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Simple and Efficient Heterogeneous Copper Catalysts for Enantioselective C–H Carbene Insertion

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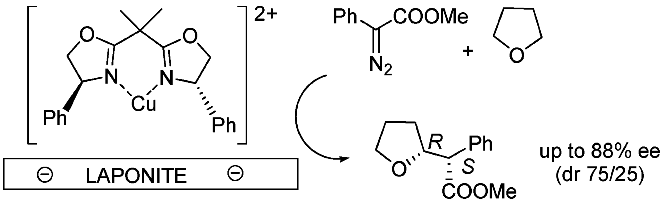
ABSTRACT



Immobilized box–Cu complexes are able to efficiently catalyze the insertion of a carbene, from methyl phenyldiazoacetate, into C–H bonds of THF, with high enantioselectivity (up to 88% ee). The immobilization not only allows recovery and reuse of the enantioselective catalyst but also provides an improvement in the selectivities from the values obtained in solution, probably due to a confinement effect of the bidimensional support.

Functionalization of C−H bonds is currently an important field of research in chemistry. Whereas catalytic oxidative addition is still challenging, the metal-catalyzed insertion of carbenes, generated from diazo compounds, is a well-established alternative method to functionalize C−H bonds.[1] Rhodium catalysts have proven to be the most efficient for the asymmetric version of this reaction, mainly the intramolecular variant,[2] and this approach has been extended in recent years to intermolecular reactions.[3] In contrast, copper catalysts have hardly been used for this type of reaction. Only in the past few years did Pérez and co-workers show that trispyrazolylborate complexes of copper, silver, and gold are active and selective in the intermolecular insertion of carbenes.[4] Regarding the asymmetric insertion reactions, copper catalysts have only been successful in the intramolecular version.[5,6] In this communication, we demonstrate that for the first time the cheap and easily accessible bis(oxazoline)−copper complexes can act as efficient catalysts for this type of reaction provided they are immobilized onto a bidimensional clay by simple cationic exchange.

Four different ligand families were chosen for this study (Figure 1): the C_2-symmetric bis(oxazoline)[7] (box, **1**) and azabis(oxazoline)[8] (azabox, **2**) ligands and the nonsymmetric quinolineoxazoline[9] (quox, **3**) system. All of these ligands are known to form copper complexes that efficiently catalyze

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[1] Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160.

[2] Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861−2903.

[3] (a) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422−6425. (b) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176−4187.

[4] Examples of carbene insertions in aliphatic C−H bonds: (a) Urbano, J.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2005**, *24*, 1528−1532. (b) Caballero, A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. *J. Am. Chem. Soc.* **2003**, *125*, 1446−1447. (c) Caballero, A.; Díaz-Requejo, M. M.; Belderraín, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. *Organometallics* **2003**, *22*, 4145−4150. For other carbene insertions, see: (d) Díaz-Requejo, M. M.; Pérez, P. J. *J. Organomet. Chem.* **2005**, *690*, 5441−5450 and references cited therein.

[5] Some examples: (a) Wee, A. G. H. *J. Org. Chem.* **2001**, *66*, 8513−8517. (b) Doyle, M. P.; Phillips, I. M. *Tetrahedron Lett.* **2001**, *42*, 3155−3158. (c) Doyle, M. P.; Hu, W. *J. Org. Chem.* **2000**, *65*, 8839−8847. (d) Lim, H.-J.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 2326−2327.

[6] Recently, an enantioselective copper-catalyzed intramolecular O−H insertion has been described: Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594−4595.

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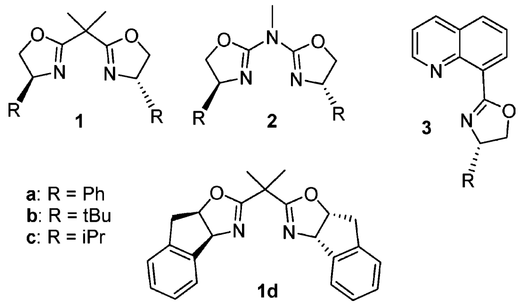

Figure 1. Ligands used for enantioselective C−H carbene insertion.

the cyclopropanation of alkenes with diazo compounds and therefore were good candidates for the insertion reaction.

Different copper salts were tested in the homogeneous phase: $Cu(OTf)_2$, $CuBr_2$, $Cu(OAc)_2$, CuCl, and $CuSbF_6$ (prepared from CuCl and $AgSbF_6$). Copper triflate was clearly better than the chloride, bromide, and acetate, as also occurs in cyclopropanation reactions,[10]and $CuSbF_6$ did not show any significant improvement. $Cu(OTf)_2$ was therefore used due to its ease of handling. Catalysts were tested in the insertion of methyl phenyldiazoacetate in THF[11] under reflux (Scheme 1), and the results of the homogeneous reactions are gathered in Table 1.

Scheme 1. Reaction between Methyl Phenyldiazoacetate and THF

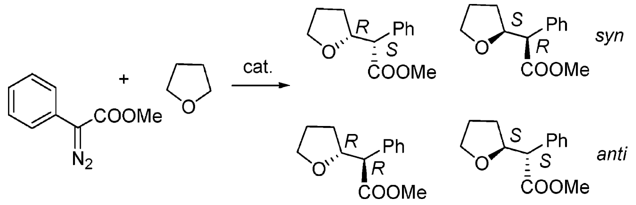

Table 1. Results of the Reactions between Methyl Phenyldiazoacetate and THF Catalyzed by Homogeneous Copper Complexes[a]

ligand	conversion[b] (%)	syn/anti	% ee syn	% ee anti
–	41	75:25	–	–
1a	48	64:36	59	40
1b	49	71:29	2	6
1d	48	71:29	14	27
2a	85	64:36	59	55
2a[c]	39	60:40	57	40
2a[d]	20	77:23	2	4
2b	54	74:26	1	12
2c	74	56:44	64	48
3a	44	72:28	6	6

[a] Reaction conditions: 2% $Cu(OTf)_2$, 2.2% ligand, THF as solvent, slow addition (2 h) of diazo compound, reflux. Conversion and diastereoselectivity were determined by gas chromatography. Enantioselectivities were determined by HPLC (Chiralcel OD-H). The major syn isomer has the absolute configuration 2*R*,α*S*, from the sign of the optical rotation (ref 11). [b] Conversion to insertion products. As total conversion of the diazo compound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. [c] Reaction carried out at room temperature with 4% catalyst. [d] Reaction carried out in hexane under reflux with 2 equiv of THF.

As can be seen, all the catalysts, including copper triflate itself, are active in this reaction, with yields in the range 40−50%. However, azabox ligands (**2**) are clearly superior, even leading to 85% in the case of the phenyl-substituted ligand (**2a**). Regarding enantioselectivity, only symmetrical ligands are efficient and both box and azabox ligands with the same substituents lead to a similar enantiomeric excess. Phenyl or isopropyl substituents show higher enantioselectivity, around 60% ee, than *tert*-butyl—a situation in contrast with the behavior of the same ligands in the related cyclopropanation reaction. However, one drawback of these systems is the lower diastereoselectivity, which is associated with the higher enantioselectivity. These results are slightly worse than those obtained with $Rh_2(S\text{-DOSP})_4$ under the same conditions (2:1 diastereomeric ratio, 72% ee syn),[11] and we tried to improve the enantioselectivity of ligand **2a** by using the same strategies, i.e., lowering the temperature or using hexane as solvent. At room temperature, the yield was lower and the enantioselectivity was not improved. The use of hexane was very detrimental, in terms of both yield and enantioselectivity, probably due to the low solubility of the **2a**−Cu complex. The stereochemical course of the insertion of carbene with copper catalysts cannot be outlined, as the reaction mechanism is still poorly understood.

There are very few examples in the literature concerning the use of heterogeneous catalysts for the enantioselective insertion of carbenes into C−H bonds.[12] The best homogeneous catalysts in our tests were selected for immobilization onto laponite clay by cationic exchange in methanol.[13] The heterogeneous catalysts were used under the same conditions as the homogeneous ones. The reactions were truly heterogeneous, as shown by filtration experiments, and leaching of copper was not detected by ICP analysis.

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(7) (a) Gosh, A. K.; Mathivanan, P.; Capiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45. (b) Jørgensen, K. A.; Johannsen, M.; Yao, S. L.; Audrain, H.; Thorhauge, J. *Acc. Chem. Res.* **1999**, *32*, 605−613. (c) Pfaltz, A. *Synlett* **1999**, 835−842. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (e) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2231. (f) Desimoni, G.; Faita, G.; Jørgensen, K. A. *Chem. Rev.* **2006**, *106*, 3561−3651.

(8) (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045−2048. (b) Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166−10168.

(9) (a) Chelucci, G.; Gladiali, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1393−1400. (b) Wu, X.-Y.; Li, X.-H.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **1998**, *9*, 4143−4150.

(10) (a) Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Chem.−Eur. J.* **2004**, *10*, 758−765. (b) Fraile, J. M.; García, J. I.; Mayoral, J. A.; Tarnai, T. *J. Mol. Catal. A* **1999**, *144*, 85−89.

(11) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063−3070.

(12) Davies, H. M. L.; Walji, A. M. *Org. Lett.* **2003**, *5*, 479−482.

(13) (a) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Reiser, O.; Socuéllamos, A.; Werner, H. *Chem.−Eur. J.* **2004**, *10*, 2997−3005. (b) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Harmer, M. A. *J. Catal.* **2004**, *221*, 532−540.

Azabox ligands form very stable complexes, which allows an efficient immobilization by electrostatic interactions.[13a] In this case, ligands **2a**−**c** lead to results very similar to those in solution, with the important practical advantage of being fully recoverable at least twice. Surprisingly, the immobilization of **3a** produces a significant increase in the enantioselectivity, from virtually zero to values in the region of 40% ee (Table 2). This result represents a new example of a surface effect, which has already been observed in cyclopropanation reactions.[14,15]

Table 2. Results of the Reaction between Methyl Phenyldiazoacetate and THF Catalyzed by Laponite-Supported Copper Complexes[a]

ligand	run	conversion[b] (%)	syn/anti	% ee syn	% ee anti
–	1	21	52:48	–	–
1a	1	66	75:25	84	39
	2	71	77:23	83	40
	3	72	75:25	82	39
	4	65	72:28	81	40
	5	37	54:46	28	24
1a[c]	1	59	78:22	88	46
	2	40	74:26	85	46
2a	1	60	74:26	58	51
	2	55	74:26	57	51
	3	61	73:27	56	54
2a[c]	1	43	71:29	71	56
	2	42	71:29	66	53
	3	44	71:29	66	56
2b	1	27	51:49	2	16
2c	1	50	59:41	62	59
	2	56	58:42	61	59
	3	62	56:44	58	56
3a	1	31	60:40	30	0
	2	44	60:40	41	2
3a[c]	1	35	62:38	44	9
	2	30	64:36	45	8

[a] Reaction conditions: 2% catalyst, THF as solvent, slow addition (2 h) of diazo compound, reflux. Conversion and diastereoselectivity were determined by gas chromatography. Enantioselectivities were determined by HPLC (Chiralcel OD-H). The major syn isomer has the absolute configuration 2*R*,α*S*, from the sign of the optical rotation (ref 11). [b] Conversion to insertion products. As total conversion of the diazo compound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. [c] Reaction carried out in hexane under reflux with 2 equiv of THF.

The best results were obtained with box **1a**. The immobilized catalyst gave rise to 84% ee with a diastereomeric ratio of 75:25, a significant improvement from the homogeneous results (61% ee and 64:36 dr). Moreover, this catalyst is also recoverable and can be used three more times with the same results, thus demonstrating the stability of the **1a**−Cu complex.[13] In fact, after four runs, each catalytic center of the **1a**−Cu−laponite catalyst has converted 137 molecules of THF to the products, with an average enantioselectivity of 82.5% ee for the syn isomers.

This enhancement in the selectivities is again in agreement with our previous results, as this same ligand showed the largest confinement effect in the case of cyclopropanation reactions.[14b,15] We previously showed that surface effects were due to the close proximity of the catalytic complex, and this proximity can be increased by using solvents with low dielectric constants.[14] In view of this, we tried to enhance the surface effect by carrying out the reaction in hexane. The detrimental effect of solvent on the yield was less marked than in the case of the homogeneous catalysts, with only marginal reductions. The enantioselectivity was slightly better in all cases. The most relevant effect was observed with azabox **2a**, leading to 71% ee in comparison with 58% ee obtained in THF. Box **1a** gave the highest enantiomeric excess, 88% ee in the first reaction.

In conclusion, readily accessible Cu(II) complexes easily immobilized on a cheap support promote insertion of carbenes into C−H bonds, with enantioselectivities up to 88% ee. This result demonstrates not only how immobilization is a method to recover and reuse the catalyst but also how the appropriate selection of support, immobilization method, and chiral catalyst enables an improvement in the catalytic performance, in terms of both yield and enantioselectivity. New experiments are underway to expand the scope of the reaction and to study its stereochemical course.

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Supporting Information Available: Full characterization of ligands, reagent, and products, catalytic reactions, and chromatographic methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Herrerías, C. I.; Legarreta, G.; Martínez-Merino, V.; Mayoral, J. A. *J. Mol. Catal. A* **2003**, *196*, 101−108. (b) Fernández, A. I.; Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Salvatella, L. *Catal. Commun.* **2001**, *2*, 165−170.

(15) Castillo, M. R.; Fousse, L.; Fraile, J. M.; García, J. I.; Mayoral, J. A. *Chem.−Eur. J.* **2007**, *13*, 287−291.