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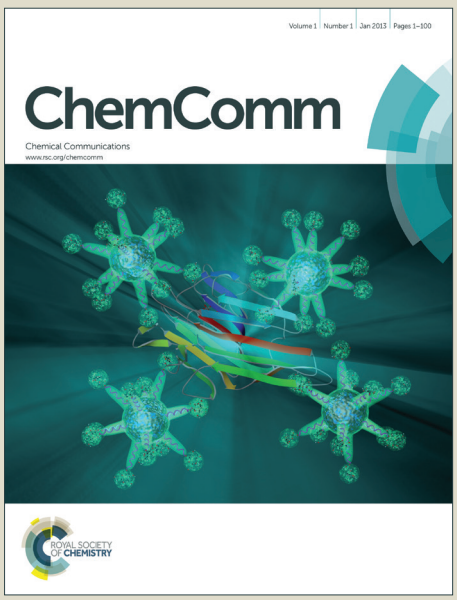

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Rhodium-Catalyzed Direct Synthesis of Unprotected NH-Sulfoximines from Sulfoxides

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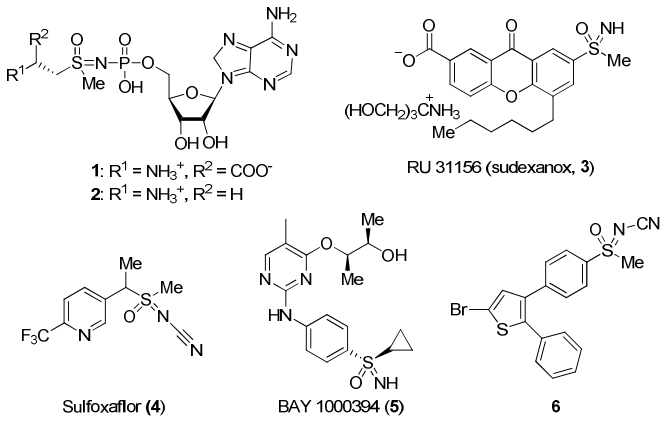
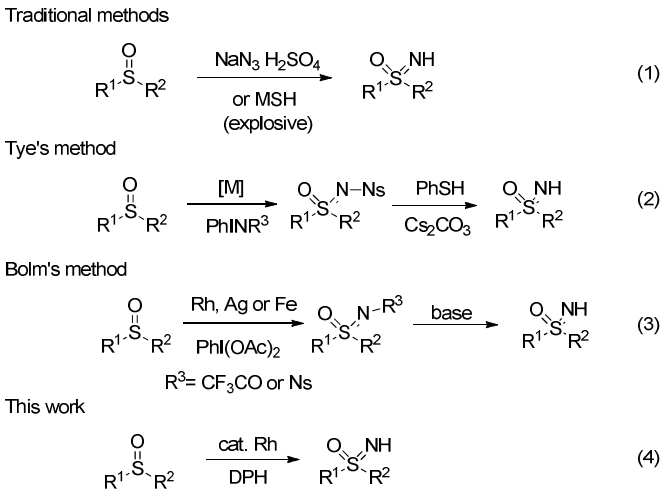
A novel rhodium-catalyzed imination of sulfoxides with *O*-(2,4-dinitrophenyl)hydroxylamine is developed under mild conditions with good functional group tolerance. This method provides an efficient excess to free NH-sulfoximines, an important structural unit in a variety of biologically active compounds.

Sulfoximines have recently attracted great attention in biochemistry and medicinal chemistry because of their versatile chemical properties and diverse bioactivities.[1] Since the discovery of the first sulfoximine, methionine sulfoximine, a number of bioactive compounds containing a sulfoximine moiety in the pharmacophore have been reported (Scheme 1). For example, compound **1** and **2** are transition-state-analogue inhibitors of L-asparagine synthetase;[2] sudexanox (RU31156, **3**) was selected for clinic studies as a prophylactic antiasthmatic;[3] sulfoxaflor (**4**) is the first commercially available sulfoximine insecticide;[4] Bay 1000394 (**5**) is an excellent cyclin-dependent kinase inhibitor, which is currently being evaluated in a Phase I clinical trial for activity against advanced solid tumors;[5] finally, one of the enantiomers of **6** shows good anti-proliferative activity against various cancer cell lines.[6]

Scheme 1 Bioactive sulfoximines



Scheme 2 Preparation of unprotected NH-sulfoximines

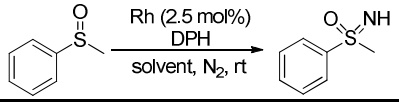


Among the small number of synthetic strategies for preparing sulfoximines, the most straightforward approach employs direct imination of sulfoxides (Scheme 2). However, traditional methods require the usage of either toxic or potentially explosive reagents, such as the combination of NaN_3 and sulfuric acid,[7] or *O*-mesitylene sulfonylhydroxylamine (MSH) (eq. 1).[8] To overcome these drawbacks, considerable efforts have been devoted to developing transition metal-catalyzed sulfoxide imination, with significant progress being achieved in recent years.[9] For example, Tye reported the synthesis of sulfoximines by copper-catalyzed imination of sulfoxides with PhI=NNs (Ns = para-nitrobenzenesulfonyl) and PhI=NSes (Ses = trimethylsilylethylsulfonyl) (eq. 2);[9f] Bolm discovered that this process could be efficiently performed via

rhodium[9h], silver[9i], or iron[9l,m] catalysis using iminoiodinanes generated *in-situ* from the oxidation of amides by $PhI(OAc)_2$ (eq. 3). In spite of this powerful approach, the transition metal-catalyzed imination of sulfoxides gives protected sulfoximines, requiring an additional step for removal of the undesired protecting group. Inspired by a recent report from Kürti and co-workers describing the rhodium-catalyzed synthesis of unprotected NH-aziridines from olefins using *O*-(2,4-dinitrophenyl)hydroxylamine (DPH),[10] we have developed the first transition metal-catalyzed *direct* synthesis of free NH-sulfoximines from sulfoxides under mild conditions (eq. 4).

Our investigation began with direct imination of phenyl methyl sulfoxide using 1.5 eq. of *O*-(2,4-dinitrophenyl)hydroxylamine (DPH) in the presence of 2.5 mol % of $Rh_2(esp)_2$ at room temperature. After screening a large number of solvents, trifluoroethanol (TFE) was found to be optimal, giving the desired free NH-sulfoximine product **2a** in 61% yield (Table 1, entry 1). Further screening of Rh(II) catalysts revealed that this process could also be catalyzed by $Rh_2(OAc)_4$, albeit with lower efficiency (entry 11). Additionally, Rh(I) did not show catalytic activity in the imination reaction (entry 13).[10] Finally, using an increased amount of DPH gave an optimal yield for the imination reaction (entry 19).

Table 1. Optimization of reaction conditions.[a]

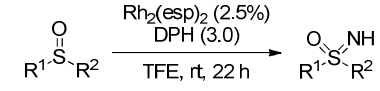


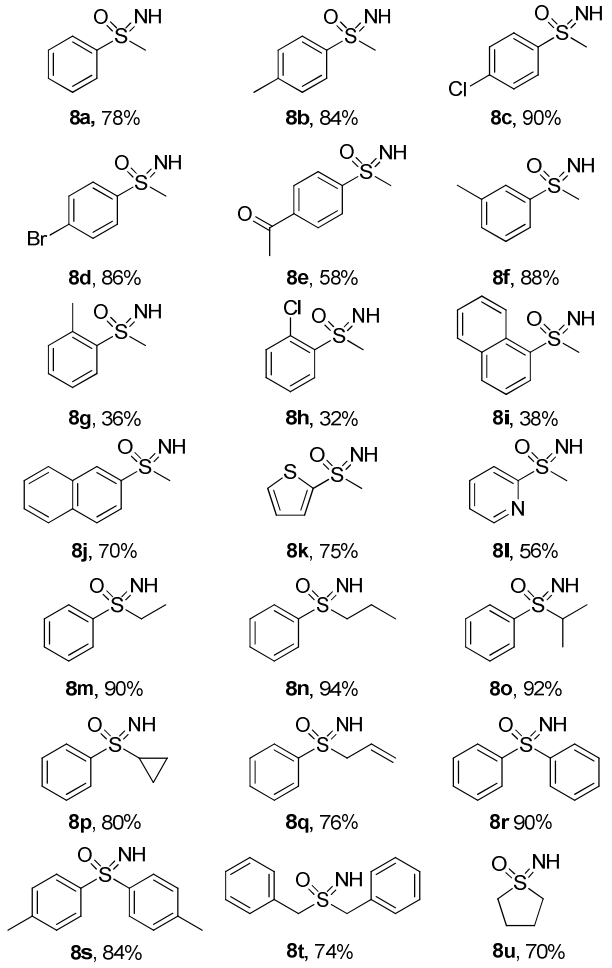
Entry	Rh catalyst	Eq. of DPH	Solvent	Yield (%)[b]
1	$Rh_2(esp)_2$	1.5	TFE	61
2	$Rh_2(esp)_2$	1.5	MeOH	32
3	$Rh_2(esp)_2$	1.5	MeCN	48
4	$Rh_2(esp)_2$	1.5	^{n}PrCN	44
5	$Rh_2(esp)_2$	1.5	PhCN	42
6	$Rh_2(esp)_2$	1.5	EtOH	30
7	$Rh_2(esp)_2$	1.5	^{i}PrOH	22
8	$Rh_2(esp)_2$	1.5	^{t}BuOH	trace
9	$Rh_2(esp)_2$	1.5	HFIP	39
10	$Rh_2(esp)_2$	1.5	DCM	12
11	$Rh_2(OAc)_4$	1.5	TFE	23
12	$Rh_2(TFA)_4$	1.5	TFE	trace
13	$Rh(PPh_3)_3Cl$	1.5	TFE	0
14	$Rh_2(oct)_4$	1.5	TFE	0
15[c]	$Rh_2(esp)_2$	1.5	TFE	50
16[d]	$Rh_2(esp)_2$	1.5	TFE	60
17	$Rh_2(esp)_2$	1.0	TFE	48
18	$Rh_2(esp)_2$	2.0	TFE	72
19	$Rh_2(esp)_2$	3.0	TFE	78

[a] Reactions were conducted on a 0.3 mmol scale. Conditions: **1a** (0.3 mmol), Rh catalyst (2.5 mol %), DPH (1 -3 eq), 3 ml solvent, room temperature under N_2 atmosphere, 22 h unless otherwise noted. [b] Isolated yields. [c] 40 °C. [d] 0 °C. DPH = *O*-(2,4-dinitrophenyl)hydroxylamine. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate. TFE = 2,2,2-tifluoroethanol. HFIP = hexafluoroisopropanol.

With optimized conditions in hand, we evaluated the generality of the method using a variety of sulfoxides as substrates (Table 2). As expected, functional groups such as methyl, halogen (Cl, Br), or an acyl group on the phenyl ring were well tolerated (**8a-8h**). Not surprisingly, the *para*-acyl substituted sulfoxide led to a lower yield, perhaps as a result of the electron-withdrawing effect of the acyl group acting to decrease the reactivity of sulfoxide (**8e**). Furthermore, an apparent steric effect was observed in the imination reaction because significantly lower yields were observed with sulfoxides bearing a substituent at the *ortho* position of the phenyl ring (**8g** and **8h**). The nature of the aryl sulfoxides was not limited, however, to the phenyl ring and naphthanyl, electron-rich 2-thiophenyl, and electron-deficient 2-pyridyl methyl sulfoxides were also found to be effective substrates for the Rh(II)-catalyzed imination reaction (**8i-8l**). On the other hand, 1-naphthanyl and 2-pyridyl methyl sulfoxides provided only modest yields, presumably due to steric and electronic factors, respectively (**8i** and **8l**). In an important observation for the preparation of sulfoximine-based small molecules, the methyl group on the phenyl methyl sulfoxide could be successfully replaced by other alkyl groups, including the cyclopropyl group, to afford the corresponding sulfoximines in high yields (**8m-8p**). Interestingly, when phenyl allyl sulfoxide was employed in the reaction, selective sulfoximination was favoured over aziridination (**8q**).[10]

Table 2. Substrate scope.





Reactions were conducted on a 0.3 mmol scale. Conditions: 1 (0.3 mmol), $Rh_2(esp)_2$ (0.0075 mmol, 2.5 mol%), DPH (0.9 mmol, 3.0 eq.), TFE (3ml, 0.1 M), room temperature, N_2 atmosphere, 22 h.

In addition, diaryl sulfoximines could be effectively prepared with this method from the corresponding sulfoxides (**8r** and **8s**), and we were pleased to find that both acyclic and cyclic dialkyl sulfoxides were compatible with this reaction (**8t** and **8u**).

Although the reaction mechanism of this transformation has not been investigated, it is likely that a rhodium-nitrene species is an intermediate based on prior literature reports.[9h,10] Thus, coordination of DPH to $Rh_2(esp)_2$, followed by loss of dinitrophenol, likely generates a reactive nitrene intermediate, which then oxidizes the metal-coordinated sulfoxide to the corresponding sulfoximine.

Conclusions

In summary, a novel, efficient, and safe method for the preparation of free NH-sulfoximines has been developed via rhodium-catalyzed imination of sulfoxides using *O*-(2,4-dinitrophenyl)hydroxylamine. This new approach features mild conditions and good functional group tolerance, which should permit its application to the synthesis of structurally complex sulfoximines with agrochemical and clinical utility.[1g]

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Electronic Supplementary Information (ESI) available: [Experimental details and spectral data]. See DOI: 10.1039/c000000x/

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