the initial rhodium catalyzed 1,2-sulfur migration in β-thio-α-diazoimines to **2a** followed by the concomitant self aza-Diels–Alder reaction of **2a**.

Table 1 Rhodium catalyzed synthesis of tetrahydropyridine **3a** from *N*-sulfonyl-1,2,3-triazole **1a**[a]



Entry	Rh(II) (2 mol%)	Solvent	Temp. (°C)	Yield[b] (%)
1	$Rh_2(OAc)_4$	$CHCl_3$	75	43
2	$Rh_2(OAc)_4$	$CHCl_3$	90	55
3	$Rh_2(OAc)_4$	Toluene	90	80
4	$Rh_2(OAc)_4$	1,2-DCE	90	94
5	$Rh_2(Oct)_4$	1,2-DCE	90	85
6	$Rh_2(DOSP)_4$	1,2-DCE	90	93
7	$Rh_2(TBSP)_4$	1,2-DCE	90	94
8	$Rh_2(OAc)_4$	1,2-DCE	90	83[c]

[a] Reaction conditions: triazole **1a** (0.15 mmol), Rh(II) (2 mol%), solvent (1 mL), temp., 5 h. [b] All are isolated yield of **3a**. [c] 3 h.

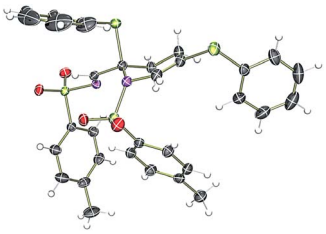
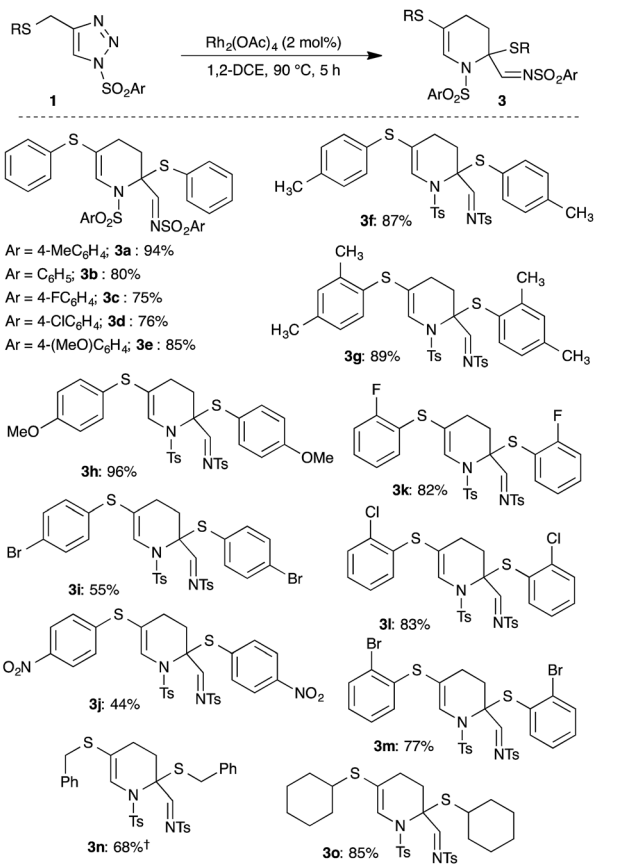


Fig. 2 ORTEP diagram of compound **3a**. The thermal ellipsoids are set at 30% probability.

To improve the reaction conditions, various critical parameters were examined. Increasing the temperature to 90 °C gave **3a** in 55% yield (Table 1, entry 2). A drastic increase in the yield to 80 and 94% was observed while changing the solvents to toluene and 1,2-dichloroethane (1,2-DCE), respectively, at 90 °C (Table 1, entries 3 and 4). Shortening the reaction time to 3 h led to a slight decrease in the yield (Table 1, entry 8). Similar results were observed with other rhodium based catalysts such as $Rh_2(Oct)_4$, $Rh_2(DOSP)_4$ and $Rh_2(TBSP)_4$ (Table 1, entries 5–7). Based on these studies, we chose the following reaction conditions for studying the scope and limitations of the present reaction: 2 mol% of $Rh_2(OAc)_4$ in 1,2-DCE at 90 °C.‡



Scheme 2 Rhodium catalyzed synthesis of tetrahydropyridines **3**: scope and limitations. †10 h.

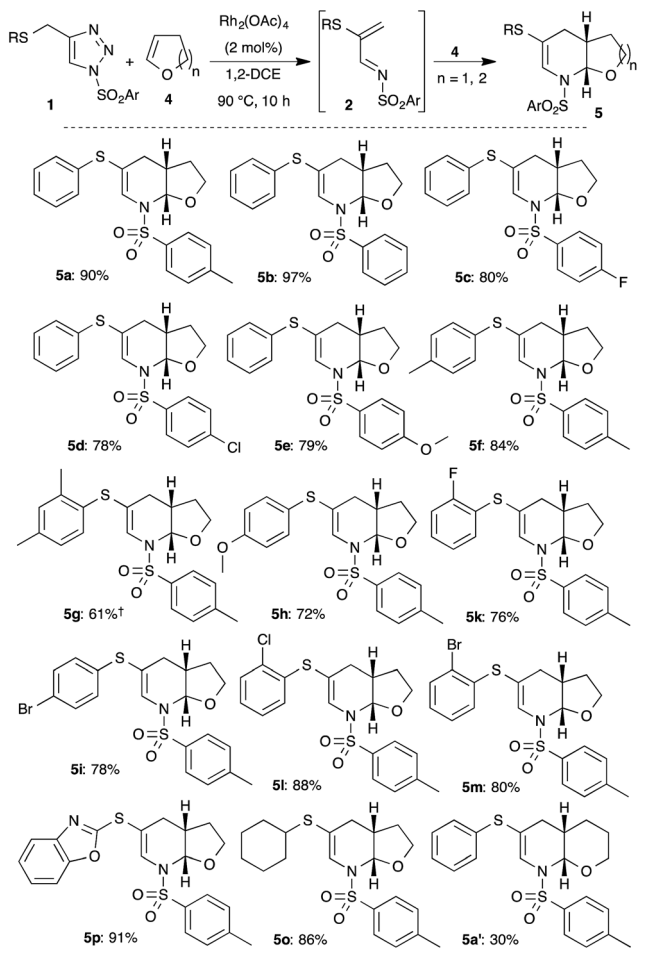
After identifying the best reaction conditions, the scope and limitations of various thio-tethered *N*-sulfonyl-1,2,3-triazoles **1** were examined. An initial change at the aryl moiety of the sulfonyl group did not show any influence on the outcome of the reaction and facilitated the formation of corresponding tetrahydropyridines (**3a–3e**) in comparable yields (Scheme 2).

Subsequently, the effect of substitution on the thio-side chain was investigated (Scheme 2). The presence of simple aryl groups like 4-methylphenyl and 2,4-dimethylphenyl were well tolerated and gave the corresponding products **3f** and **3g** in 87% and 89% yield, respectively. Both electron-rich and electron-deficient aryl sulfides were also tolerated under the optimized conditions, but an electron deficient aryl sulfide furnished the product **3j** in low yield compared to an electron rich aryl sulfide (**3h**). Interestingly, synthetically useful halogen-substituted aryl-containing tetrahydropyridines **3i**, **3k–3m** were achieved in good to excellent yield. Also, sterically hindered aryl sulfides underwent smooth reaction to afford products **3g**, **3k–3m** in good yield. Furthermore, benzyl and alkyl sulfides also gave the products **3n** and **3o** in 68% and 85% yield, respectively.

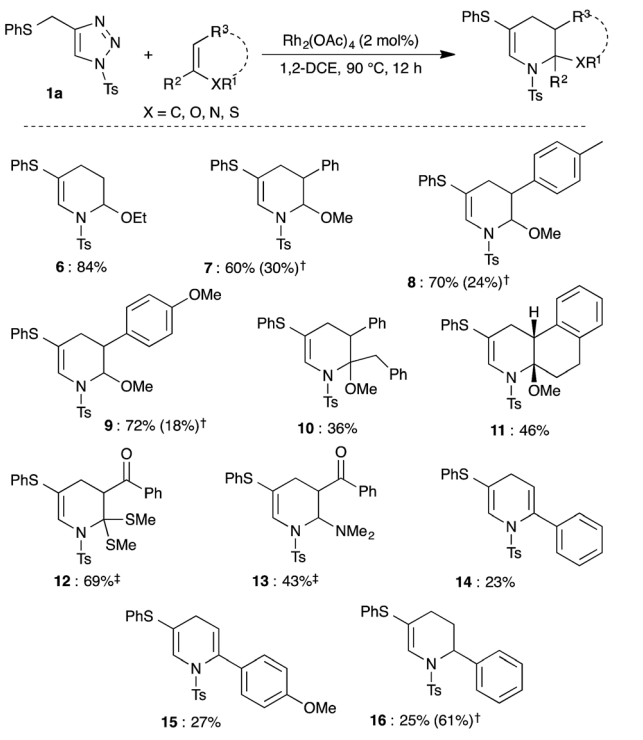
After successful demonstration of generation of various 1-azadienes and the self aza-Diels–Alder reaction, we were interested in the *in situ* trapping of the formed 1-azadiene **2** with external dienophiles, such as dihydrofuran **4**. Gratifyingly, the reaction of triazole **1a** with 4 equivalents of dihydrofuran **4** under the optimized conditions at prolonged reaction time (10 h) afforded the bicyclic compound, tetrahydrofuran fused tetrahydropyridine **5a** in 90% yield (Scheme 3).§

Having shown the efficient synthesis of fused-tetrahydropyridines through *in situ* trapping of 1-azadiene, we focused our attention on the generality of the reaction. Keeping the dienophile, dihydrofuran **4** (4 equiv.) as constant, various substituted thio-tethered *N*-sulfonyl-1,2,3-triazoles **1** were studied under the optimized conditions (Scheme 3). Electronically and sterically different aryl substituted sulfonyl triazoles furnished the fused tetrahydropyridines **5a–5e** in good to excellent yield. Similarly, various thioaryl containing tetrahydropyridines (**5f–5i** and **5k–5m**) were also achieved in good yields from corresponding 1,2,3-triazoles. Interestingly, heteroaryl, benzoxazol-2-yl substituted sulfide-containing triazole was also tolerated under the reaction conditions to give the corresponding product **5p** in 91% yield. Cyclohexyl sulfide, an alkyl sulfide substituted triazole also furnished the product **5o** in 86% yield. Furthermore, synthesis of pyran-fused tetrahydropyridine **5a′** was also achieved on replacement of dihydrofuran with dihydropyran.

All the above studies prompted us to investigate various other potential dienophiles under the rhodium catalyzed tandem 1,2-sulfur migration and aza-Diels–Alder reaction with **1a** to further widen the scope of the reaction. Thus, reaction of **1a** and ethylvinyl ether in the presence of $Rh_2(OAc)_4$ at 90 °C for 12 h gave the tetrahydropyridine **6** in 84% yield (Scheme 4).



Scheme 3 Rhodium catalyzed synthesis of fused-tetrahydropyridines **5**: scope and limitations. †Isolated as mixture of **5g** : **3g** in 1 : 0.18 ratio.



Scheme 4 Rhodium catalyzed reaction of **1a** with various dienophiles. †Yield of **3a**. ‡NMR yield.

β-Aryl substituted enol ethers underwent smooth reaction at prolonged reaction time (12 h) to afford the expected products (**7–9**) in good to moderate yield, along with an isolable amount of self aza-Diels–Alder reaction product **3a**. Next, reaction of α,β-disubstituted enol ether with **1a** gave the corresponding tetrahydropyridine **10** in 36% yield. Interestingly, the present method also allows the synthesis of tricyclic compound **11** in 46% yield from the cyclic enol ether derived from β-tetralone. Reaction of ketene *S*,*S*-acetal[25] with **1a** furnished the product **12** in 69% ^{1}H NMR yield, as an inseparable mixture along with ketene *S*,*S*-acetal. Similarly, enamine was also tolerated under the optimized conditions to afford the corresponding product **13**. Consequently, neutral dienophiles such as alkynes and alkenes were also examined (Scheme 4). Reaction of **1a** with phenylacetylene and *p*-methoxyphenylacetylene gave dihydropyridines **14** and **15**, respectively, in low yield along with decomposition of starting material. Similar results were observed on reaction of **1a** with styrene, which led to the formation of tetrahydropyridine **16** in 25% yield along with 61% of **3a**.

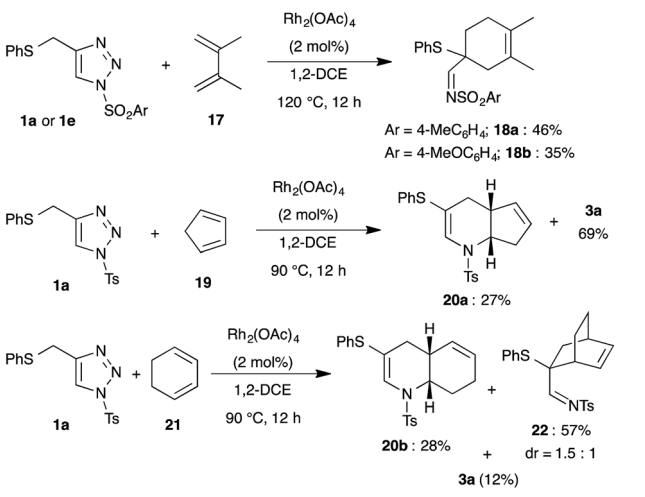
Likewise, dienes were also employed as reaction partners to examine the mode of reactivity (Scheme 5). Treatment of **1a** and 2,3-dimethyl-1,3-butadiene **17** in the presence of $Rh_2(OAc)_4$ at 90 °C led to the formation of cyclohexene **18a** in very low yield following normal Diels–Alder mode, wherein the formed 1-azadiene **2a** acted as a dienophile instead of diene. Increasing the reaction temperature to 120 °C afforded the product **18a** in 46% yield along with decomposition of the starting material. A similar result was also observed with 1,2,3-triazole **1e** and **17**.

Interestingly, bicyclic[4.3.0]-compound **20a** was isolated in moderate yield upon reaction with cyclopentadiene **19**, where cyclopentadiene acted as a dienophile. Reaction of **1a** with cyclohexadiene **21** furnished a mixture of bicyclic[4.4.0]-compound **20b**, bridged bicyclic[2.2.2]-compound **22** and **3a** in 28%, 57% and 12% yield, respectively. Thus, the isolated product showed that cyclohexadiene reacted mainly as a diene similar to **17**.

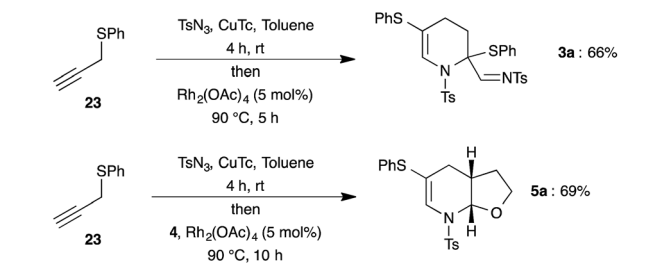
After successful demonstration of reactivity of various dienophiles and dienes with *N*-sulfonyl-1,2,3-triazoles, we focused our attention on the direct synthesis of (fused)-tetrahydropyridines (**3a** and **5a**) from propargyl sulfide **23** through integration of copper catalyzed azide–alkyne cycloaddition and rhodium catalyzed tandem 1,2-sulfur migration *cum* aza-Diels–Alder reaction (Scheme 6). To our delight, treatment of phenyl propargyl sulfide **23** with TsN_3 in the presence of CuTc for 4 h at room temperature in toluene followed by addition of $Rh_2(OAc)_4$ and subsequent elevation of temperature to 90 °C afforded the expected product **3a** in 66% yield. Likewise, fused tetrahydropyridine **5a** was also isolated in 69% yield from phenyl propargyl sulfide **23** on reaction with CuTc followed by addition of $Rh_2(OAc)_4$ and dihydrofuran **4**, in one-pot.

Next, the synthetic potential of the developed methodology was investigated (Scheme 7). The imine moiety in the product **3m** can be readily converted to aldehyde functionality in high yield through treatment with K_2CO_3 in methanol. Interestingly, spiro-bicyclic compound **25** was accomplished from the tetrahydropyridine **3m** through $NaBH_3CN$ reduction of imine followed by copper catalyzed intramolecular C–N bond formation (Scheme 7). Additionally, the synthesized tetrahydropyridines can also be readily transformed to pyridine derivatives. Thus, the reaction of **9** with TMSOTf furnished the aromatized product **26** in 75% yield.

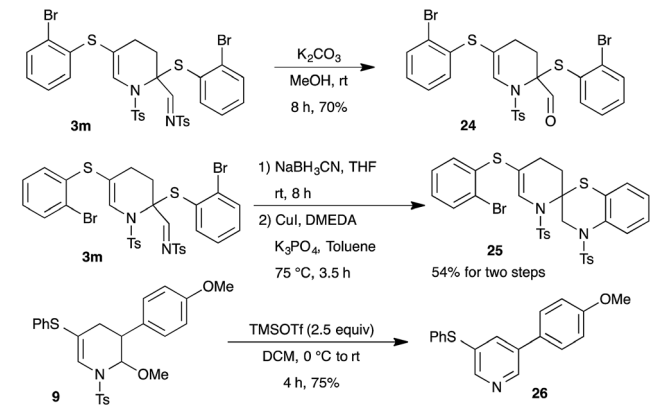
Based on the earlier report of 1,2-sulfur migration[1a] and denitrogenative functionalization of 1,2,3-triazoles,[5a,5b] we postulated the mechanism for the synthesis of tetrahydropyridines from *N*-sulfonyl-1,2,3-triazoles (Scheme 8). First, trapping of α-diazoimines **A**, generated from 1,2,3-triazole **1**, with the rhodium



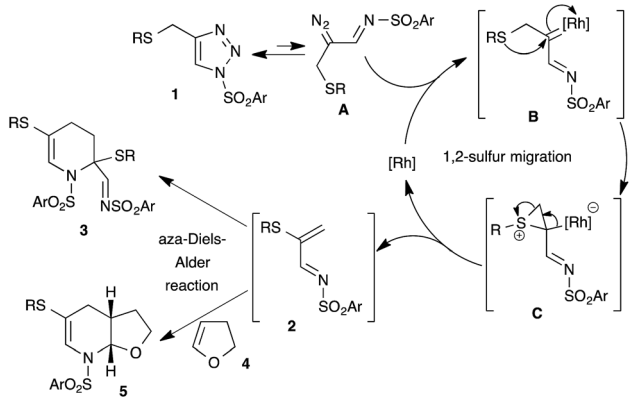
Scheme 5 Rhodium catalyzed reaction of **1a** with dienes.



Scheme 6 One-pot conversion of propargyl sulfide **23** to **3a** and **5a**.



Scheme 7 Synthetic applications.



Scheme 8 Plausible mechanism.

catalyst would afford the reactive rhodium carbenoid **B**. Intramolecular attack of the sulfur atom onto the electrophilic carbenoid carbon would lead to the formation of thiiranium intermediate **C**, which upon rearrangement would furnish the 1-azadiene **2** and active rhodium species for the next catalytic cycle. Dimerization of the formed 1-azadiene **2** under thermal aza-Diels–Alder conditions furnishes the expected tetrahydropyridines **3**. On the other hand, *in situ* trapping of 1-azadiene **2** with other dienophiles and dienes would afford the corresponding heterocycles and carbocycles.

Conclusions

In conclusion, we developed an efficient rhodium catalyzed tandem 1,2-sulfur migration and aza-Diels–Alder reaction of thio-tethered *N*-sulfonyl-1,2,3-triazoles. The present method allows the synthesis of various substituted tetrahydropyridines, fused tetrahydropyridines, tricyclic and (bridged)bicyclic compounds and cyclohexenes in moderate to excellent yield. Interestingly, the developed strategy was successfully integrated with copper catalyzed azide–alkyne cycloaddition for the direct conversion of propargyl sulfide to the target compounds. Furthermore, the synthetic potential of the methodology was demonstrated through the synthesis of spiro-bicyclic and substituted pyridine derivatives.

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Notes and references

‡ Synthesis of tetrahydropyridine **3a**: to an oven dried 10 mL reaction tube equipped with stir bar, *N*-sulfonyl-1,2,3-triazole **1a** (50 mg, 0.144 mmol) and $Rh_2(OAc)_4$ (1.28 mg, 0.0028 mmol, 2 mol%) were added under a nitrogen atmosphere and dissolved in 1,2-DCE (1 mL). The reaction tube was sealed and the reaction mixture was stirred at 90 °C for 5 h. After the completion of reaction, based on TLC analysis, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resultant crude was purified by column chromatography using hexane/ethyl acetate (9 : 1) as eluant to afford tetrahydropyridine **3a** in 94% yield. Mp: 131–133 °C; FTIR (KBr): 3101, 2956, 1620, 1595, 1472, 1439, 1331, 1163, 1088, 1040, 960, 835, 812, 787, 743, 691, 664, 566, 538, 502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 8.71 (s, 1H), 7.87 (d, 2H, J = 8.24 Hz), 7.44–7.34 (m, 7H), 7.32–7.25 (m, 6H), 7.22–7.20 (m, 3H), 7.13 (s, 1H), 2.49 (s, 3H), 2.44 (s, 1H), 2.41 (s, 3H), 2.05 (dd, 1H, J = 6.09, 18.12 Hz), 1.92 (dd, 1H, J = 6.92, 14.66 Hz), 1.66–1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 24 °C): δ 168.7, 145.2, 144.9, 137.5, 135.3, 134.8, 133.1, 130.6, 130.0, 129.3, 129.3, 129.2, 129.1, 128.6, 127.7, 127.0, 126.7, 119.0, 71.8, 28.0, 25.3, 21.8, 21.7; HRMS: calcd for $C_{32}H_{30}N_2O_4S_4$ + H: 635.1161; found: 635.1152.

§ Synthesis of fused tetrahydropyridines **5a**: to an oven dried 10 mL reaction tube equipped with stir bar, *N*-sulfonyl-1,2,3-triazole **1a** (50 mg, 0.144 mmol) and $Rh_2(OAc)_4$ (1.28 mg, 0.0028 mmol, 2 mol%) were added under a nitrogen atmosphere and dissolved in 1,2-DCE (1 mL). Next, 2,3-dihydrofuran **4** (40 mg, 0.576 mmol, 4 equiv.) was introduced through a syringe. The reaction tube was sealed and the reaction mixture was stirred at 90 °C for 10 h. After the completion of reaction, based on TLC analysis, the reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The resultant crude was purified by column chromatography using hexane/ethyl acetate (92 : 8) as eluant to furnish the fused tetrahydropyridine **5a** in 90% yield. Mp: 121–123 °C; FTIR (KBr): 3052, 2941, 2889, 1640, 1598, 1475, 1436, 1404, 1351, 1240, 1106, 1027, 967, 862, 803, 746, 695, 667, 587, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 24 °C): δ 7.83 (d, 2H, J = 8.16 Hz), 7.33 (d, 2H, J = 8.36 Hz), 7.29–7.26 (m, 2H), 7.23–7.17 (m, 3H), 7.14–7.13 (m, 1H), 5.55 (d, 1H, J = 4.36 Hz), 3.84–3.77 (m, 1H), 2.45 (s, 3H), 2.35–2.32 (m, 1H), 2.22 (dd, 1H, J = 6.64, 17.14 Hz), 2.13–2.08 (m, 1H), 1.98–1.92 (m, 1H), 1.74–1.70 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 24 °C): δ 144.4, 136.8, 135.5, 129.8, 129.1, 128.7, 128.6, 127.6, 126.3, 108.9, 83.9, 64.4, 35.8, 29.9, 28.4, 21.7; HRMS: calcd for $C_{20}H_{21}NO_3S_2$ + H: 388.1041; found: 388.1056.

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