PAPER

Enantioselective C–H carbene insertions with homogeneous and immobilized copper complexes†

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The efficiency of chiral bis(oxazoline)- and azabis(oxazoline)-copper complexes in the enantioselective carbene insertion into C–H bonds of cyclic ethers in homogeneous phase strongly depends on the structure of the substrate. The immobilization on laponite clay by electrostatic interactions not only allows the recovery and reuse of the heterogeneous catalysts, but in some cases also improves enantioselectivity and overall chemoselectivity, making possible reactions that do not take place or lead to low yields in solution, even with the commonly used $Rh_2[S\text{-}DOSP]_4$ catalyst.

Introduction

The great potential of carbene insertion reactions for the carbon-carbon bond formation from the poorly reactive carbon-hydrogen bonds has attracted considerable interest towards this type of reaction.[1] Catalysis is very important to control the high reactivity of the free carbenes in order to obtain chemoselective processes. Dirhodium(II) compounds have been the most used and versatile catalysts for carbene insertions, mostly the enantioselective version of both intra- and intermolecular reactions.[2] Very recently the use of a salen-Ir complex as catalyst for the enantioselective insertion into THF and 1,4-cyclohexadiene has been described with very high enantioselectivity (83–99% ee).[3] Coinage metals (copper, silver, and gold) are emerging as alternatives to rhodium,[4] although mostly for non-enantioselective reactions using non-chiral trispyrazolylborate and analogous ligands.[5] The use of these metals in enantioselective carbene insertions is rather scarce and poor results are commonly reported. Copper complexes with chiral bis(oxazolines) and related ligands have been described as catalysts for intramolecular insertions of carbenoids from phenyliodonium ylides[6] or diazocompounds.[7] Those reactions take place with low yields or chemoselectivities, and moderate to low enantiomeric excess, 15–60% e.e. and 6–74% e.e. respectively. Only very recently Maguire and coworkers have described the efficient intramolecular insertion of α-diazosulfones with high to excellent enantioselectivities.[8] Even less examples of enantioselective intermolecular carbene insertions catalyzed by metals different from rhodium can be found in the literature. A copper-bis(imine) complex was used in the synthesis of methyl phenidate with low enantioselectivity (18% e.e.).[9]

In this context, our group described the first use of chiral bis(oxazoline)- and azabis(oxazoline)-copper complexes as catalysts for the enantioselective intermolecular carbene insertion into C–H bonds of THF.[10] The immobilization by electrostatic interactions on laponite clay, forming a catalyst-support ion pair, led to improved catalysts, not only in activity and recoverability, but also in enantioselectivity due to a surface effect of the support.[11] In this paper we extend the study to other ethers to analyze several factors on the different selectivities (chemo-, regio-, diastereo-, and enantioselectivity) of the reactions. It is important to note that, to the best of our knowledge, the enantioselective version of these reactions had not been previously described.

Results and discussion

Reactions of methyl phenyldiazoacetate with tetrahydropyran (THP), 1,4-dioxane, and 1,3-dioxolane (Scheme 1) were studied using several copper complexes with chiral bis(oxazoline)[12] (**1**) and azabis(oxazoline)[13] (**2**) ligands (Chart 1). For the sake of comparison, the previously described results of the reaction with THF,[10] as well as those obtained with the commercially available $Rh_2[S\text{-}DOSP]_4$ catalyst, are also included (Table 1). Two diastereomers are obtained with THF, THP, and 1,4-dioxane. The *unlike* and *like* terms[14] have been used instead of the *syn/anti* nomenclature also used in the literature. In all cases homogeneous catalysts are compared, under the same conditions, with the analogous catalysts immobilized by cation exchange on laponite clay (Scheme 2),[15] forming an ion pair between the clay and the cationic complex, and precluding metal leaching unless copper neutral species are generated. The reactions were truly heterogeneous, as shown by the lack of activity of the filtrate, and elemental analyses showed the absence of metal leaching.

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Table 1 Results of the enantioselective reaction between methyl phenyldiazoacetate and different substrates catalyzed by copper complexes in solution and immobilized on laponite clay[a]

Entry	Substrate	Ligand	Type of catalyst	Conv. (%)[b,c]	unlike/like[c]	% ee unlike[d]	% ee like[d]
1	THF	[Rh][e]	Homog	—	67:33[f]	72(90)[f]	nd
2		1a	Homog	48	64:36	59	40
3		2a	Homog	85	64:36	59	55
4		2b	Homog	54	74:26	0	−12
5		2c	Homog	74	56:44	64	48
6		1a	Immob	66	75:25	84	39
7		2a	Immob	60	74:26	58	51
8		2b	Immob	27	51:49	4	16
9		2c	Immob	50	59:41	62	59
10	THP	[Rh][e]	Homog	37(26)[g]	63:37	52(72)[g]	28(42)[g]
11		1a	Homog	9	65:35	33	17
12		2a	Homog	43	58:42	53	48
13		2b	Homog	19	62:38	−11	38
14		2c	Homog	40	51:49	51	71
15		1a	Immob	39	58:42	68	41
16		2a	Immob	77	63:37	58	60
17		2c	Immob	43	46:54	39	71
18	1,4-Dioxane	[Rh][e]	Homog	<1(16)[g]	39:61	− (41)[g]	− (59)[g]
19		1a	Homog	10	37:63	62	71
20		2a	Homog	8	32:68	−7	45
21		2b	Homog	3	43:57	0	0
22		2c	Homog	11	29:71	24	35
23		1a	Immob	7	43:57	48	45
24		2a	Immob	30	37:63	11	54
25		2c	Immob	38	30:70	36	50
26	1,3-Dioxolane	[Rh][e]	Homog	21(10)[g]	—	49(76)[g]	—
27		1a	Homog	0	—	—	—
28		1a	Immob	51	—	38	—
29		2a	Immob	66	—	33	—
30		2b	Immob	47	—	56	—
31		2c	Immob	76	—	31	—

[a] Reaction conditions: 2% catalyst (Cu/diazocompound ratio), substrate as solvent, slow addition (2 h) of diazo compound, reflux. [b] Conversion to insertion products. As total conversion of diazocompound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. [c] Determined by GC. [d] THF: determined by HPLC (Chiralcel OD-H); (αS,2R) is the major *unlike* product. THP: determined by GC (Cyclodex-β); (αS,2R) was tentatively assigned as the major *unlike* product. 1,4-Dioxane and 1,3-dioxolane: determined by GC (Cyclodex-γ). [e] Results with Rh₂[S-DOSP]₄. [f] Ref. 16 In parenthesis % ee at −50 °C (increased up to 97% ee in hexane). [g] In parenthesis results at rt.
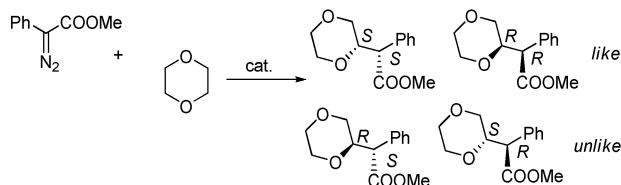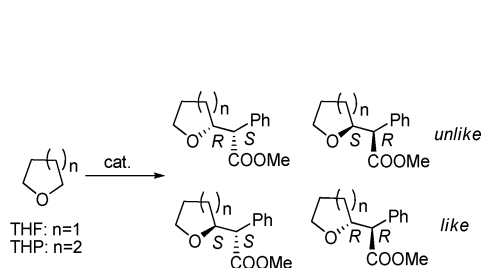
Scheme 1 Insertion reactions of methyl phenyldiazoacetate with different cyclic ethers.
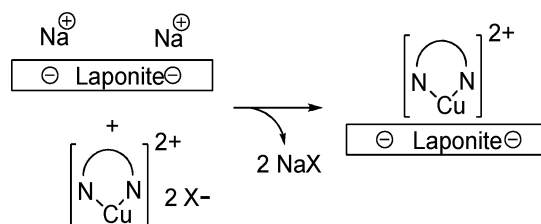
Scheme 2 Cationic exchange on laponite.
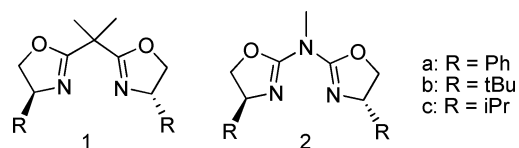

a: R = Ph
b: R = tBu
c: R = iPr

Chart 1 Oxazoline-containing ligands used along this work.

## Catalytic activity in C–H insertion (chemoselectivity)

As in the case of Rh catalysts[16] the conversion of diazocompound to C–H insertion products is limited by side reactions, mainly the dimerization of the diazocompound to give both *cis* and *trans* alkenes, and then the values of conversion are representative for the chemoselectivity of the reaction. Tests of insertion into

THF with **1a**/Cu(OTf)$_2$ ratios in the range of 0.8–2.0 showed constant enantioselectivities for ratios higher than 1.1, whereas catalytic activity was reduced, demonstrating that the formation of 2:1 complexes has no positive effect on the insertion reaction. A ligand/Cu ratio = 1.1 was used with the rest of ligands and substrates in homogeneous phase. The performance of triflate was shown to be better than that of other anions such as acetate, bromide, chloride, and SbF$_6^-$.

All the copper triflate complexes were active for the insertion reaction, with yields in the range 40–85% for THF (Table 1, entries 2–5). A significant effect of ligand on catalytic activity (chemoselectivity to insertion) is observed, with azabox ligands (**2**) being clearly superior, a fact that may be related to their higher coordinating ability[17] and that has been also observed in other reactions.[18] The substituent in position 4 of the oxazoline ring shows also an important effect on activity (chemoselectivity), according to results in other reactions,[18] in the order Ph > ^{i}Pr > ^{t}Bu. This methodology was then extended to the insertion in tetrahydropyran (THP) due to the structural similarity to THF and to the interest of the insertion product as an analogue of methyl phenidate for dopamine and serotonin transporter inhibition.[19] As can be seen (Table 1, entries 11–14) THP is less reactive than THF and leads to moderate to low conversions (9–43%), in the same range of result obtained with commercially available Rh$_2$[S-DOSP]$_4$ (Table 1, entry 10). This effect of ring size is analogous to that previously observed for N-Boc-piperidine in comparison with N-Boc-pyrrolidine with Rh catalysts.[20] The donor character of the ligand[17] seems to play again a role, with the same general trend observed for THF: **2a** ≥ **2c** ≫ **2b** ≥ **1a**.

The next substrate tested was 1,4-dioxane. In spite of having four active positions for insertion, very low yields (3–11%, up to 16% with Rh$_2$[S-DOSP]$_4$ at rt) were obtained in solution (Table 1, entries 18–22). Similar detrimental effects of the presence of an oxygen in β-position had been observed in the enantioselective insertion of methyl phenyldiazoacetate into both crown ethers and 1,2-dimethoxypropane with Rh catalysts,[21] and in the non-enantioselective insertion of ethyl diazoacetate into 1,4-dioxane with homogeneous copper[5b] and silver scorpionates.[22] The presence of a second oxygen in α-position was tested in the case of 1,3-dioxolane. In principle position 2 in this substrate is more activated, due to the presence of the two adjacent oxygen atoms.

Analogue Rh-catalyzed insertion reactions had been carried out on 2-aryl-1,3-dioxolanes, as equivalent to a Claisen condensation,[23] but the insertion on the unsubstituted 1,3-dioxolane, which had not been described in the literature, leads to low yields (up to 21% under reflux, entry 26). Surprisingly, in the case of the homogeneous reactions with copper catalysts, the first drop of diazocompound converted the reaction solution into a gel-like mass. The ^{1}H-NMR spectrum of this gel showed broad signals at 4.74 (2H) and 3.71 ppm (4H), compatible with a polymer formed by dioxolane ring opening, and confirmed by the detection of species in the m/z range of 300–1600 with differences of 74 (supplementary material†). Even under hexane dilution conditions, the only detectable product of the homogeneous reaction was this polymer. This polymerization reaction may take place through an attack of the oxygen to the electrophilic carbon of the carbenoid (Scheme 3), in the same fashion proposed for the attack of THF to carbene-iron-porphyrin complexes, in which one O–C$_\alpha$ bond is broken leading to a C–C double bond.[24] The attack
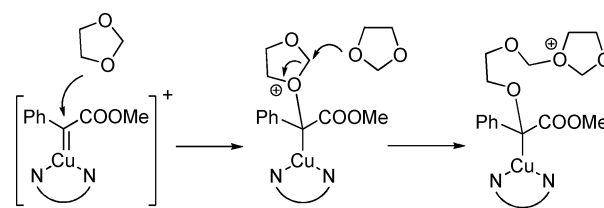
Scheme 3 Proposed mechanism for polymerization of 1,3-dioxolane.

of the oxygen to the carbene may occur with all the substrates in a reversible way, but in this case it leads to a productive reaction. The reason for this difference is not clear but it must be related to the presence of the second oxygen, which increases the electrophilic character of the carbon in position 2, favouring the attack of a second molecule of 1,3-dioxolane.

A similar behaviour would be expected in other cases in which the breakage of the C–O was irreversible for example in the case of elimination of an alkene. Diisopropylether was chosen as model for this test, because the break of the O–C bond and the transfer of a proton would produce the elimination of propylene (Scheme 4), in an irreversible step. Confirming this hypothesis the product of C–H insertion was not detected. On the contrary the product coming from the insertion of the carbene in the O–H bond of isopropanol was always obtained with both homogeneous and heterogeneous catalysts (Scheme 4).
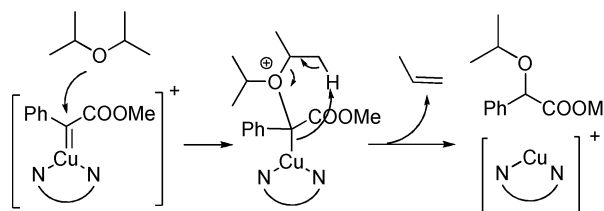
Scheme 4 Reaction between methyl phenyldiazoacetate and diisopropylether.

The same reasoning would justify the lower chemoselectivity observed with 1,4-dioxane, with a breakdown process leading to methyl 2-hydroxy-2-phenylacetate, detected in the reaction medium, and volatile by-products such as acetaldehyde and ethylene.

Whereas immobilization is only moderately positive for chemoselectivity of insertion in THF with **1a** (66% vs. 48 in solution, entries 6 and 2) and detrimental with azabis(oxazolines) (27–60% conversion vs. 54–85% in solution, entries 7–9 vs. 3–5), it has a significant positive effect with the rest of less reactive substrates (Table 1). In the case of THP immobilization is highly beneficial for phenyl substituted ligands **1a** (39% vs. 9% in solution, entries 15 and 11) and **2a** (77% vs. 43% in solution, entries 16 and 12), although this effect is not observed for the isopropyl substituted azabox **2c** (entry 17). The immobilized catalysts also led to moderate to excellent conversions to the expected insertion product in 1,3-dioxolane (47–76%, entries 28–31), in contrast with the homogeneous catalysts. Given that polymerization does not take place with the immobilized catalyst, it may be speculated the need for a coordination of both oxygens, making the carbon atom much more reactive, impossible with the solids due to the site isolation effect. This is not the case with diisopropyl ether,

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because the elimination of propylene is an intramolecular reaction. Probably the fact that breakdown in the case of 1,4-dioxane does not require the participation of two molecules of catalyst makes the increase in chemoselectivity not so noticeable, with the highest values not exceeding the 30–38% obtained using azabox ligands (entries 24–25).

It is worthy to note that insertions of methyl phenyldiazoacetate into THP, 1,4-dioxane, and 1,3-dioxolane had not been previously described. Thus, taking into account the reactivity problems detected in homogeneous phase, even in the case of $Rh_2[S$-DOSP]$_4$ and in agreement with those described for closely related substrates, the values of conversion to insertion products (77% with THP, 38% with 1,4-dioxane, and 76% with 1,3-dioxolane) obtained with the immobilized catalysts are remarkable.

Stereoselectivity

The insertions into THF in homogeneous phase lead to the *unlike* product as major diastereoisomer with moderate to low selectivity (56 : 44–74 : 26, entries 1–5). Enantioselectivities in the *unlike* isomer are also moderate, up to 64% ee (entry 5). Phenyl or isopropyl substituents in box and azabox lead to similar enantioselectivity, better than *tert*-butyl, a situation in contrast with the behaviour of the same ligands in the related cyclopropanation reaction. Another important feature is the relationship between diastereoselectivity and enantioselectivity, as can be seen in Fig. 1. In general lower diastereoselectivity is associated with higher enantioselectivity. The results with THF are slightly worse than those obtained with $Rh_2(S$-DOSP)$_4$ under the same conditions (67 : 33 diastereomeric ratio, 72% ee *syn*, entry 1).[16b] With Rh catalysts enantioselectivity was improved by lowering the temperature or using hexane as solvent (up to 97% ee at −50 °C).[16b] However none of those methods improved enantioselectivity in the case of **2a**-Cu(OTf)$_2$. Enantioselectivity of the *like* isomers follows a similar trend, up to 55% ee.
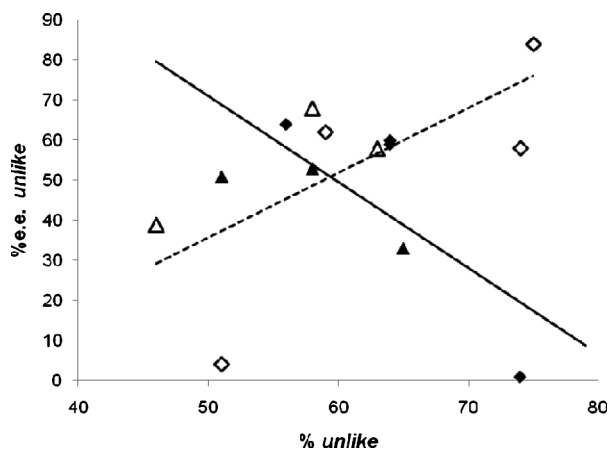

Fig. 1 Relationship between diastereo- (% *unlike*) and enantioselectivity (% ee *unlike*) of the reactions of methyl phenyldiazoacetate with THF (◆) and THP (▲) in homogeneous (filled symbols, tendency in full line) and heterogeneous (open symbols, tendency in dashed line) phase.

The insertions into THP in homogeneous phase also lead to the *unlike* product as major diastereoisomer with similar selectivity (51 : 49–65 : 35, entries 11–14), again in the same range as that obtained with Rh (entry 10). Enantioselectivities are also

moderate, up to 53% ee in the *unlike* isomers (entry 12) and up to 71% ee in the *like* isomers (entry 14). The substituents in box and azabox follow the same trend as that observed with THF. The results of enantioselectivity *unlike* with THP are similar to those obtained with $Rh_2(S$-DOSP)$_4$ under the same conditions (52% ee, entry 10), although in this case again enantioselectivity can be improved by lowering the temperature. On the contrary the results of enantioselectivity *like* are in general better with copper complexes.

One interesting consequence of the immobilization was the modification of the stereoselectivities, highly dependent on the nature of the ligand. Whereas the immobilization of azabox-Cu complexes produces only marginal variations of enantioselectivity (entries 7–9 and 16–17), the immobilization of **1a**-Cu produces a significant improvement in enantioselectivity of *unlike* isomers, 84% ee *vs.* 59% ee in solution with THF (entry 6), 68% ee *vs.* 33% ee in solution with THP (entry 15). Perhaps less important, but also significant, is the simultaneous variation of diastereoselectivity. In Fig. 1 it can be seen how the correlation between *enantio*- and diastereoselectivity completely changes after immobilization, mainly with THF. Interestingly, with the immobilized catalysts the general trend is to obtain at the same time high diastereo- and enantioselectivity. It is important to note that the immobilized Cu catalysts allow reaching enantioselectivities in the same range as those obtained with $Rh_2(S$-DOSP)$_4$, but in general with higher yields of insertion products.

It might be speculated whether the changes in yield and stereoselectivity are due to a surface effect, as proposed for cyclopropanation reactions,[25] or to a change in the reaction mechanism with the immobilized catalyst. The mechanism was checked by kinetic isotopic effect, determined by competitive reaction in the presence of equimolar amounts of THF and THF-d_8. An isotopic effect $k_H/k_D = 2$ was obtained for both homogeneous and heterogeneous reactions, showing that the changes observed in stereoselectivities cannot be ascribed to deep changes in the reaction mechanism, but to changes in the relative energies of the transition states leading to the four products. This value is lower than that was obtained for the Rh-catalyzed reaction ($k_H/k_D = 3$),[16b] probably due to a slightly different geometry of the transition state, whereas the same value of 2 was found for the Rh-catalyzed insertion into cyclohexene. This value is in agreement with the insertion as the rate limiting step, a situation different from that of the cyclopropanation of styrene with ethyl diazoacetate promoted by the same catalysts, in which the formation of the copper-carbene intermediate is the rate limiting step.[26]

In order to get some deeper insight in the stereochemical course of the reactions, the reaction products were separated by semi-preparative chiral HPLC[27] (see ESI†). The four insertion products in THF were obtained in enantiopure form. In this way the absolute configuration of the major *unlike* product was confirmed to be (2R,αS) with $[\alpha]_D^{25}$ −88.1° (c 0.159, CHCl$_3$).‡ The major *like* product showed also negative value of the specific rotation, $[\alpha]_D^{25}$ −19.3° (c 0.7, CHCl$_3$).

In order to check the absolute configuration, an epimerization of the α-carbon of this product under basic conditions was tested to

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‡ The value reported in ref. 16 is $[\alpha]_D^{25}$ −74.0° (c 0.2, CHCl$_3$). In our case the value obtained for the minor *unlike* isomer, absolute configuration (2S,αR), is $[\alpha]_D^{25}$ +78.1° (c 0.167, CHCl$_3$).

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obtain the corresponding mixture of *unlike*/*like* products with the same absolute configuration in position 2 of the furan (Scheme 5). Unexpectedly the reaction with sodium methoxide led to a 25 : 75 mixture of *unlike*:*like* in racemic form. To discard the possible abstraction of the proton in position 2 of THF, the reaction was carried out in d_4-methanol obtaining in this way the same mixture of products but deuterated only in α-position and in the methyl ester (Scheme 5). The ring opening must then take place through a mechanism outlined in Scheme 3, similar to that proposed to explain the ring opening of bicyclic *N,O*-acetal serine derivatives.[28] Unfortunately this result did not allowed the absolute configuration of the *like* products to be determined.
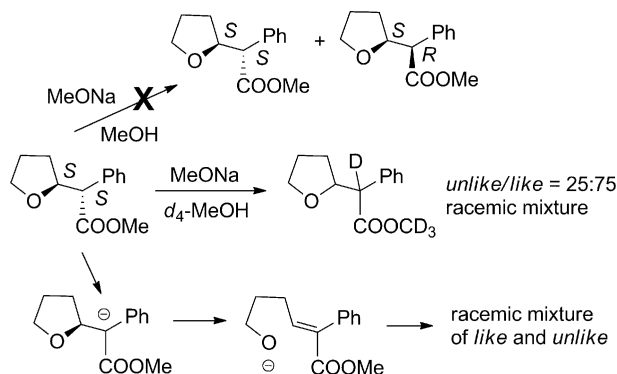
Scheme 5 Epimerization reaction of the major *like* product of insertion into THF.

With respect to the absolute configuration of the major isomer of insertion into THP, the separation by semi-preparative HPLC was performed in a similar way to that described for the products of THF insertion, but in this case the separation was more difficult, due to the lower solubility of the mixture (ESI†). Both *unlike* enantiomers were obtained in enantiopure form, but *like* enantiomers were obtained only as a 5/95 mixture. The major *unlike* compound showed $[\alpha]_D^{25}$ −76.4° (c 0.55, CCl$_4$). Taking into account the similar nature of THP and THF, the induction mechanism should be the same and (2R,αS) configuration can be tentatively assigned to the major *unlike* product, also confirmed by the same sign of the specific rotation. Additionally the sign is also the same as the product with 2 chlorine atoms in 3,4 positions of the aromatic ring described in the literature.[19a]

In the case of 1,4-dioxane the presence of the oxygen in the ring produces a change in the priority of the substituents of the stereogenic centre of the ring, and hence in its absolute configuration. This means that the product coming from the attack by the same face will have different relative configuration *unlike*/*like* with respect to that of THP. This relative configuration was assigned from the shielding effect of the phenyl group on protons in C3 in the most stable antiperiplanar conformation (Fig. 2).[29] Due to this change, the *like* preference obtained with 1,4-dioxane does not represent any change in reaction mechanism.

Enantioselectivities were moderate in solution with azabox **2a** and **2c**, whereas the highest values were obtained with box **1a** (71% ee, entry 19). This result is clearly better than that obtained with Rh$_2$[*S*-DOSP]$_4$. at r.t. (59% ee, entry 18). The use of the immobilized catalysts produced variations in enantioselectivity, but without any pattern, with improvements for azabox (50–54%)
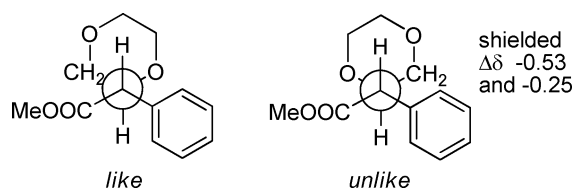

Fig. 2 Newman projections of *like* and *unlike* compounds of insertion into 1,4-dioxane.

ee, entries 24–25) and reduction for box **1a** (45% *vs.* 71% ee in solution, entry 23).

In the case of 1,3-dioxolane, only products of insertion in position 2 of the dioxolane ring were detected in all cases, showing a very high regioselectivity. Products of insertion in position 4 had been obtained with 2-aryl-1,3-dioxolanes as substrates, in proportions ranging from 29% at 50 °C to 18% at −30 °C.[23] Enantioselectivity was moderate with all the ligands, with values in the range of 31–56% ee (entries 28–31). The best enantioselectivity was obtained with the ligand bearing *tert*-butyl groups (56% ee), in contrast with results obtained with the rest of substrates. This result is analogous to that obtained with Rh$_2$[*S*-DOSP]$_4$ under the same conditions (49% ee, entry 26), and slightly worse than the result at r.t. (76% ee), although this higher ee is accompanied by an important decrease in yield up to only 10%.

Recoverability

An additional advantage of immobilized catalysts is the possibility of recovery and reuse (Table 2). In the case of THF recovery was very efficient with box **1a** in three reuses, leading to a total TON of 134 with 75 : 25 diastereoselectivity and 83% ee, much better than TON 24 with 64 : 36 and 59% ee of the homogeneous catalyst. With the rest of catalysts only one or two reuses were tried, with similar results to those obtained in the first run, showing the high stability of the catalysts under the reaction conditions.

In the case of THP most catalysts were efficiently recovered, even with improved catalytic activity as it happens with **2c**. Whereas **1a**-Cu loses activity and selectivity upon recovery probably due to a partial loss of ligand, the higher stability of **2a**-Cu and **2c**-Cu complexes[17] makes them more suitable for this reaction, keeping the activity and enantioselectivity for 3 cycles.

The low chemoselectivity of the insertion into 1,4-dioxane, with the generation of the corresponding by-products, that poison the catalyst or favor leaching of the chiral ligand, may be the origin for the poor recyclability of the immobilized catalysts in this reaction. Only azabox **2c** allows efficient recovery regarding both activity and selectivity in one recycle.

The high chemoselectivity obtained with immobilized catalysts in the insertion into 1,3-dioxolane, probably due to site isolation as pointed above, allows efficiently recovering the catalysts with similar enantioselectivity and even improved activity, as in the case of **2c**. Unfortunately the lower stability of **2b**-Cu makes the recovery inefficient, with loss of enantioselectivity.

It is the clear that there is a close relationship between chemoselectivity and catalyst recovery, as observed in the closely related cyclopropanation,[30] because of the detrimental effect of by-products.

Table 2 Results of recovery of the copper complexes immobilized on laponite clay in the enantioselective reaction between methyl phenyldiazoacetate and different substrates[a]

Substrate	Ligand	Run	Conv. (%)[b,c]	unlike/like[c]	% ee unlike[d]	% ee like[d]
THF	**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
	2a	1	60	74:26	58	51
		2	55	74:26	57	51
		3	61	73:27	56	54
	2c	1	50	59:41	62	59
		2	56	58:42	61	59
		3	62	56:44	58	56
THP	**1a**	1	39	58:42	68	41
		2	25	55:45	33	16
		3	31	55:45	31	13
	2a	1	77	63:37	58	60
		2	54	60:40	62	65
		3	59	59:41	58	59
	2c	1	43	46:54	39	71
		2	53	46:54	42	70
		3	57	47:53	36	67
1,4-Dioxane	**1a**	1	7	43:57	48	45
		2	10	45:55	18	41
		3	12	47:53	7	25
	2a	1	30	37:63	11	54
		2	34	38:62	9	33
		3	26	36:64	12	20
	2c	1	38	30:70	36	50
		2	37	28:72	30	46
		3	8	35:65	16	37
1,3-Dioxolane	**1a**	1	51	—	38	—
		2	54	—	27	—
		3	49	—	26	—
	2a	1	66	—	33	—
		2	58	—	34	—
		3	44	—	30	—
	2b	1	47	—	56	—
		2	38	—	42	—
		3	37	—	36	—
	2c	1	76	—	31	—
		2	86	—	28	—
		3	85	—	27	—

[a] Reaction conditions: 2% catalyst (Cu/diazocompound ratio), substrate as solvent, slow addition (2 h) of diazo compound, reflux. [b] Conversion to insertion products. As total conversion of diazocompound was observed in all cases, this value reflects the chemoselectivity to the insertion reaction. [c] Determined by GC. [d] THF: determined by HPLC (Chiralcel OD-H); (αS,2R) is the major unlike product. THP: determined by GC (Cyclodex-β); (αS,2R) was tentatively assigned as the major unlike product. 1,4-Dioxane and 1,3-dioxolane: determined by GC (Cyclodex-γ).

Conclusions

Homogeneous box- and azabox-copper complexes are able to catalyze the enantioselective insertion of methyl phenyldiazoacetate into C–H bonds of cyclic ethers. Chemo-, diastereo-, and enantioselectivities strongly depend on the nature of the substrate. The best results are obtained with THF (up to 64% ee), whereas 1,4-dioxane is much less reactive (up to 11% conversion) and 1,3-dioxolane leads only to polymerization products.

When the same complexes are immobilized by electrostatic interactions with laponite clay, the catalytic performance considerably improves. In all cases the productivity increases, either in one single reaction, up to 38% conversion with 1,4-dioxane vs. 11% in solution, or by efficient recovery in at least three consecutive runs. Moreover, the immobilized catalysts are able to efficiently promote the insertion in position 2 of 1,3-dioxolane, with up to 56% ee preventing the insertion in position 4 and other side reactions. An additional advantage of the immobilized catalysts is the improvement of the stereoselectivity, up to 84% ee with THF and 68% ee with THP combined with high diastereoselectivity. In summary the immobilized copper complexes are promising catalysts for carbene insertion reactions, given that in the most demanding reactions they allow reaching higher chemoselectivities, with similar stereoselectivities, than the commonly used Rh$_2$(S-DOSP)$_4$ catalyst, an advantage probably due to the site isolation effect.

Experimental

General procedure for carbene insertion with heterogeneous catalysts

A suspension of dried heterogeneous catalyst (100 mg) in anhydrous substrate (THF, THP, 1,4-dioxane, or 1,3-dioxolane,

10 mL) with n-decane (100 mg) as internal standard was heated under reflux under an inert atmosphere. A solution of methyl phenyldiazoacetate (1 mmol) in anhydrous substrate (10 mL) was slowly added during 2 h with a syringe pump. Once the addition had finished, the reaction mixture was stirred and heated under reflux for 30 min. The catalyst was filtered off and washed with substrate (5 mL). The yield and diastereoselectivity were determined by GC and enantioselectivities were determined by HPLC or GC. The catalyst was dried under vacuum and reused under the same conditions.

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