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Regioselectivity in Lewis acids catalyzed X–H (O, S, N) insertions of methyl styryldiazoacetate with benzyl alcohol, benzyl thiol, and aniline

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Abstract—Different from Rh(II) catalysts, X–H (X = O, S, N) insertion of methyl styryldiazoacetate catalyzed by Lewis acids including Cu(I), Cu(II) and Ag(I) complexes occurred at γ-position preferably. Only (*E*)-isomer was observed in the reactions. This method provides an alternative for the synthesis of γ-hydroxyl or γ-amino acid derivatives.

The catalytic insertion of α-diazo compounds into X–H (X = N, O, S) bond is a powerful transformation to build versatile functionality in organic synthesis.[1] Rhodium(II) complexes are most efficient and widely used catalysts for the transformation through rhodium carbenoid intermediates.[2] For example, rhodium(II) acetate catalyzed insertion of vinyldiazoacetates with amines, alcohols, and thiols has been applied to prepare α-substituted β,γ-unsaturated compounds.[3] In the case of Rh(II) catalyzed X–H insertion of vinyldiazoacetate lacking functionality at the vinyl terminus, the reaction occurred at both carbeniod site and the vinyl terminus.[4] For O–H insertion of γ-substituted vinyl diazoacetate, the reaction took place predominantly at the carbeniod site with a dirhodium catalyst. To enhance selectivity at γ-position, Davies and Yokota further reported a molybdenum catalyst which predominantly gave O–H insertion at the vinylogous position for some vinyl diazoacetates.[4e] But the regioselectivity was only moderate for methyl styryldiazoacetate. In addition, olefin geometry (*Z*/*E* ratio) of the γ-insertion products was poor. In this Letter, we report Cu(I), Cu(II), and Ag(I) complexes catalyzed X–H (X = O, S, N) insertion reactions of methyl styryldiazoacetate with alcohols, thiols, and anilines. γ-Substituted α,β-unsaturated products were obtained predominantly, and only (*E*)-isomers were observed in the reaction.

Because of our interest in the differences between copper and rhodium catalysts in the diazo decomposition reactions,[5] we sought to explore regioselectivity of Cu catalyzed O–H insertion of vinyl diazoacetates. For comparison, $Rh_2(OAc)_4$ catalyzed O–H insertion of methyl styryldiazoacetate with benzyl alcohol was initially conducted and the reaction gave α-insertion product **4a** in 78% yield (Table 1, entry a). We were surprised to find that $Cu(OTf)_2$ catalyst gave a mixture of O–H insertion products at both α and γ positions favoring γ-regioisomer (Table 1, entry b). Since $Cu(OTf)_2$ could serve as a Lewis acid in the diazodecomposition reaction,[6] we then screened a range of Lewis acid catalysts trying to enhance selectivity and the results are summarized in Table 1, entries c–j. We were delighted to find that Ag and Sn complexes gave O–H insertion regiospecfically at γ-position (Table 1, entries c–f). Other Lewis acids such as $FeCl_3$ and $BF_3{\cdot}Et_2O$ did give O–H insertion product, but with lower regioselectivity (Table 1, entries g and h). Only trace amount of O–H insertion products were observed by using a $Yb(OTf)_3$ catalyst even in prolonged reaction time (Table 1, entry i). TMSOTf also catalyzed the reaction to give O–H insertion product in a moderate yield favoring the γ-isomer (Table 1, entry j). Similar reaction conditions with Cu

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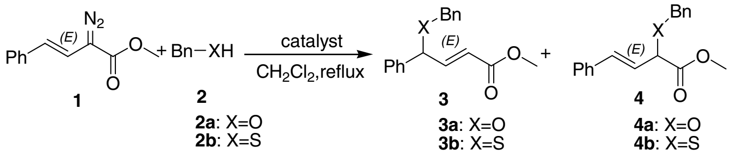
Table 1. X–H (X = O, S) insertion of alcohol and thiol with methyl styryldiazoacetate **1** with different catalysts



[a] Entry	X	Catalyst	3	4	Yield (**3** + **4**)[b] (%)	**3**:**4**[c]
a	X = O	$Rh_2(OAc)_4$, 1%	**3a**	**4a**	78	<2:98
b	X = O	$Cu(OTf)_2$, 10%	**3a**	**4a**	53	72:28
c	X = O	$AgBF_4$, 10%	**3a**	**4a**	67	>98:2
d	X = O	$AgClO_4$, 10%	**3a**	**4a**	71	>98:2
e	X = O	AgOTf, 10%	**3a**	**4a**	63	>98:2
f	X = O	$Sn(OTf)_2$, 10%	**3a**	**4a**	63	>98:2
g	X = O	$FeCl_3$, 10%	**3a**	**4a**	57	86:14
h	X = O	$BF_3{\cdot}Et_2O$, 10%	**3a**	**4a**	68	50:50
i	X = O	$Yb(OTf)_3$, 10%	**3a**	**4a**	<10[d]	
j	X = O	TMSOTf, 10%	**3a**	**4a**	48	81:19
k	X = S	$Cu(OTf)_2$, 10%	**3b**	**4b**	68	78:22
l	X = S	$AgBF_4$, 10%	**3b**	**4b**	69	69:31
m	X = S	$AgClO_4$, 10%	**3b**	**4b**	71	68:32
n	X = S	AgOTf, 10%	**3b**	**4b**	59	72:28

[a] All the reactions were carried out in refluxing CH_2Cl_2 for 2 h with **1**:**2** = 1.0:1.2 mmol unless otherwise indicated.

[b] Isolated yields after chromatography purification.

[c] Determined by ^1H NMR of crude reaction mixtures.

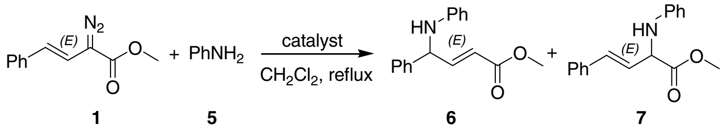
[d] The reaction was carried out in refluxing CH_2Cl_2 for 36 h.

and Ag catalysts were then applied to phenylmethanethiol. The desired S–H insertion products were obtained predominately at γ-position, but the regioselectivity was lower than that from benzyl alcohol (Table 1, entries k–n).

We continued to investigate whether the regioselectivity in N–H insertion is similar to that of O–H insertion. Landais and Planchenault reported that dirhodium(II) acetate catalyzed N–H insertion of methyl styryldiazoacetate with aniline gave only α-substituted product **7**.[3] As anticipated, when using AgOTf as a catalyst, γ-substituted amino acid derivative **6** was obtained as a major regioisomer (Table 2, entry b). Encouraged with the result, a number of Lewis acids were employed in the reaction. As shown in Table 2, the highest regioselectivity of **6**:**7** = 85:15 was obtained with $Cu(OTf)_2$ as a catalyst (Table 2, entry e). Rather low yield (<10%) of N–H insertion product was obtained with $Sn(OTf)_2$ and $FeCl_3$. Additional Lewis acids such as $BF_3{\cdot}Et_2O$, $Ti(O\textit{i}Pr)_4$, $Yb(OTf)_3$, $SnCl_2$, and $Zn(OTf)_2$ failed to produce any desired N–H insertion product.

Even though the mechanism of rhodium(II) carbenoid mediated X–H (X = O, S, N) insertion has been elaborately described,[1,2] the mechanism of Cu catalyzed

Table 2. Cu(I), Cu(II), and Ag(I) complexes catalyzed N–H insertion of methyl styryldiazoacetate **1** with aniline **5**

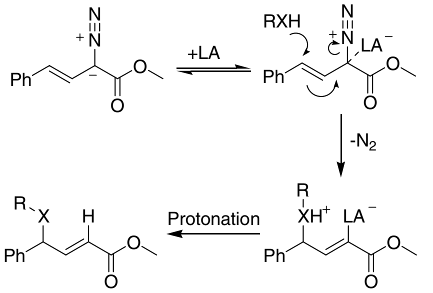


Entry	Catalyst	Yield (**6** + **7**)[b] (%)	**6**:**7**[c]
a	$Rh_2(OAc)_4$, 1%	79	<2:98
b	AgOTf, 10%	66	65:35
c	$AgClO_4$, 10%	64	67:33
d	$AgBF_4$, 10%	67	73:27
e	$Cu(OTf)_2$, 10%	72	85:15
f	Cu(OTf), 10%	65	73:27
g	$CuPF_6(CH_3CN)_4$, 10%	83	53:47
h	$Cu(pfacac)_2$, 10%	76	36:64

[a] All the reactions were carried out in refluxing CH_2Cl_2 for 2 h with **1**:**5** = 1.0:1.2 mmol.

[b] Isolated yields after chromatography purification.

[c] Determined by ^1H NMR of the crude reaction mixtures.



Scheme 1. Proposed Lewis acid catalyzed reaction of methyl styryldiazoacetate **1** with alcohol, thiol, and aniline (LA = $Cu(OTf)_2$, AgOTf, $AgBF_4$, $AgClO_4$, etc.).

X–H (X = O, S, N) insertion is less precendented.[1,5–7] Our experiments suggested that Cu catalyst might behave as a Lewis acid in the insertion reaction.[6] A plausible mechanistic pathway for the formation of the γ-regioisomer is proposed in Scheme 1.[1,2a,4e,5]

In summary, we have developed a regioselective Lewis acid catalyzed insertion reactions of methyl styryldiazoacetate with aniline and benzyl alcohol. While dirhodium acetate specifically gave α-regioisomers, γ-regioisomers were obtained preferably when Lewis acid such as $AgBF_4$ was used as a catalyst. It is commonly accepted that rhodium catalyzed diazo decomposition is through a metal carbenoid intermediate. The difference of reaction regioselectivity suggests a different reaction pathway. Since Cu complexes may behave as a Lewis acid in the reaction, we propose that metal carbenoid may not be the only intermediate in the current Cu catalyzed insertion reactions.

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