

Iridium-Catalyzed X–H Insertions of
Sulfoxonium Ylides

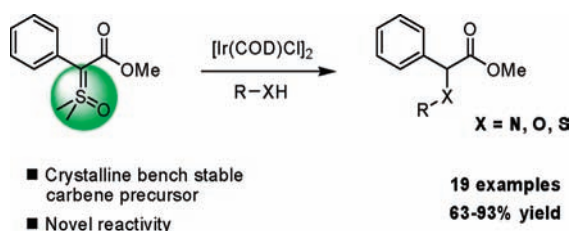
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ABSTRACT



The unique reactivity of sulfoxonium ylides as a carbene source is described for a variety of X–H bond insertions, taking advantage of a simple, commercially available iridium catalyst. This method has applications in both intra- and intermolecular reactivity, including a practical ring-expansion strategy for lactams. The safety and stability of sulfoxonium ylides recommend them as preferable surrogates to traditional diazo ketones and esters.

Metal-catalyzed insertion of organic diazo compounds into X–H bonds (X = C, N, O, S) has long been recognized as a mild and efficient method for accessing an array of important functionalized structural motifs.¹ In particular, α -diazocarbonyls have found broad utility as metal carbene precursors and have been applied in a variety of intra- and intermolecular bond insertion strategies.² Despite the widespread acceptance of α -diazocarbonyls in carbene methodology, there are important limitations due to the safety issues associated with their synthesis and the procedural inconvenience of their instability to extended storage.³ We took great interest in a report from Baldwin et al.⁴ that demonstrated the ability of β -keto sulfoxonium ylides to perform intramolecular N–H insertions mediated by a rhodium(II) catalyst.

Rhodium carbenoids were invoked as intermediates in analogy to known α -diazocarbonyl chemistry. Surprisingly, no further applications of sulfoxonium ylides in carbene chemistry have been reported, perhaps owing to the modest yields reported or the limited substrate scope.⁵ Herein we describe our initial findings of a more general approach for generation of metal carbenes from sulfoxonium ylides.

We began investigations by treating ylide **1** with transition metal catalysts in the presence of aniline to look for intermolecular N–H insertion reactivity (Table 1).⁶ To our delight, it was found that in the presence of $\text{Rh}_2(\text{OAc})_4$ (5 mol %) the insertion product **2a** could be obtained, albeit in just 7% yield (entry 1).⁷ Use of $\text{Rh}_2(\text{TFA})_4$ increased the yield somewhat (22% yield, entry 2), but conversion of **1** consistently stalled, suggesting catalyst deactivation was

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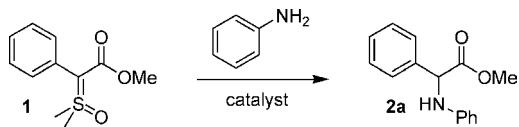
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(5) For the synthesis of metal carbenes from sulfonium ylides, see: (a) Gandelman, M.; Rybtchinski, B.; Ashkenazi, N.; Gauvin, R. M.; Milstein, D. *J. Am. Chem. Soc.* **2001**, 123, 5372. (b) Gandelman, M.; Naing, K. M.; Rybtchinski, B.; Poverenov, E.; Ben-David, Y.; Ashkenazi, N.; Gauvin, R. M.; Milstein, D. *J. Am. Chem. Soc.* **2005**, 127, 15265.

(6) For reviews on the reactivity of related donor/acceptor diazo compounds, see: (a) Davies, H. M. L.; Antoulnakis, E. G. *Org. React.* **2001**, 57, 1. (b) Davies, H. M. L.; Loe, Ø. *Synthesis* **2004**, 16, 2595. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, 451, 417.

(7) In the absence of catalyst, no reaction was observed.

Table 1. Catalyst Development for N–H Insertion of Aniline with Sulfoxonium Ylide **1**^a



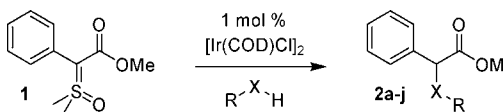
entry	catalyst	mol % ^b	solvent	yield (%) ^c
1	Rh ₂ (OAc) ₄	5	toluene	7
2	Rh ₂ (TFA) ₄	5	toluene	22
3	[Ru(cym)Cl ₂] ₂	2	toluene	12
4	RuCl ₂ (PPh ₃) ₃	2	toluene	55
5	RuCl ₂ (Cp)(PPh ₃) ₂	2	toluene	66
6	RuCl ₂ (DMSO) ₄	2	toluene	59
7	[Ir(COD)Cl] ₂	1	toluene	85
8	[Ir(COD)Cl] ₂	1	THF	79
9	[Ir(COD)Cl] ₂	1	DMF	77
10	[Ir(COD)Cl] ₂	1	CH ₂ Cl ₂	91
11	[Ir(COD)Cl] ₂	1	DCE	90
12	Ir(COD) ₂ BF ₄	1	CH ₂ Cl ₂	84
13	Ir(COD) ₂ BARF	1	CH ₂ Cl ₂	78

^a All reactions conducted at 0.1 M at 23 °C for 10 h in degassed solvent under nitrogen. ^b Catalyst loading. ^c Isolated yield.

occurring. We suspected that DMSO, the byproduct of sulfoxonium ylide decomposition, was inhibiting rhodium catalysis.⁸ This idea was confirmed by control experiments in which addition of 25 mol % DMSO was sufficient to suppress reactivity in reactions catalyzed by Rh₂(OAc)₄ or Rh₂(TFA)₄. To overcome this deactivation pathway, we began screening a variety of metals to find a more robust catalyst system.⁹ Ruthenium-based catalysts afforded higher yields at a lower loading (12–66% yield, entries 3–6).¹⁰ Notably, RuCl₂(DMSO)₄ was a competent catalyst, perhaps supporting the idea that resistance to DMSO deactivation is key to ruthenium activity. Surprisingly, even better results were obtained with an iridium catalyst, [Ir(COD)Cl]₂, in noncoordinating solvents such as CH₂Cl₂ (91% yield, entry 10). Alternative iridium(I) catalysts afforded comparable conversion (78–84% yield, entries 12 and 13). This represents a rare instance of iridium catalysis in carbene catalysis and the first instance we have found where iridium has been shown to mediate an N–H bond insertion.¹¹

A range of nucleophiles was evaluated in the iridium-catalyzed decomposition of **1** (Table 2). Both electron-withdrawing and -donating groups are tolerated in the N–H

Table 2. X–H Insertion Reactions of Ylide **1**^a



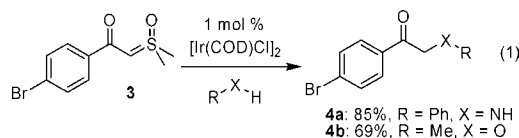
entry	R	X	product	yield (%) ^b
1	Ph	NH	2a	91
2	<i>p</i> -FC ₆ H ₄	NH	2b	93
3	<i>p</i> -MeOC ₆ H ₄	NH	2c	76
4	<i>p</i> -CF ₃ C ₆ H ₄	NH	2d	85
5	Ph	NMe	2e	89 ^c
6	2-naphthyl	NH	2f	82
7	Et	O	2g	86 ^{d,e}
8	<i>i</i> -Pr	O	2h	63 ^f
9	TMSCH ₂ CH ₂	O	2i	73 ^d
10	Ph	S	2j	80

^a All reactions conducted at 0.1 M at 23 °C for 4–18 h in degassed CH₂Cl₂ under nitrogen using 2.0 equiv of nucleophile except where noted.

^b Isolated yield. ^c Reaction conducted at 70 °C using DCE as solvent.

^d Reaction conducted at 35 °C. ^e Performed in neat EtOH. ^f Performed in neat *i*-PrOH at 80 °C.

insertion of substituted anilines (76–93% yield, entries 2–4). A secondary aniline also afforded good yield of the desired α-amino ester (**2e**, entry 5), though only with elevated temperature.¹² Alcohols perform well in analogous O–H insertions; surprisingly, these reactions can be performed in neat alcohol as solvent for optimal conversion (63–86% yield, entries 7–9). S–H insertion was also demonstrated in high yield with thiophenol (80% yield, entry 10). In a similar fashion, β-keto sulfoxonium ylide **3** can engage in N–H or O–H insertion processes (eq 1).



Efforts were then dedicated toward demonstrating other carbene transformations such as C–H insertion and cyclopropanation.¹³ Ylides **1** and **3** were subjected to a range of alkanes and alkenes with known reactivity in α-diazocarbonyl chemistry.¹⁴ However, neither of the desired transformations was ever observed. To simplify the problem, β-keto sulfoxonium ylide **5** was synthesized to probe for intramolecular reactivity. It was expected that the comparative lability of

(8) Modulation of metal carbene reactivity by coordinating solvents has been observed previously. See, for example: Nelson, T. D.; Song, Z. J.; Thompson, A. S.; Zhao, M.; DeMarco, A.; Reamer, M. A.; Huntington, M. F.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **2000**, *41*, 1877.

(9) Production of DMSO during the reaction was confirmed by ¹H NMR.

(10) For Ru-based carbene catalysis, see: (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223. (b) Del Zotto, A.; Baratta, W.; Rigo, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3079. (c) Deng, Q.-H.; Xu, H.-W.; Yuen, A. W.-H.; Xu, Z.-J.; Che, C.-M. *Org. Lett.* **2008**, *10*, 1529.

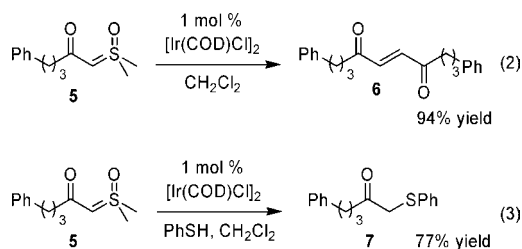
(11) For Ir-catalyzed cyclopropanation or polymerization, see also: (a) Kanchiku, S.; Suematsu, H.; Matsumoto, K.; Uchida, T.; Katsuki, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 3889. (b) Xiao, X.-Q.; Jin, G.-X. *J. Organomet. Chem.* **2008**, *693*, 3363.

(12) Aliphatic amines did not react under these conditions and suppressed catalyst activity for other substrates.

(13) For C–H insertion of iridium complexes, see: (a) Liu, F.; Goldman, A. S. *Chem. Commun.* **1999**, 2273. (b) Kawamura, K.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 8422. (c) Whited, M. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 5874. (d) Romero, P. E.; Whited, M. T.; Grubbs, R. H. *Organometallics* **2008**, *27*, 3422. (e) Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534.

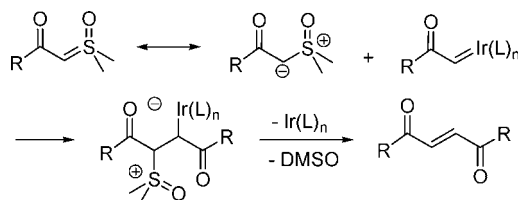
(14) (a) Doyle, M. P.; Protopenova, M. N. *Tetrahedron* **1998**, *54*, 7919. (b) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247. (c) Kennedy, M.; McKervy, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc., Chem. Commun.* **1997**, 983.

the benzylic C–H bonds would allow for facile cyclopentanone formation as seen with the analogous diazo compound.¹⁵ Surprisingly, only dimerization was observed in a range of solvents and concentrations (eq 2). However, formation of dimer **6** could be avoided with the presence of an appropriate X–H nucleophile such as thiophenol (eq 3).



C–H insertion appears to be too slow to compete with dimerization. This undesired reactivity may stem from nucleophilic attack of a sulfoxonium ylide onto an iridium carbene followed by elimination of DMSO and regeneration of the iridium catalyst (Scheme 1). The enhanced propensity

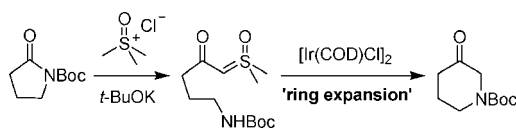
Scheme 1. Proposed Dimerization Pathway



of sulfoxonium ylides to dimerize relative to diazo compounds could then be ascribed to a greater carbanion character¹⁶ leading to faster nucleophilic attack. Ylide dimerization was also observed to be the exclusive product in the presence of $\text{Rh}_2(\text{OAc})_4$ or $\text{Rh}_2(\text{TFA})_4$, both of which have been applied successfully in C–H insertion applications. This result further suggests that dimerization of **5** is driven by mechanistic considerations particular to sulfoxonium ylides.

We began to focus on intramolecular N–H insertion as a ring-forming strategy (Scheme 2). A lactam (or ester) can

Scheme 2. Lactam Ring Expansion Strategy



be converted into a β -keto sulfoxonium ylide by treatment with the methylide resulting from reaction of a trimethylsulfoxonium halide with a strong base.¹⁷ A subsequent N–H insertion would effect a net ring expansion of the starting

lactam into a β -amino ketone. In this way, a range of cyclic β -amino ketones might be accessible while circumventing more stepwise traditional synthetic approaches.

This strategy was applied in practice for several different ring sizes (Table 3).¹⁸ Sulfoxonium ylide **8a** (derived from

Table 3. Intramolecular N–H Insertions for β -Amino Ketones

entry	sulfoxonium ylide	product	yield (%) ^b
1			74
2			82
3			86
4			90
5			67

^a All reactions conducted at 0.05 M at 70 °C for 8–18 h in degassed DCE with 1 mol % $[\text{Ir}(\text{COD})\text{Cl}]_2$ under nitrogen. ^b Isolated yield.

the lactam)¹⁹ was designed as an optimal case in which N–H insertion should be favored over intermolecular processes due to the structural proximity of the reacting functionalities. At room temperature there was no reaction, perhaps due to the attenuated nucleophilicity of the *t*-Bu carbamate. Switching solvents to DCE and elevating the reaction temperature, however, allowed for good conversion (74% yield, entry 1). More challenging cases, such as six- and seven-membered ring formation, also proceeded smoothly in good yield (67–90% yield, entries 2–5).

To highlight the differential reactivity of carbamates compared with anilines in N–H insertion, ylide **8a** reacted cleanly with aniline providing **10** without any measurable competing ring formation (eq 4). Despite the entropic cost

(15) Kennedy, M.; McKervy, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.

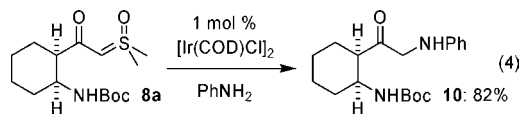
(16) For a study on the nucleophilicity of diazo compounds, see: Bug, T.; Hartnagel, M.; Schlierf, C.; Mayr, H. *Chem.–Eur. J.* **2003**, *9*, 4068.

(17) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. (b) Wang, D.; Schwinden, M. D.; Radesca, L.; Patel, B.; Kronenthal, D.; Huang, M.-H.; Nugent, W. A. *J. Org. Chem.* **2004**, *69*, 1629.

(18) Applying this strategy to lactones was unsuccessful because of spontaneous relactonization of hydroxy sulfoxonium ylides.

(19) See Supporting Information for details.

of the intermolecular process, N–H insertion of aniline occurs at room temperature, allowing for a chemoselective N–H insertion process.



Sulfoxonium ylides offer promise as alternatives to traditional diazo compounds for the development and application of metal carbene chemistry. These ylides are typically crystalline, stable to chromatography, and stable for months on benchtop storage. Moreover, they do not produce gas or rapid exotherms during reaction, making them

preferable for large scale processing. Identification of a relatively inexpensive, commercially available iridium catalyst greatly enhances the practicality of this system. Efforts are currently underway to identify chiral ligands to promote asymmetric X–H bond insertions.

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Supporting Information Available: Experimental procedures and characterization data for compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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