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Support Effect on Stereoselectivities of Vinylogous Mukaiyama–Michael Reactions Catalyzed by Immobilized Chiral Copper Complexes

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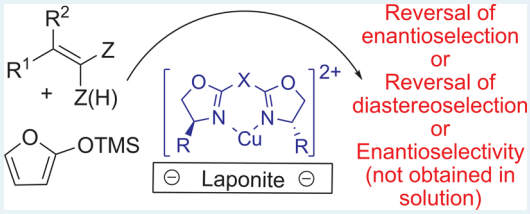
Supporting Information

ABSTRACT: Chiral bis(oxazoline)- and azabis(oxazoline)-copper complexes, used as homogeneous catalysts or immobilized onto laponite, are able to catalyze vinylogous Mukaiyama–Michael reactions between 2-(trimethylsilyloxy)furan and several electron-deficient alkenes. A study of the support effect has been conducted and different changes on the diastereoselectivities and enantioselectivities has been observed. The behavior of the catalyst is different, depending on the structure of the substrate (Michael acceptor). When diethyl benzylidenemalonate was used, the major diastereomer was that with *syn* configuration, but the homogeneous and the heterogeneous catalysts lead to opposite enantiomers (−80% ee in solution and 38% ee in the heterogeneous phase). This change represents a support effect of ∼1.8 kcal/mol. With *N*-(*E*)-but-2-enoyloxazolidinone, the most relevant change is in the diastereomer preference. In solution, the *anti* isomer is the major one (*anti*/*syn* = 98/2); however, in contrast, *syn* isomer is preferred with the immobilized catalyst (*anti*/*syn* = 19/81). This *syn* preference has not been previously reported in the literature. Finally, in the case of α,β-unsaturated ketones, the homogeneous catalysts are not able to induce enantioselectivity, whereas the immobilized ones lead to moderate values (up to 70%), similar to those values described in the literature with organocatalysts.



KEYWORDS: *asymmetric catalysis, bis(oxazolines), copper, supported catalyst, support effect*

INTRODUCTION

Enantioselective catalysis is, in theory, the most interesting method to prepare organic compounds in enantiopure form. In contrast with this idea, and apart from the cases of enzymatic kinetic resolutions, the examples of industrial applications of enantioselective catalysts are rather scarce and mostly concentrated in a short number of hydrogenation reactions.[1] One of the reasons adduced for this situation is the high cost and low productivity of most of the enantioselective metal-based catalysts.[2] One method to improve their productivity is the immobilization on solid supports,[3−6] which, in principle, should allow the recovery and reuse of the expensive enantioselective catalyst, or even permit its use in continuous-flow reactors.[7] However, immobilization has an additional cost, mainly in the most popular covalent method, because of the required supplementary substitution on the ligand, which is also a source of unexpected effects on enantioselectivity. The use of noncovalent strategies of immobilization[8] should help to minimize its cost impact, since the same homogeneous catalysts can be supported and the immobilization procedure is simple and efficient. Moreover, additional advantages should be obtained to compensate the preparation effort, even if not so hard, of the immobilized catalyst (for example, modification of the stereoselectivities of the reaction[9]). A good number of examples have been described in which stereoselectivities in homogeneous catalysis are reversed by modifications in reaction parameters such as metal, solvent, or additives.[10] In contrast, only a handful of examples dealing with immobilized catalysts have been reported. Some examples described on silica[11] have been explained by the change in the coordinating ability of the anion by hydrogen-bonding with the surface silanols,[12] which is a change that is also produced in the case of supported ionic liquid phases.[13]

The mesoporous materials have been considered as suitable supports for chiral catalysts, as the regular pore system would restrict the conformational freedom of the catalysts and limit the possible pathways for the attack of reagents[14] in a sort of confinement effect, invoked also in the case of catalysts supported on zeolites.[15] Another type of support for the immobilization of chiral catalysts are the clays, which are layered silicates that have been recognized for a long time as interesting catalysts and supports for organic synthesis.[16−18] Our group described, for the first time, the effect of the regular flat surface of clays on the stereoselectivity of copper-catalyzed reactions when the catalyst had been immobilized by electrostatic interactions.[9] In the case of cyclopropanation, even the nonchiral catalyst had some influence on diastereoselectivity,[19] and the chiral catalysts with bis(oxazoline)

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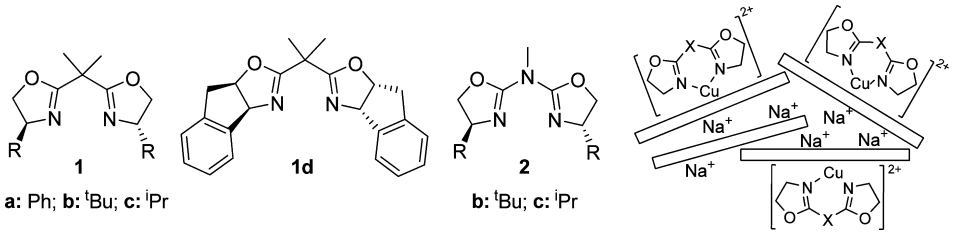

Figure 1. Ligands used in this work and an idealized view of the supported catalysts.

ligands were able to reverse both diastereoselectivity and enantioselectivity.[20] Since then this effect has been studied in-depth by using different supports,[21] ligand substituents,[22] unsymmetrically substituted bis(oxazolines),[22,23] monooxazoline ligands,[24−26] and substrates and diazocompounds.[22] Unfortunately, the system was revealed to be rather unpredictable to get a full picture of the surface effect, probably because of its high conformational flexibility, and different effects on selectivities (enhancement, decrease, or reversal) were obtained. In the meantime, effects on other reactions were also observed. In the case of carbene insertions into C−H bonds of cyclic ethers, stereoselectivities and also chemoselectivity were improved.[27,28] An impressive effect, with reversal of diastereoselectivity and great enhancement of enantioselectivity, was observed in the case of the vinylogous Mukaiyama aldol reaction using 2-(trimethylsilyloxy)furan.[29] This enolsilane is very useful from a synthetic point of view, because it leads to γ-butenolides[30] that are present in a large number of natural products. The related vinylogous Mukaiyama−Michael reaction[31,32] has been less explored, with only a limited number of examples of the enantioselective version catalyzed by bis(oxazoline)-metal complexes described in the literature.[33] In this case, it is also important to highlight that, to our knowledge, there are no reported examples of using heterogeneous catalysis to promote this reaction.

In this paper, we present an extensive study of the surface effect on enantioselective vinylogous Mukaiyama−Michael reactions between 2-(trimethylsilyloxy)furan and several electron-deficient alkenes, showing how the structure of the substrate (Michael acceptor) conditions the results of both diastereoselectivity and enantioselectivity. Cu(II) complexes of different bis(oxazoline) (box)[33] and azabis(oxazoline) (azabox)[34,35] ligands (Figure 1) were tested as catalysts. Laponite, which is a synthetic layered magnesio-silicate,[36] was used as a support for the immobilized catalysts. Immobilization was carried out via the exchange of some of the Na^+ cations by box-$Cu(OTf)_2$ complex in methanol,[37] leading to a more disordered material (Figure 1).[38] The catalysts were characterized by copper and elemental analysis (see the Supporting Information) and by infrared (IR) spectroscopy,[22,37,38] to confirm the structural integrity of the complex after cation exchange.

RESULTS AND DISCUSSION

Reaction with Diethyl Benzylidenemalonate. The first Michael acceptor considered was diethyl benzylidenemalonate (Scheme 1), which had been used in nonvinylogous Mukaiyama−Michael reactions catalyzed by the same type of complexes.[39] The results, both in homogeneous and heterogeneous phase, are collected in Table 1.

In the homogeneous phase, *syn* (unlike) products are the major ones, as it happened in the reaction catalyzed by $Cu(OTf)_2$ (*syn*/*anti* = 98:2),[40] but in general, the presence of the chiral ligand reduces the diastereoselectivity, slightly in the case of ligands with aromatic substituents (**1a** and **1d**) and more significantly in the case of ligands with aliphatic substituents, and mainly with ^{t}Bu (**1b** and **2b**), leading to the lowest diastereoselectivity values (around 78/22). With respect to enantioselectivity, box ligands are slightly better than the analogous azabox ones, whereas the worse results are obtained with the *tert*-butyl substituted ligands. Under these conditions (room temperature (rt), toluene solvent, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) additive), **1c** and **1d** (ee over 80%) are the best ligands for the homogeneous reaction, despite the better results described for **1b** at low temperature. The enantioselectivity in the minor *anti* isomer did not show any correlation with that of the major *syn* isomer, with 63% ee as the best value obtained with **1c**.

The fluorinated alcohol was necessary to accelerate the reaction,[39] but its role in the control of the enantiomeric excess has not been described. Several fluorinated alcohols (2,2,2-trifluoroethanol as a primary alcohol; 1,1,1,3,3,3-hexafluoro-2-

Scheme 1. Reaction between Diethyl Benzylidenemalonate and 2-(Trimethylsilyloxy)furan

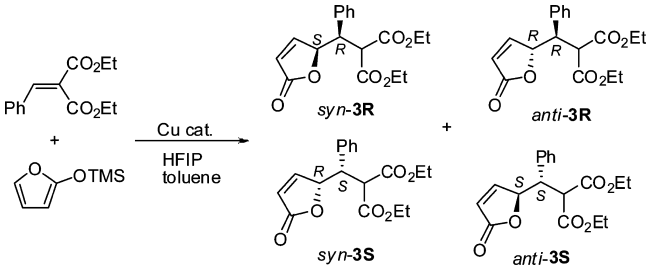

Table 1. Results of the Reaction between Diethyl Benzylidenemalonate and 2-(Trimethylsilyloxy)furan[a]

	Homogeneous				Immobilized			
ligand	yield (%)	*syn*/*anti*	%ee *syn*[b]	%ee *anti*[b]	yield (%)	*syn*/*anti*	%ee *syn*[b]	%ee *anti*[b]
1a	100	94/6	−52	27	100	79/21	26	−6
1b	100	79/21	−23	−26	86	67/33	4	1
1c	100	90/10	−83	63	100	78/22	15	21
1d	100	94/6	−80	2	98	83/17	38	17
2b	100	77/23	15	−50	71	75/25	−3	−2
2c	100	86/14	−62	50	65	74/26	2	7

[a]Reaction conditions: 1 mmol of diethyl benzylidenemalonate (226 μL), 1.5 mmol of HFIP (159 μL), catalyst (0.10 mmol of homogeneous and 0.15 mmol of heterogeneous), 5 mL of anhydrous toluene, slow addition (5 h) of 2 mmol of 2-(trimethylsilyloxy)furan (347 μL) in 10 mL of anhydrous toluene at room temperature (rt). Reaction time after addition: 5 h in the homogeneous phase and 24 h in the heterogeneous phase. [b]Considered positive when the major product is that of lower retention time.

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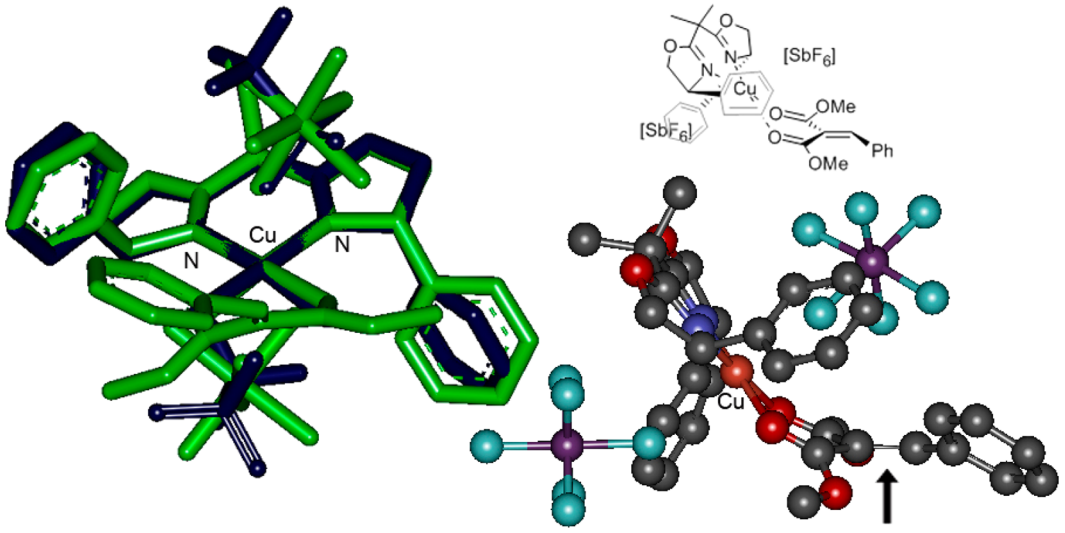

Figure 2. (Left) Overimposed geometries (according to X-ray diffraction) of the [**1a**-Cu-benzylidenemalonate]$(SbF_6)_2$ (green) and [**1a**-$Cu(H_2O)_2$]$(OTf)_2$ (deep blue) complexes. Hydrogen atoms are omitted for the sake of clarity. (Right) Proposed attack route.

methyl-2-propanol as a tertiary one; 1,3-(2,2,2-trifluoroethoxy)-2-propanol[41] as a more hindered secondary one) were tested in the reaction catalyzed by **1c**-$Cu(OTf)_2$. In all cases, the selectivities were very similar, with a *syn*/*anti* ratio between 85:15 and 90:10 and an enantiomeric excess of the *syn* isomer between 79% and 83%. This seems to indicate that the kinetic effect is due to a change in the rate-determining step, but the participation of fluorinated alcohol does not take place in the stereoselectivity-determining step (furane attack) but in the silane transfer step necessary to close the catalytic cycle.

Although crystals of the major *syn* isomer were obtained, they were not suitable to determine the absolute configuration. Hence, the sense of the asymmetric induction cannot be inferred from experimental data. The structure of the **1a**-Cu-benzylidenemalonate complex has been described, albeit with SbF_6 anions,[39] and this structure is very similar to that of the diaquo complex with triflate anions.[42] In fact, the overimposition of both structures (Figure 2) indicates that the oxygens are nearly in the same position, slightly distorted from the equatorial plane, and the anions are also in the same position, irrespective from their nature. The only significant variation corresponds to the rotation of the phenyl groups around the bond to the oxazoline ring, probably due to the presence of the benzylidenemalonate. Thus, it can be speculated that the attack would take place through the *Re* face of the benzylidenemalonate (Figure 2), leading to *syn*-**3S** as the major product. However, in the related reaction between benzylidenemalonate and indole catalyzed by **1c**-Cu, the attack through the *Si* face has been proposed to explain the induction sense in nonpolar solvents,[43] based on the square pyramidal structure of the analogous [**1b**-$Cu(H_2O)_2$]$(OTf)_2$ complex.[44] With this model, the major product would be *syn*-**3R**. Interestingly, the induction sense in the *syn* isomers with all the bis(oxazolines) is the same irrespective from the substituent nature, in contrast with the result reported in the non-vinylogous Mukaiyama−Michael reaction on the same substrate.[39]

In the case of the immobilized catalysts, the diastereoselectivity was generally lower than that obtained in solution with their analogous catalysts. This immobilization effect had been already observed with the nonchiral heterogeneous catalyst (*syn*/*anti* = 75:25)[40] and the presence of the ligand does not significantly modify this selectivity, with values in the range from 67/33 to 83/17. At the same time, the sense of the asymmetric induction in the major *syn* isomer was reversed with respect to the homogeneous values and the major enantiomer was that of opposite configuration. A similar effect had been already observed in the case of cyclopropanation catalyzed by bis(oxazoline)-Cu(I) complexes immobilized on laponite, and it had been ascribed to the disposition of the complex with respect to the surface of the support.[20,26] In this case, the effect is observed with Cu(II) catalytic complexes, showing its general character. The most remarkable reversal was observed with **1d** ligand, from 80% ee in solution to 38% ee of the other enantiomer with the immobilized catalyst. Such a change in enantioselectivity represents a variation of ∼1.77 kcal/mol in the relative energies of the corresponding transition states, which must be due to the surface effect. In fact it can be speculated that the box-Cu-benzylidenemalonate complex, once the two anions have been exchanged by the negative charges of the support, will be placed on the surface to minimize the steric interactions, so probably the less hindered face in solution will be shielded by the surface, explaining, in this way, the reversal in the induction sense. The low enantioselectivity would be the consequence of the shielding effect of the ligand on the less-hindered face. However, this hypothesis, which considers the intermediate as a rigid body, is a simplification, as demonstrated in analogous examples.[22,23,25,26]

Reaction with *N*-(*E*)-but-2-enoyloxazolidinone. The *N*-acyloxazolidinones are among the most-used Michael acceptors, and specifically the reaction with 2-(trimethylsilyloxy)furan had been described in the literature, using BINOL-lanthanides,[45] bis(oxazoline) and pyridinebis(oxazoline) complexes with different metals,[46] or binaphthyldiimine−Ni[47] chiral catalysts. In our case, the results obtained with *N*-(*E*)-but-2-enoyloxazolidinone (Scheme 2) and bis(oxazoline)-copper complexes in solution and in heterogeneous phase are gathered in Table 2.

In this case, the major diastereomer has *anti* relative configuration (*syn*/*anti* ratio from 8/92 to 2/98) in the homogeneous reaction, in agreement with the results obtained with other chiral catalysts[45−47] and with $Cu(OTf)_2$ or Lap-Cu without chiral ligands.[40] The use of the immobilized catalysts

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Scheme 2. Reaction between *N*-(*E*)-but-2-enoyloxazolidinone and 2-(Trimethylsilyloxy)furan

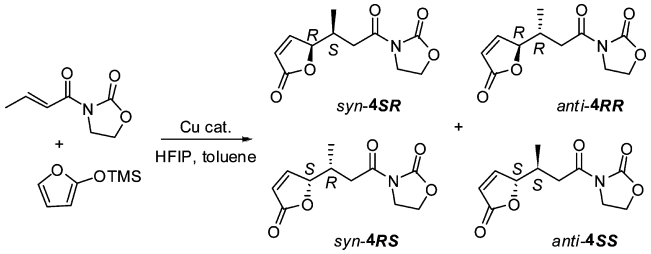

Table 2. Results of the Reaction between *N*-(*E*)-but-2-enoyloxazolidinone and 2-(Trimethylsilyloxy)furan[a]

	Homogeneous				Immobilized			
ligand	yield (%)	*syn*/*anti*	%ee *syn*[b]	%ee *anti*[c]	yield (%)	*syn*/*anti*	%ee *syn*[b]	%ee *anti*[c]
1a	100	2/98	69	36	81	64/36	32	32
1b	100	7/93	19	62	70	35/65	2	20
1c	100	7/93	23	16	100	81/19	0	52
1d	100	8/92	34	59	76	67/33	52	46
2b	100	7/93	13	92	85	35/65	15	29
2c	100	4/96	21	26	81	57/43	9	28

[a]1.5 mmol of HFIP (159 μL), catalyst (0.10 mmol of homogeneous phase and 0.15 mmol of heterogeneous phase), 5 mL of anhydrous toluene, slow addition (5 h) of 2 mmol of 2-(trimethylsilyloxy)furan (347 μL) in 10 mL of anhydrous toluene at rt. Reaction time after addition: 5 h in the homogeneous phase and 24 h in the heterogeneous phase. [b]*syn*-**4*SR*** is the major *syn* isomer. [c]*anti*-**4*SS*** is the major *anti* isomer.

promotes the formation of the *syn* isomer in different degrees, depending on the chiral ligand used—from *syn*/*anti* 35/65 with *tert*-butyl substituted ligands **1b** and **2b** up to *syn*/*anti* 81/19 with **1c**, showing that this result is a combined effect of the support and the ligand. This is a remarkable result since, to the best of our knowledge, none of the catalysts described in the literature promotes the formation of the *syn* isomer. Unfortunately, enantioselectivities are always lower than those obtained with the homogeneous catalysts, especially for the major *syn* isomer. The only exception is the result with Indane box **1d**, leading to moderate diastereoselectivities (67/33 d.r.) and enantioselectivities (52% ee for *syn*). Again, the decrease in enantioselectivity can be ascribed to a disposition of the complex with the less-hindered face toward the solid, leading to a competition between the shielding effect of the ligand substituent and the surface.

The explanation for the reversal of the diastereoselectivity is, by far, more difficult to justify, mainly because the reaction mechanism is not well understood. The enantioselectivity is explained by the disposition of the Michael acceptor in an *s-cis* conformation, in agreement with X-ray diffraction (XRD) data,[48] and the approach of furan by the less-hindered *Si* face (Figure 3). However, the disposition of furan, with respect to the acceptor, is still a matter of debate. Both open transition states and cyclic ones (similar to the Diels–Alder transition states) have been proposed to explain the stereochemical outcome of Mukaiyama-type reactions of silyloxyfurans.[49] Open-chain transition states allow one to explain the results of uncatalyzed Mukaiyama–Michael reactions with quinones,[50,51] but they have been also proposed for Sc-catalyzed reactions with unsaturated ketones,[52] although in that case, a coordination of furan to Sc has been also envisaged. Diels–Alder-like transition states have been always proposed in both Lewis-acid-catalyzed Mukaiyama aldol[53] and Mukaiyama–Michael[54] reactions. In the case of copper catalyzed reactions of simple enolsilanes with *N*-acyloxazolidinones, a mechanism through a hetero-Diels–Alder state has been observed, but in that case the Michael acceptor acts as heterodiene and the enolsilane as dienophile.[55,56]

When all the possible approaches of furan by the *Si* face of the Michael acceptor are represented (Figure 3), no clear preference for any of the transition states can be observed. In the case of Diels–Alder-like transition states (TS-DA), the one leading to the major *anti* diastereomer corresponds to the *endo* approach, the kinetically favored in a Diels–Alder reaction,[57] although it has been described that reactions with furan as a diene are reversible up to −20 °C.[58] The presence of HFIP might prevent this reversibility and TS-DA would explain the observed diastereoselectivity. Regarding the open-chain transition states (TS1 and TS2), the antiperiplanar disposition of the double bonds in TS1 has been always proposed as the most favorable approach. TS1-*anti* has also the advantage over TS1-*syn* that H atoms are in antiperiplanar, minimizing the steric interactions between the substituents. However, TS1-*anti* places the bulky TMS group toward the catalytic complex

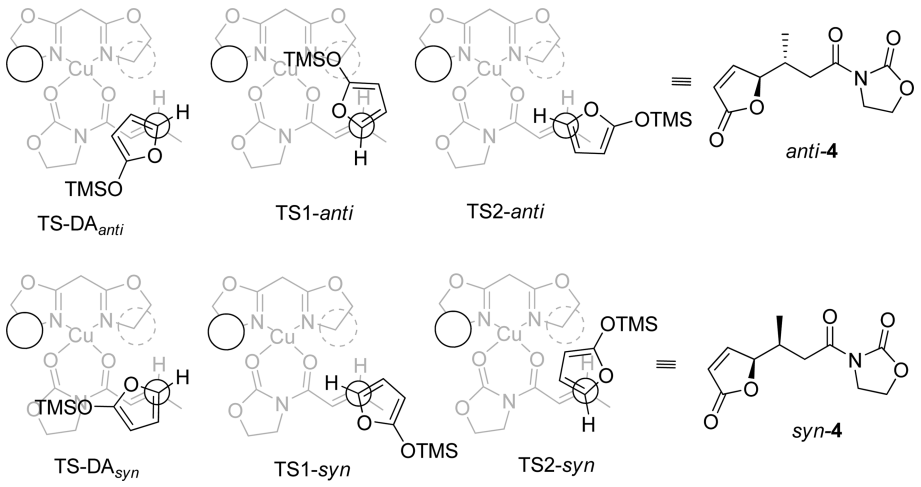

Figure 3. Possible approaches of 2-(trimethylsilyloxy)furan to the *Si* face of coordinated *N*-(*E*)-but-2-enoyloxazolidinone.

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and higher enantioselectivity than that obtained would be expected. TS2 present a synclinal disposition of the two double bonds, and it has never been considered as a possibility in the reaction mechanism.[49−52] TS-DA$_{anti}$ and TS2-*syn* would present a correct disposition for a hetero-Diels−Alder mechanism.[55]

In the case of the heterogeneous catalysts, the proximity of the support surface eliminates the C_2 symmetry of the complex, and two dispositions can be considered (Figure 4). If the

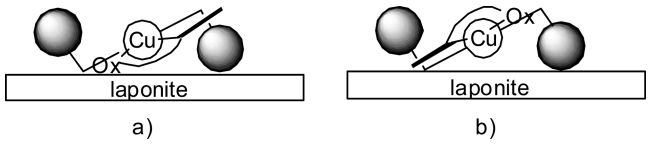

Figure 4. Possible orientations of the intermediate box-Cu-acceptor, with respect to the laponite surface: a) oxazolidinone (Ox) toward the surface; b) the double bond (thick line) toward the surface.

oxazolidinone ring were placed close to the surface (Figure 4a), the steric hindrance of the surface would work in the same direction as the substituent of the ligand, and enantioselectivity should increase in all the cases. As the effect of immobilization is the opposite, the disposition with the double bond close to the surface (Figure 4b) seems to be more probable, and, in that case, each face of the double bond would be shielded by one element, either the surface or the oxazoline substituent, with a decrease in enantioselectivity. Moreover, the angle of the chelate plane, with respect to the surface, would also force the furan to react close to the surface, leading to a change in the diastereoselectivity. Of course, this model is an oversimplification, since it considers the intermediate complex as a rigid model. In fact, the proximity of the surface might also change the geometry of the complex, for example in a distortion of the chelate or even favoring the *s-trans* conformation of the Michael acceptor. In such case, the conformational equilibrium would control the stereoselectivity of the process. This might be very interesting in the case of substrates with poor control of the conformational equilibrium in solution, for example those unable to form chelate complexes, such as *α,β*-unsaturated ketones, where the support might help to this control, leading to an enhanced enantioselectivity.

Reaction with *α,β*-Unsaturated Ketones. Excellent results have been obtained in this type of reaction using organocatalysts, mainly with unsaturated aldehydes[59] or also in the direct Michael reaction with *γ*-butenolide.[60] However, the results with metal catalysts are scarce,[52] probably by the poor control of the *s-cis*/*s-trans* equilibrium and the possible formation of intermediate complexes with different stoichiometry.

The results of the study with *α,β*-unsaturated ketones (Scheme 3) are gathered in Table 3. The first substrate chosen was chalcone (R^1 = R^3 = Ph, R^2 = H (**5a**)). The diastereoselectivity obtained in the homogeneous phase is slightly better (*syn*/*anti* up to 14/86) than that observed with $Cu(OTf)_2$ in the absence of ligand (*syn*/*anti* = 29:71).[40] As expected, the homogeneous reactions do not produce any asymmetric induction (ee <5%). In contrast, the immobilized catalysts lead to modest but significant enantioselectivities, although, unfortunately, in the minor *syn* diastereomer. Isopropyl-substituted ligands **1c** and **2c** show the best performance, 64% and 71% ee for the *syn* isomer, respectively, combined with a lower *anti* preference. This encouraging result prompted us to test the effect of the substituent size in both positions of the unsaturated ketone.

The substituent in *α*-position of the ketone (R^3) should be placed close to the metal center, with a deep effect on the coordination mode. In fact, when 4-phenylbut-3-en-2-one (R^1 = Ph, R^2 = H, R^3 = Me (**5b**)) is used, the diastereoselectivity is significantly modified in the heterogeneous phase, despite the similar results obtained in solution. Even a slight *syn* preference is observed, mainly with **1c** ligand (*syn*/*anti* 64/36), a preference only observed in nonenantioselective reactions using iodine as a catalyst.[61] With regard to enantioselectivity, the presence of the methyl instead of phenyl in *α* position of the carbonyl group produces a lower effect in the *syn* isomers (up to 47% ee with **2b**) but a higher effect in the *anti* (up to 37% ee with **2c**). Azabis(oxazolines) perform significantly better than the analogous bis(oxazolines), and again the isopropyl-substituted ligand **2c** leads to the best overall results: ∼40% ee in both isomers.

In contrast, when 1-phenylbut-2-en-1-one is used as a substrate (R^1 = Me, R^2 = H, R^3 = Ph (**5c**)), the diastereoselectivity is not modified with respect to chalcone, and the effect of immobilization on enantioselectivity is only marginal (up to 10% ee). These results demonstrate that the substituent in *β* position plays a key role in the interaction with the surface, and the larger phenyl group shows a more important effect than the methyl group to promote enantioselectivity under heterogeneous conditions.

Given the improvement of enantioselectivity by the presence of aromatic rings in both ends of the conjugated system, a 2-naphthyl group was introduced in *α* position to the carbonyl (**5d**), in an attempt to enhance the effect. However, this substitution does not have any positive effect. Diastereoselectivity is only moderate, without reversal of the major diastereomer, and enantioselectivity is only obtained in the minor *syn* isomer but up to values (52% ee) lower than in the case of chalcone.

Although the methyl groups were detrimental for the surface effect when compared with aromatics, mesityl oxide (**5e**) was used as an example of double substitution in the terminal position of the conjugated system, which, in principle, should force its *s-cis* conformation. Immobilization again produces a modest enhancement of the enantioselectivity, up to 43% ee with ligand **2c**, which is the ligand that has consistently shown the best results in all cases. This result is much better than that obtained with 1-phenylbut-2-en-1-one (R^1 = Me, R^2 = H, R^3 = Ph (**5c**)), and analogous to the result with 4-phenylbut-3-en-2-one (R^1 = Ph, R^2 = H, R^3 = Me (**5b**)). This seems to indicate that the enantioselectivity obtained is representative of the *s-cis*

Scheme 3. Reaction between *α,β*-Unsaturated Ketones and 2-(Trimethylsilyloxy)furan

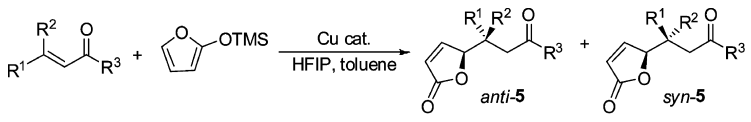

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Table 3. Results of the Reaction between α,β-Unsaturated Ketones and 2-(Trimethylsilyloxy)furan[a]

	Homogeneous				Immobilized			
ligand	yield (%)	syn/anti	%ee syn[b]	%ee anti[b]	yield (%)	syn/anti	%ee syn[b]	%ee anti[b]
Substrate **5a**								
1a	100	15/85	1	−3	100	22/78	16	−10[c]
1b	100	19/81	4	−2	82	21/79	15	−2[c]
1c	100	19/81	4	−2	100	38/62	64	−5[c]
1d	100	16/84	−1	1	78	28/72	9	−4[c]
2b	100	14/86	0	2	80	27/73	20	−7[c]
2c	100	23/77	2	2	83	35/65	71	−1[c]
Substrate **5b**								
1a	100	21/79	1	0	98	48/52	5	−1
1b	100	25/75	0	0	79	51/49	15	21
1c	100	23/77	0	0	99	64/36	11	24
1d	100	25/75	2	−1	88	48/52	4	−6
2b	100	23/77	0	0	71	52/48	47	0
2c	100	20/80	1	0	78	56/44	43	37
Substrate **5c**								
1a	100	24/76	0	0	89	26/74	−10	9
1c					82	28/72	1	−3
1d					77	27/73	−9	4
2c					84	28/72	1	2
Substrate **5d**								
1a	100	26/74	0	0	68	32/68	−19	0
1c					70	27/73	−8	2
1d					55	36/64	−15	8
2c					73	44/56	−52	1
Substrate **5e**								
1a	100		0		100		−1	
1b	100		0		83		−11	
1c	100		0		100		−18	
1d	100		0		77		−17	
2b	100		0		85		−12	
2c	100		0		79		−43	

[a]Reaction conditions: 1 mmol of α,β-unsaturated ketone, 1.5 mmol of HFIP (159 μL), catalyst (0.10 mmol of homogeneous phase and 0.15 mmol of heterogeneous phase), 5 mL of anhydrous toluene, slow addition (5 h) of 2 mmol of 2-(trimethylsilyloxy)furan (347 μL) in 10 mL of anhydrous toluene at rt. Reaction time after addition: 5 h in the homogeneous phase and 24 h in the heterogeneous phase. [b]Considered positive when the major product is that of lower retention time. [c]In this case, the major *anti* isomer has *RR* configuration when the sign is negative.

conformation on the surface, which is favored by the single substitution in β position with a phenyl group and its steric interaction with the surface. The second phenyl group in the α position of chalcone increases this enantioselectivity even more, probably by a double steric interaction, although with an unknown geometry.

Recycling Experiments. Although recycling was not the main objective of this work, some experiments were carried out in a similar way to those performed with the analogous nonchiral catalyst.[40] Two combinations were tested, diethyl benzylidenemalonate as substrate with Lap-Cu-**1c** catalyst, and *N*-(*E*)-but-2-enoyloxazolidinone with Lap-Cu-**1d**. As can be seen in Table 4, the catalysts were recoverable once, irrespective of the chiral ligand and the substrate, whereas its activity decreases significantly in the third run while maintaining the same selectivities. These results demonstrate that deactivation is due to poisoning of the Lewis acid sites by coordination, as it happened in the case of the analogous nonchiral catalyst.[40] In that case, the catalyst was reactivated by Soxhlet extraction with THF, which enabled elimination of the coordinated products. However, when the chiral catalyst was treated in the same way, the activity was fully recovered but enantioselectivity was lost, indicating the decomplexation of the chiral ligand in the process. Attempts of recomplexation with new chiral ligand after Soxhlet extraction were unsuccessful, probably by the difficulty in replacing the solvent molecules, presumably THF, from the coordination sphere of the metal

Table 4. Recycling Experiments in the Reactions of 2-(Trimethylsilyloxy)furan and Diethyl Benzylidenemalonate or *N*-(*E*)-but-2-enoyloxazolidinone

run	yield (%)	*syn*/*anti*	%ee *syn*	%ee *anti*
Diethyl Benzylidenemalonate Substrate,[a] Ligand **1c**				
1	100	78/22	15	21
2	100	76/24	24	25
3	31	77/23	22	22
3[b]	100	77/23	0	0
N-(*E*)-but-2-enoyloxazolidinone Substrate,[c] Ligand **1d**				
1	76	67/33	52	46
2	73	66/34	50	49
3	12	67/33	50	49

[a]Reaction conditions as described in Table 1. [b]The catalyst used was extracted with THF in a Soxhlet apparatus. [c]Reaction conditions as described in Table 2.

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with a stoichiometric amount of ligand. Alternative methods are currently under study.

CONCLUSIONS

The presence of the support greatly conditions the stereochemical course of vinylogous Mukaiyama−Michael reactions of 2-(trimethylsilyloxy)furan and different Michael acceptors catalyzed by bis(oxazoline) and azabis(oxazoline) copper complexes immobilized onto laponite clay. The modification of the stereoselectivities depends on the structure of the Michael acceptor, probably by the differences in the disposition of the intermediate complex with respect to the surface, although this point is difficult to assess. With ethyl benzylidenemalonate, an intermediate with forced *s-trans* conformation is formed, which leads to a reversal in enantioselectivity from solution to the heterogeneous phase, with values of −80% and 38% ee in the most relevant case. In the case of *N*-(*E*)-but-2-enoyloxazolidinone, the total reversal of diastereoselectivity leads to the unprecedented *syn* selectivity, up to a diastereomeric ratio of 81/19. The possible effect of the surface on the *s-cis*/*s-trans* conformational equilibrium seems to be confirmed by the enantioselectivity obtained in the reaction with *α*,*β*-unsaturated ketones. Although the homogeneous catalysts are unable to induce enantioselectivity, the supported ones lead to variable enantiomeric excess, depending on the substitution in the unsaturated ketone and the chiral ligand. These results demonstrate that it is possible to use the immobilization of chiral catalysts not only to facilitate their recovery and recycling, but also to modify the reaction stereoselectivities with respect to those obtained in solution, even to obtain new (stereomeric) products, which can be an added value to the immobilization.

EXPERIMENTAL SECTION

General. Chiral box (**1a**−**1d**) and azabox ligands (**2b** and **2c**) were prepared by methods described in the literature.[34,35,62] Laponite clay was obtained as a generous gift from Rockwood Additives. All the Michael acceptors were purchased from Aldrich and used without further purification, except *N*-(*E*)-but-2-enoyloxazolidinone, which was prepared according to the literature.[63]

General Procedure of the Heterogeneous Vinylogous Mukaiyama−Michael Reaction. The dried immobilized catalyst (0.15 mmol Cu) was added to a mixture of the corresponding Michael acceptor (1 mmol) and 1,1,1,3,3,3-hexafluoroisopropanol (160 μL, 1.5 mmol) in 5 mL of anhydrous toluene under argon atmosphere. Then, a solution of 2-(trimethylsilyloxy)furan (347 μL, 2 mmol) in 10 mL of solvent was slowly added with a syringe pump to the suspension for 5 h. The mixture was stirred at room temperature for 24 h. At the end of the reaction, the catalyst was removed by filtration and washed with anhydrous dichloromethane (10 mL). The reaction crude was purified by column chromatography on silica. Yield and diastereoselectivity were determined by GC in the case of **3**, and by ^{1}H NMR using mesitylene as a standard. In the case of **4** and **5a**−**5e**, the enantioselectivity was determined by high-pressure liquid chromatography (HPLC), using chiral columns.

The products *anti*-**4**, *anti*-**5a**, *anti*-**5b**, *syn*-**5b**, and **5e** were identified according to data in the literature[45,52,64] (see the Supporting Information).

Diethyl (S,R*)-2-[(5-Oxo-2,5-dihydrofuran-2-yl)(phenyl)-methyl]-malonate (syn-**3**).* The reaction crude was purified by column chromatography on silica, using hexane/^{i}PrOH 7:3 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak IB column, 210 nm, *n*-hexane/^{i}PrOH 9:1, 1 mL/min, t_R *syn*$_1$ = 13.0 min and t_R *syn*$_2$ = 14.9 min, mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.09 (m, 6H), 5.78 (dd, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 5.54−5.53 (m, 1H), 4.27 (q, J = 7.1 Hz, 2H), 4.22 (d, J = 11.8 Hz, 1H), 3.89−3.83 (m, 3H), 1.30 (t, J = 7.1 Hz, 3H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.5, 168.0, 167.1, 154.8, 133.6, 128.9, 128.4, 128.1, 122.1, 82.2, 62.1, 61.5, 53.6, 47.3, 14.0, 13.5. HR-MS (ESI+): m/z (%): 333.1335 [M^+−H]. Calcd. for $C_{18}H_{21}O_6$: 333.1333.

Diethyl (R,R*)-2-[(5-Oxo-2,5-dihydrofuran-2-yl)(phenyl)-methyl]-malonate (anti-**3**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/^{i}PrOH 7:3 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak IB column, 210 nm, *n*-hexane/^{i}PrOH 9:1, 1 mL/min, t_R *anti*$_1$ = 18.9 min and t_R *anti*$_2$ = 19.6 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.30−7.09 (m, 6H), 6.05 (dd, J_1 = 5.8 Hz, J_2 = 2.0 Hz, 1H), 5.39 (dt, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 4.23−4.18 (m, 3H), 3.94−3.82 (m, 2H), 3.70 (dd, J_1 = 9.6 Hz, J_2 = 8.0 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 171.9, 167.8, 166.9, 154.7, 136.0, 128.9, 128.8, 128.3, 121.9, 84.2, 62.0, 61.5, 54.4, 48.8, 13.8, 13.6.

(R,S*)-3-(2,5-Dihydro-5-oxo-2-furyl)butanoyl-1,3-oxazolidin-2-one (syn-**4**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 8:2 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak AD-H column, 245 nm, *n*-hexane/^{i}PrOH 66:34, 0.5 mL/min, t_R *syn*$_1$ (*R*,*S*) = 28.1 min and t_R *syn*$_2$ (*S*,*R*) = 43.5 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.45 (dd, J_1 = 5.8 Hz, J_2 = 1.5 Hz, 1H), 6.17 (dd, J_1 = 5.8 Hz, J_2 = 2.1 Hz, 1H), 5.20−5.18 (m, 1H), 4.44 (t, J = 8.1 Hz, 2H), 4.03 (t, J = 8.1 Hz, 2H), 2.90 (dd, J_1 = 17.5 Hz, J_2 = 6.4 Hz, 1H), 2.68−2.58 (m, 1H), 0.94 (d, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.9, 171.6, 155.7, 153.4, 122.6, 85.3, 62.1, 42.5, 38.0, 32.0, 13.9. HR-MS (ESI+): m/z (%): 240.0869 [M^+−H]. Calcd. for $C_{10}H_{14}NO_5$: 240.0872.

(R,S*)-5-(3-Oxo-1,3-diphenylpropyl)furan-2(5H)-one (syn-**5a**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 95:5 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak AD-H column, 245 nm, *n*-hexane/^{i}PrOH 66:34, 0.5 mL/min, t_R *syn*$_1$ = 14.5 min and t_R *syn*$_2$ = 16.9 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.90 (m, 2H), 7.52−7.11 (m, 9H), 5.77 (dd, J_1 = 5.7 Hz, J_2 = 2.1 Hz, 1H), 5.37 (m, 1H), 3.88 (m, 1H), 3.73 (dd, J_1 = 18.0 Hz, J_2 = 8.3 Hz, 1H), 3.37 (dd, J_1 = 13.1 Hz, J_2 = 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.8, 172.8, 155.2, 139.7, 137.2, 133.5, 128.9, 128.7, 128.3, 128.0, 127.6, 122.0, 84.3, 42.9, 40.1. HR-MS (ESI+, of the *anti*/*syn* mixture): m/z (%): 293.1176 [M^+−H]. Calcd. for $C_{19}H_{17}O_3$: 293.1172.

(S,S*)-5-(4-Oxo-4-phenylbut-2-yl)furan-2(5H)-one (anti-**5c**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 95:5 as an eluent. The enantiomeric

excess was determined by HPLC: Chiralpak AD-H column, 210 nm, *n*-hexane/^{i}PrOH 95:5, 1 mL/min, t_R *anti*$_1$ = 46.6 min and t_R *anti*$_2$ = 50.3 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.89 (d, J = 8.3 Hz, 1H), 7.57−7.52 (m, 2H), 7.50−7.42 (m, 3H), 6.17 (dd, J_1 = 5.7 Hz, J_2 = 1.9 Hz, 1H), 5.05 (dt, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1H), 3.04 (dd, J_1 = 17.5 Hz, J_2 = 5.3 Hz, 1H), 2.85 (dd, J_1 = 17.5 Hz, J_2 = 7.3 Hz, 1H), 2.72−2.62 (m, 1H), 1.15 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.1, 172.6, 155.3, 136.5, 133.2, 133.1, 128.5, 127.8, 127.1, 121.3, 86.7, 39.5, 32.4, 16.7. HR-MS (ESI+, of the *anti*/*syn* mixture): *m*/*z* (%): 231.1016 [M^+−H]. Calcd. for $C_{14}H_{15}O_3$: 231.1013.

(R,S*)-5-(4-Oxo-4-phenylbut-2-yl)furan-2(5H)-one (syn-**5c**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 95:5 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak AD-H column, 210 nm, *n*-hexane/^{i}PrOH 95:5, 1 mL/min, t_R *syn*$_1$ = 56.9 min and t_R *syn*$_2$ = 61.9 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.94 (d, J = 8.1 Hz, 1H), 7.57−7.53 (m, 2H), 7.50−7.42 (m, 3H), 6.08 (m, 1H), 5.20 (m, 1H), 3.10 (dd, J_1 = 17.6 Hz, J_2 = 6.9 Hz, 1H), 2.94 (dd, J_1 = 17.6 Hz, J_2 = 6.5 Hz, 1H), 2.79−2.73 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 198.3, 172.9, 155.2, 136.5, 133.2, 133.1, 128.5, 127.8, 127.1, 121.3, 86.7, 39.5, 32.4, 16.7.

(S,S*)-5-(3-(2-Naphthyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (anti-**5d**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 95:5 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak IB column, 210 nm, *n*-hexane/^{i}PrOH 85:5, 0.8 mL/min, t_R *anti*$_1$ = 36.8 min and t_R *anti*$_2$ = 37.8 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.41 (m, 1H), 8.03−7.84 (m, 4H), 7.60−7.53 (m, 2H), 7.39−7.22 (m, 6H), 6.09 (dd, J_1 = 5.7 Hz, J_2 = 1.9 Hz, 1H), 5.31 (dt, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1H), 3.78−3.73 (m, 1H), 3.63−3.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.7, 172.7, 155.6, 139.6, 135.7, 133.9, 132.4, 129.7, 129.5, 128.9, 128.6, 128.5, 128.3, 128.1, 127.7, 126.6, 122.0, 85.8, 44.5, 40.1. HR-MS (ESI+, of the *anti*/*syn* mixture): *m*/*z* (%): 343.1261 [M^+−H]. Calcd. for $C_{23}H_{19}O_3$: 343.1257.

(R,S*)-5-(3-(2-Naphthyl)-3-oxo-1-phenylpropyl)furan-2(5H)-one (anti-**5d**) (from the Spectrum of an anti/syn Mixture).* The reaction crude was purified by column chromatography on silica, using hexane/ethyl acetate 95:5 as an eluent. The enantiomeric excess was determined by HPLC: Chiralpak IB column, 210 nm, *n*-hexane/^{i}PrOH 85:5, 0.8 mL/min, t_R *syn*$_1$ = 32.7 min and t_R *syn*$_2$ = 40.6 min. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 8.52 (m, 1H), 8.03−7.84 (m, 4H), 7.62−7.53 (m, 2H), 7.39−7.22 (m, 6H), 5.87 (dd, J_1 = 5.8 Hz, J_2 = 2.1 Hz, 1H), 5.50 (m, 1H), 4.04−3.99 (m, 1H), 3.69−3.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 197.2, 172.9, 155.3, 137.2, 135.7, 129.9, 129.6, 128.6, 128.4, 128.3, 127.7, 126.8, 122.1, 84.4, 43.1, 40.2.

■ ASSOCIATED CONTENT

Supporting Information

Catalysts preparation and characterization, general homogeneous procedure, and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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