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Gold (I) catalysis of X–H bond insertions

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ABSTRACT

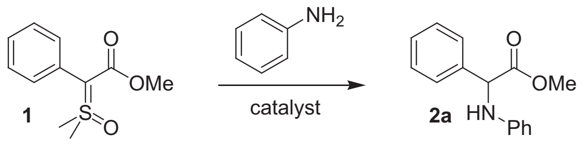
The utility of gold catalysis for carbene X–H bond insertion chemistry is described for the first time, taking advantage of the unique reactivity of sulfoxonium ylides as metal carbene precursors.

Transition metal-catalyzed reactions of α-diazocaronyls have been widely explored, with numerous applications encompassing a variety of bond formations.[1] Notably, copper,[2] rhodium[3] and ruthenium[4] catalysts occupy a privileged place among transition metals in mediating carbene reactions. Recently, however, there has been a growing interest in new applications of gold catalysis,[5] including reactions intercepting gold carbene intermediates.[6] Previous work in our labs has shown sulfoxonium ylides to be safe alternatives to α-diazocaronyls as metal carbene precursors,[7] and we sought to further develop their use in the synthesis through the development of new, differentiated catalyst systems. Herein, we describe our findings of simple gold catalysts that promote carbene transformations.

Based on our earlier finding that iridium catalysts efficiently mediate carbene transformations of sulfoxonium ylides, we further examined the utility of iridium in the prototypical reaction of **1** with aniline (Table 1).[8] It was found that $[Ir(Cp^*)Cl_2]_2$ reacted in comparable efficiency to $[Ir(COD)Cl]_2$ (Table 1, entry 2), a result that was surprising given the failure of other Ir(III) catalysts (Table 1, entries 3 and 4). In surveying Group 11–12 metals, it was observed that simple Pt(II), Au(I), and Au(III) catalysts are all capable of mediating the reaction with good efficiency (Table 1, entries 6–13). Within the gold and platinum catalysts tried, $AuCl(SMe_2)$ was found to provide the best yield at a low catalyst loading (Table 1, entry 12), whereas related phosphine complexes gave poor reactivity (entries 10 and 11). AuCl (Table 1, entry 9) gave poorer reactivity than the DMS complex but this is attributed in part to its limited solubility. This result is consistent with our previous observations that Ir(I) catalysts require a weakly coordinating ligand such as COD to be both soluble and active. Indeed, addition of phosphine ligands was found to suppress reactivity in otherwise viable catalyst systems, suggesting the importance of a labile ligand for high conversion (Table 1, entries 6 and 14).

The high catalytic efficiency of Au(I) in the above transformation demanded further investigation, though gold carbenes in catalysis are certainly not unprecedented. The utility of Au and Pt in forming transient carbene species has been examined in several synthetic contexts.[9] Indeed, an Au(I) catalyst was recently demonstrated by Nolan to be effective in carbene transfer from ethyl diazoacetate in cyclopropanations and X–H insertions.[6a] However, we are interested in expanding the scope and understanding of the reactivity of sulfoxonium ylides through gold catalysis to complement existing methods. Therefore we examined the X–H insertions of **1** with a variety of nitrogen and oxygen nucleophiles (Table 2). As in the related Ir(I) system, a range of anilines all

Table 1
N–H insertion of **1** with aniline using different metal catalysts[a]



Entry	Catalyst	Mol %[b]	% Yield[c]
1	$[Ir(COD)Cl]_2$	1	91
2	$[Ir(Cp^*)Cl_2]_2$	3	88
3	$IrCl_3$	3	0
4	$Ir(acac)_3$	3	0
5	AgCN	3	24
6	$Pt(PPh_3)_2Cl_2$	5	0
7	$Pt(COD)Cl_2$	3	81
8	$PtCl_4$	5	3
9	AuCl	1	30
10	$Au(PPh_3)Cl$	1	0
11	$Au(PEt_3)Cl$	1	12
12	$AuCl(SMe_2)$	1	94
13	$AuCl_3$	1	78
14	$AuCl(SMe_2)$	1	6[d]

[a] All reactions conducted in 0.2 M degassed CH_2Cl_2 under nitrogen at 23 °C with 1.5 equiv of aniline.
[b] Catalyst loading.
[c] Isolated yield.
[d] 2 mol % PPh_3 added.

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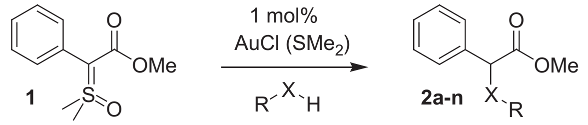
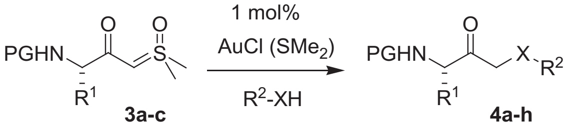
Table 2
Gold-catalyzed X–H insertions of ylide **1**[a]



Entry	R	X	Product	% Yield[b]
1	Ph	NH	**2a**	94
2	*p*-BrC_6H_4	NH	**2b**	87
3	*p*-CNC_6H_4	NH	**2c**	82
4	*p*-$CF_3C_6H_4$	NH	**2d**	93
5	*o*-ClC_6H_4	NH	**2e**	91
6	*p*-$MeOC_6H_4$	NH	**2f**	89
7	*p*-*t*BuC_6H_4	NH	**2g**	87
8	*o*-MeC_6H_4	NH	**2h**	80
9	2-Naphthyl	NH	**2i**	92
10	Ph	NMe	**2j**	84[c]
11	Et	O	**2k**	89[d]
12	$TMSCH_2CH_2$	O	**2l**	82[d]
13	Bn	O	**2m**	76[d]
14	*i*-Pr	O	**2n**	69[e]

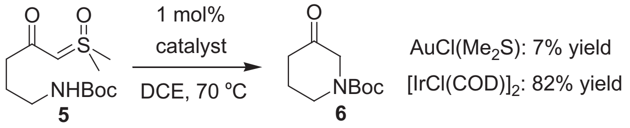
[a] All reactions conducted in 0.2 M degassed CH_2Cl_2 under nitrogen at 23 °C with 1.5 equiv of nucleophile unless otherwise noted.
[b] Isolated yield.
[c] Reaction conducted at 70 °C using DCE as solvent.
[d] Reaction conducted at 40 °C using 4 equiv of alcohol.
[e] Reaction conducted at 80 °C in neat *i*-PrOH.

Table 3
X–H insertions of amino acid derived sulfoxonium ylides[a]



Entry	Ylide	PG	R^1	R^2	X	Product	% Yield[b]
1	**3a**	Cbz	Me	Ph	NH	**4a**	90
2	**3b**	Cbz	*i*Pr	Ph	NH	**4b**	87
3	**3c**	Boc	Bn	Ph	NH	**4c**	80
4	**3a**	Cbz	Me	Bn	O	**4d**	81[c]
5	**3b**	Cbz	*i*Pr	Bn	O	**4e**	73[c]
6	**3c**	Boc	Bn	Bn	O	**4f**	60[c]
7	**3a**	Cbz	Me	*p*-$CF_3C_6H_4$	NH	**4g**	91
8	**3a**	Cbz	Me	*o*-MeC_6H_4	NH	**4h**	84

[a] All reactions conducted in 0.2 M degassed CH_2Cl_2 under nitrogen at 23 °C with 1.5 equiv of nucleophile unless otherwise noted.
[b] Isolated yield.
[c] Reaction conducted at 40 °C using 4 equiv of alcohol.



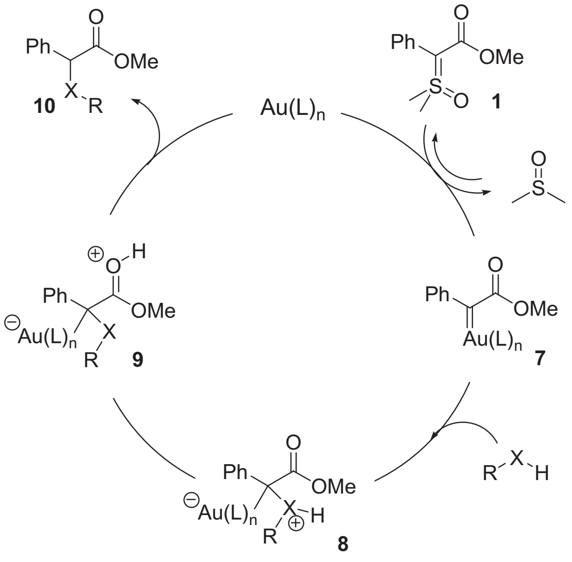
Scheme 1. Comparison of catalysts for intramolecular N–H insertion.

reacted to provide the corresponding N–H insertion product in high yield (Table 2, entries 1–10).[10] Electron-withdrawing substituents on the aromatic ring were well tolerated furnishing high yield of the N–H insertion product (entries 3 and 4). Electron-donating substituents (entries 6 and 7) were also well tolerated as well as increased steric demand from either the ylide or the nucleophile (entries 8–10). Likewise, alcohols were found to provide the O–H insertion products in good yield (Table 2, entries 11–14), though higher temperature was found to be necessary for optimal conversion.[11]

Similarly, a variety of sulfoxonium ylides derived from commercial amino acids were found to be excellent substrates for catalytic X–H insertions (Table 3). Following the method of Nugent,[12] ylides **3a–c** were synthesized without loss of stereochemical integrity, and likewise were found to undergo N–H and O–H insertions without racemization.[13] It was found that N–H insertion of anilines was robust to steric influence of the amino acid side chain (Table 3, entries 1–3), while the yield of O–H insertions became slightly more modest with α-branching in the side chain (Table 3, entries 4–6). Notably, in the absence of catalyst no reaction was observed in all cases.

In contrast to $[Ir(COD)Cl]_2$, $AuCl(SMe_2)$ does not efficiently mediate the N–H insertion of carbamates, a weaker nucleophile. As shown in Scheme 1, intramolecular N–H insertion of **5** proceeds in only 7% yield with 1 mol % $AuCl(SMe_2)$. This result may suggest that the gold carbene presumably generated during the course of the reaction is not sufficiently electrophilic to initiate attack of the carbamate. However, the addition of chloride-abstracting agents such as $AgSbF_6$ did not improve the efficiency of this reaction.

Efforts to demonstrate the intermediacy of a gold carbene in a catalytic cycle for the reactions described herein have not yet been successful. Following the proposed mechanism in Scheme 2, gold should liberate DMSO from sulfoxonium ylide (**1**), generating a gold carbene complex (**7**). This process is expected to be reversible based on previous reports that DMSO can react with carbenes and carbenoids to generate sulfoxonium ylides,[14] and the empirical observation that elevated concentrations of DMSO suppress conversion to **10**.[15] It was hoped that intermediate **7** might be observable by NMR, as had been the case during our research on $[Ir(COD)Cl]_2$ and related catalysts.[16] However, this intermediate, if generated,[17] appears not to have a sufficient lifetime for NMR observation at low temperature. Therefore support for a carbene mechanism, as opposed to an alternative mechanism such as Lewis acid activation, currently relies on empirical observations; most notably the sensitivity of the reaction to atmospheric oxygen, or the inability of simple Lewis acids to effect conversion of **1** in the absence of a transition metal catalyst.[18] Attack of **7** with a nucleophile is thought to first generate a zwitterionic intermediate (**8**), which can undergo proton transfer and then elimination of the metal to yield product **10** and regenerate the catalyst.[19]



Scheme 2. Proposed mechanistic cycle for Au catalysis.

In conclusion, we have found that a simple gold catalyst can mediate X–H insertion chemistry of sulfoxonium ylides. Sulfoxonium ylides merit attention as safe alternatives to traditional diazo compounds for the development and application of metal carbene chemistry. Their bench and thermal stability make them particularly attractive for large scale chemical processing. Moreover, we have demonstrated a surprising preference of these ylides to engage with late transition metals that are arguably underdeveloped in carbene catalysis. Continued exploration of sulfoxonium ylides may reveal further discoveries of novel reactivity.

Acknowledgments

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