



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

Nan Jiang,^a Jianbo Wang^{a,*} and Albert S. C. Chan^b

^aKey Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemistry, Peking University, Beijing 100871, China

^bDepartment of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong

Received 20 July 2001; accepted 28 September 2001

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.

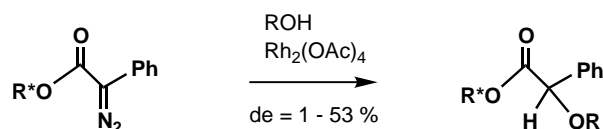
Along with the well established intramolecular C–H insertion reactions by Rh(II)-mediated carbenoids, there has been considerable attention directed to the corresponding insertion into polar X–H bonds (X=N, O, S, etc.) by metal carbenes. The X–H bonds (X=N, O, S, etc.) are generally more reactive than 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.

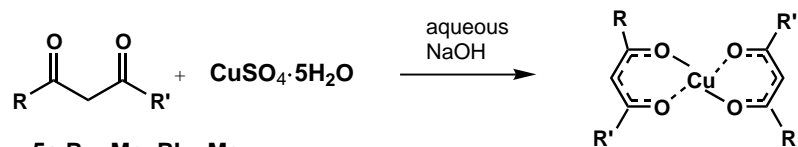
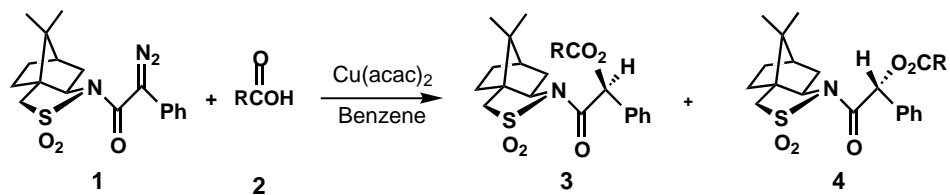
As shown in Table 1, it is obvious that the carboxylic acid structure has a marked influence over the diastereoselectivity. Sterically bulkier acids enhance the diastereoselectivity. On the other hand, the reaction temperature can also greatly affect the diastereoselectivity: the data show that low temperatures 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-

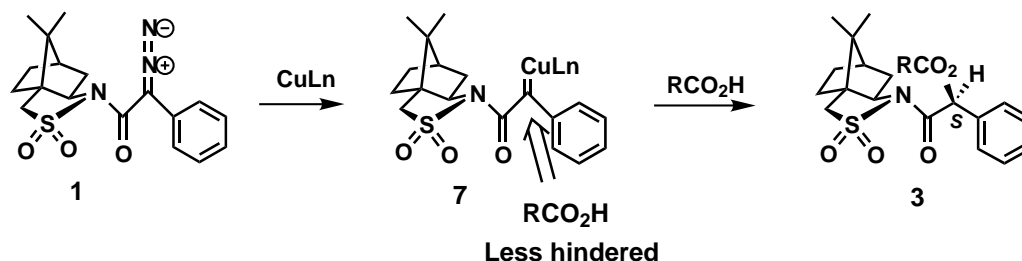


Scheme 1.

* Corresponding author.



- 5a $\text{R} = \text{Me}$, $\text{R}' = \text{Me}$
 5b $\text{R} = \text{Ph}$, $\text{R}' = \text{Me}$
 5c $\text{R} = \text{Me}$, $\text{R}' = \text{OEt}$
 5d $\text{R} = p\text{-NO}_2\text{Ph}$, $\text{R}' = \text{OEt}$
 5e $\text{R} = p\text{-MeOPh}$, $\text{R}' = \text{OEt}$
 5f $\text{R} = 2,3\text{-(methylenedioxy)phenyl}$, $\text{R} = \text{OEt}$



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

Financial support by NSFC (Grant No. 299722002) and Peking University–Hong Kong Polytechnic Univer-

sity joint project on asymmetric synthesis is gratefully acknowledged.

References

1. For reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; (b) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *44*, 1091; (c) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811.
2. (a) Aller, E.; Cox, G. G.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 5949; (b) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. *J. Org. Chem.* **1995**, *60*, 4449.
3. Moody et al. recently reported an acid-mediated insertion into an alcoholic O–H bond with considerably improved diastereoselectivity. See: Miller, D. J.; Moody, C. J.; Morfitt, C. N. *Aust. J. Chem.* **1999**, *52*, 97.
4. (a) Wang, J.; Hou, Y. *J. Chem. Soc., Perkin Trans* **1999**, 1999.