



Diastereoselective intermolecular O–H insertions by Cu(II)-mediated carbenoids derived from phenyldiazoacetamide

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Abstract—The diastereoselective insertion into carboxylic O–H bonds was investigated with camphorsultam as a chiral auxiliary, and moderate to good selectivity was achieved. © 2001 Elsevier Science Ltd. All rights reserved.

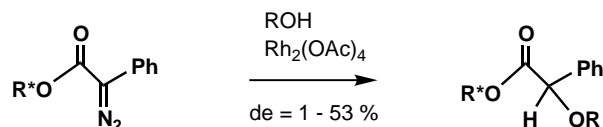
Along with the well established intramolecular C–H insertion reactions by Rh(II)-mediated carbenoids, there has been considerable attention directed to the corresponding insertion into polar X–H bonds (X=N, O, S, etc.) by metal carbenes. The X–H bonds (X=N, O, S, etc.) are generally more reactive than the corresponding C–H bond toward metal carbenes, so in contrast to the C–H insertion in which only the intramolecular reaction gives reasonable selectivity, the intermolecular X–H insertion in many cases is highly selective and thus synthetically useful.¹

Intermolecular O–H insertions by carbenoids have been investigated by several groups, the results suggest that this type of insertion is highly efficient.^{1c} The O–H insertion by a metal carbene derived from α -diazo carbonyl compounds gives α -hydroxy acid derivatives, which are found as structural units in many natural products, as well as being useful synthetic building blocks. The asymmetric version of Rh(II)-mediated carbenoid insertion into alcoholic O–H bonds was exploited with the aid of a chiral auxiliary (Scheme 1). However, the diastereoselectivity so far obtained is still low to moderately high.^{2,3} In connection with our interest in the synthetic application of α -diazo carbonyl compounds,⁴ we have investigated the Cu(II) complex-mediated metal carbene insertion into the O–H bonds of carboxylic acids⁵ in the presence of a chiral auxiliary. We found that reasonably high diastereoselectivity can be obtained in this case. The scope and limitation of this diastereoselective O–H insertion reaction is presented in this communication.

Oppolzer's camphorsultam⁶ was employed as a chiral auxiliary in this investigation. The phenyldiazoacetyl derivative **1** was prepared according to the literature procedure^{2b} through a tosylhydrazone. This diazo compound was decomposed with a catalytic amount of Cu(acac)₂ in the presence of 2 equiv. of various acids in dry benzene (Scheme 2). The diastereoselectivity of the product was analyzed using 400 MHz NMR spectroscopy. The results are collected in Table 1.

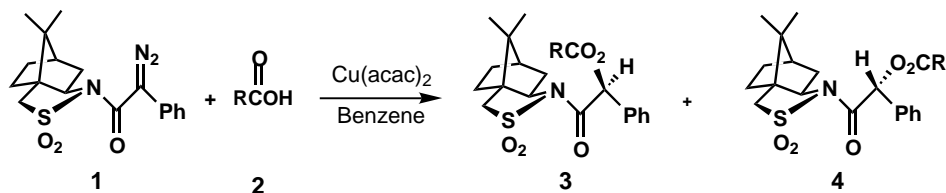
As shown in Table 1, it is obvious that the carboxylic acid structure has a marked influence over the diastereoselectivity. Sterically bulkier acids enhance the diastereoselectivity. On the other hand, the reaction temperature can also greatly affect the diastereoselectivity: the data show that low temperatures generally improve the selectivity. However, when the reaction was run below 55°C, it took a very long time for the reaction to reach completion. The insertion with 2,2-dimethylpropanoic acid at 60°C gave a diastereoselectivity of 95:5, which is the highest diastereoselectivity achieved in O–H insertion reactions by carbenoids.

Since it is well known that the nature of the transition metal catalyst can exert a significant influence over the regio- and chemoselectivity, as well as the stereoselec-



Scheme 1.

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Scheme 2.

Table 1. The effect of the carboxylic acid and reaction temperature on the diastereoselectivity⁷

Entry	Carboxylic acid 2	Temperature (°C)	Yield (%) ^a	Product ratio (3:4) ^{b,c}
1	R = Me	70	84	62:38
2	R = Me	65	74	80:20
3	R = Me	55	62	83:17
4	R = <i>iso</i> -Propyl	70	80	81:19
5	R = <i>tert</i> -Butyl	80	72	73:27
6	R = <i>tert</i> -Butyl	70	93	90:10
7	R = <i>tert</i> -Butyl	60	76	95:5
8	R = Ph	70	87	84:16
9	R = PhCH ₂	70	82	76:24

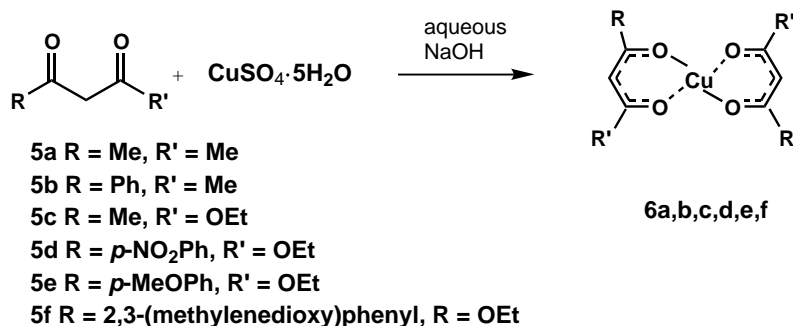
^a Isolated yield after chromatography.^b Diastereoselectivity was determined by ¹H NMR (400 MHz) spectroscopy before column chromatography.^c Absolute configuration was determined by comparing with an authentic sample prepared from (*S*)-mandelic acid.

tivity of the corresponding metal carbene reactions,¹ we examined the effect of the ligand of the Cu(II) catalyst on the diastereoselectivity of the carboxylic O–H insertion. For this purpose, 1,3-diketone and β-ketoacetate derivatives were synthesized, and the corresponding Cu(II) diketonate and Cu(II) ketoacetate were prepared following a method similar to that for the preparation of Cu(acac)₂⁸ (Scheme 3). The diazo decomposition was conducted with these catalysts at 65°C in the presence of either acetic acid or 2,2-dimethylpropanoic acid. The catalysts were all found to be as effective as Cu(acac)₂ in promoting carboxylic O–H bond insertion. The yields and the product ratios are summarized in Table 2. For comparison, the data with Cu(acac)₂ as the catalyst are also shown in Table 2.

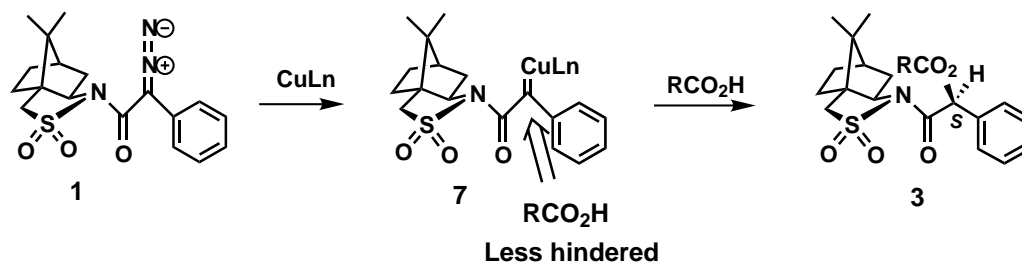
From the results summarized in Table 2, we can conclude that ligands have a detectable effect on the diastereoselectivity. The general trend is that electron-donating ligands enhance the diastereoselectivity (com-

Table 2. The effect of the catalyst ligand on the diastereoselectivity

Entry	Catalyst	Carboxylic acid 2	Yield (%) ^a	Product ratio (3:4) ^b
1	6a	R = Me	74	80:10
2	6b	R = Me	79	86:14
3	6c	R = Me	85	67:33
4	6d	R = Me	69	71:29
5	6e	R = Me	85	84:16
6	6f	R = Me	87	86:14
7	6a	R = <i>tert</i> -Butyl	76	95:5
8	6b	R = <i>tert</i> -Butyl	37	67:33
9	6f	R = <i>tert</i> -Butyl	40	67:33

^a Isolated yield after chromatography.^b Diastereoselectivity was determined by ¹H NMR (400 MHz) spectroscopy before column chromatography.

Scheme 3.



Scheme 4.

pare catalyst **6a** with **6c**, as well as **6d** with **6f** and **6e**). It has been reported that electronic properties of the ligand of a Cu(II) catalyst can exert influence over the chemoselectivity of copper carbenoids. This influence might be due to the reactivity of the intermediate carbenoids, with electron-donating ligands making the electrophilic carbenoids less reactive and thus more selective.⁹ Among the catalysts screened, **6f** and **6b** gave the best diastereoselectivity when the reaction was run in the presence of acetic acid at 65°C. However, the reaction with **6f** as the catalyst in the presence of the bulkier 2,2-dimethylpropanoic acid gave decreased diastereoselectivity as well as diminished yields. This might be due to steric overcrowding around the reaction center, which makes it difficult for the reaction to proceed through a well-defined transition state structure.

The stereochemical outcome of the insertion reaction could be interpreted in terms of the structure of the copper carbene intermediate. We suppose that the predominant conformation of diazoamide **1** in solution will be similar to its X-ray structure^{2b} in the solid state, as shown in Scheme 4. The intermediate copper carbene is expected to keep this conformation. The carboxylic acid approaching from the less hindered front side results in the formation of the product with *S* configuration in the newly formed chiral center.

In conclusion, intermolecular insertion into carboxylic O–H bonds by copper(II)-mediated carbenoids can be achieved with moderate to high diastereoselectivity. The fact that the ligands of the copper catalyst can significantly affect the diastereoselectivity suggests the possibility of catalytic asymmetric O–H insertion, which has not been achieved so far.¹⁰ An investigation aimed at this goal is currently being carried out in our laboratory and results will be reported in due course.

Acknowledgements

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