

# A non-fluorous copper catalyst for the styrene cyclopropanation reaction in a fluorous medium

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The complex  $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$  (**1**), containing no fluorine atoms, can be dissolved in the perfluoropolyether FOMBLIN<sup>®</sup> and employed as a catalyst for the styrene cyclopropanation reaction with ethyl diazoacetate, with activities and diastereoselectivities identical to those observed under homogeneous conditions with the advantage of being able to use a fluorous separation technique for catalyst recycling.

With barely ten years since the appearance of the seminal work by Horváth and Rábai,<sup>1</sup> fluorous biphasic catalysis (FBC) has nowadays become one of the most interesting areas in the field of catalysis.<sup>2</sup> The increasing number of contributions related to this field has compelled the need for a strict definition of what should be named with the “fluorous” appellative,<sup>3</sup> whether applied to a reaction medium, catalyst, or separation technique, amongst others. A common feature of systems tagged as FBC is the existence of a fluorous medium, in which a catalyst, containing a certain number of carbon–fluorine bonds, is either soluble or partially soluble. A second, immiscible phase is employed as a carrier for the reagents and products. In many cases, the phases become mixed upon heating, a fact that favours catalytic reactions. Upon cooling back to room temperature (or below), separation of the phases takes place, and recycling of the catalyst and removal of the products can then be performed. A usual rule of thumb for a catalyst employed in FBC is that it should contain at least a 60 wt% of fluorine, although some exceptions have been found.<sup>4</sup>

In the recent years we have reported the catalytic properties of a family of complexes of general formula  $\text{Tp}^{\text{x}}\text{Cu}(\text{L})$  ( $\text{Tp}^{\text{x}}$  = homoscorpionate ligand)<sup>5</sup> towards the decomposition of ethyl diazoacetate and subsequent transfer of the carbene unit : $\text{CHCO}_2\text{Et}$  to several saturated and unsaturated substrates under homogeneous conditions.<sup>6–8</sup> After these results, we decided to investigate the potential of these catalysts, under heterogeneous conditions, to be subject to the well-known and advantageous processes of catalyst recovery, recycling and product separation. Amongst these  $\text{Tp}^{\text{x}}\text{Cu}(\text{L})$  complexes, that containing the hydrotris(3,4,5-tribromopyrazolyl)borate ligand  $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$  (**1**) showed very interesting catalytic properties.<sup>7,8</sup> Complex **1** includes

nine bromine atoms in the  $\text{Tp}^{\text{x}}$  ligand skeleton (Fig. 1), accounting for ca. 70% of the overall molecular weight of this compound. With this very high percentage of halide, we wondered if it were possible to dissolve it in halide-containing media, with the aim of using it for catalytic purposes. We focused particularly on perfluoropolyethers, which should provide some degree of polarity to help dissolve the copper complex. From this search, we found that **1** could be dissolved in FOMBLIN<sup>®</sup>, a perfluoropolyether of general composition  $\text{CF}_3\text{O}[-\text{CF}(\text{CF}_3)\text{CF}_2\text{O}-]_x(-\text{CF}_2\text{O}-)_y\text{CF}_3$  and commercially available due to its use as a vacuum oil. When dichloromethane or cyclohexane solutions of **1** were stirred for several hours with FOMBLIN<sup>®</sup>, some of the copper complex was absorbed by the fluorous phase, as determined by AAS studies of the supernatant organic phases at the end of the process. The initial experiments were carried out using two different types of FOMBLIN<sup>®</sup>, with different compositions as well as viscosities.† The mixtures were stirred for 20 h, after which the organic (dichloromethane or cyclohexane) phases were studied by AAS to determine the amounts of Cu still dissolved; the remaining amount of the initial 0.25 mmol of **1** now being retained in the fluorous phase. As shown in Table 1 entries 1–4, the more viscous 1400 cSt (1St = 0.0001 m<sup>2</sup> s<sup>-1</sup>; 1cSt = 0.01 St) samples absorbed a higher quantity of **1** and the cyclohexane solutions also induced higher phase absorptions.

The aim of this first series of experiments was to evaluate whether or not complex **1** could be dissolved in this fluorous phase. However, the concentrations of **1** in FOMBLIN<sup>®</sup> shown in Table 1 do not necessarily correspond to the distribution equilibrium. Because of this, we have also studied the effect of time on the absorption process, choosing 60 cSt FOMBLIN<sup>®</sup> as the fluoro phase. A series of identical experiments were performed using cyclohexane as the carrier for **1** and the FOMBLIN<sup>®</sup> (60 cSt) sample over 8, 30 and 45 h. Fig. 2 displays a plot of [I] vs. employed absorption time. The existence of a saturation limit for the amount of the complex  $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$  that can be dissolved in this medium is observed. Regarding the intimate nature of the

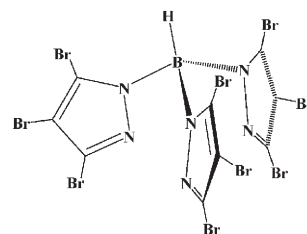


Fig. 1 The hydrotris(3,4,5-tribromopyrazolyl)borate ligand,  $\text{Tp}^{\text{Br}_3}$ .

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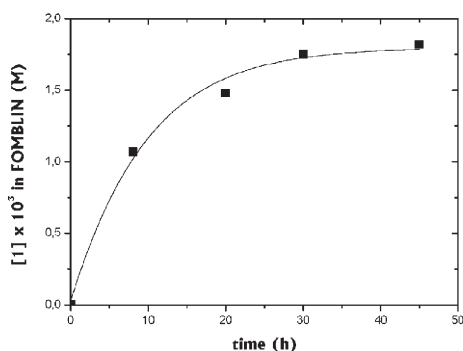
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**Table 1** Absorption of complex  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  (**1**) in FOMBLIN<sup>®</sup> at room temperature

Entry	Time/h	FOMBLIN <sup>®</sup> /cSt <sup>a</sup>	Solvent	Amount of <b>1</b> absorbed/mmol <sup>b</sup>	[ <b>1</b> ] in FOMBLIN <sup>®</sup> /M
1	20	60	$\text{CH}_2\text{Cl}_2$	$4.2 \times 10^{-3}$	$1.05 \times 10^{-3}$
2	20	1400	$\text{CH}_2\text{Cl}_2$	$5.7 \times 10^{-3}$	$2.85 \times 10^{-3}$
3	20	60	$\text{C}_6\text{H}_{12}$	$5.9 \times 10^{-3}$	$1.48 \times 10^{-3}$
4	20	1400	$\text{C}_6\text{H}_{12}$	$8.0 \times 10^{-3}$	$4.0 \times 10^{-3}$
5	8	60	$\text{C}_6\text{H}_{12}$	$4.3 \times 10^{-3}$	$1.07 \times 10^{-3}$
6	30	60	$\text{C}_6\text{H}_{12}$	$7.0 \times 10^{-3}$	$1.75 \times 10^{-3}$
7	45	60	$\text{C}_6\text{H}_{12}$	$7.3 \times 10^{-3}$	$1.82 \times 10^{-3}$

<sup>a</sup> The volume of FOMBLIN<sup>®</sup> employed was 4 mL for the 60 cSt samples and 2 mL for the 1400 cSt samples. <sup>b</sup> Determined by AAS.



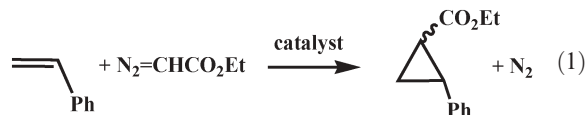
**Fig. 2** Variation of [**I**] in FOMBLIN<sup>®</sup> (60 cSt) with the time employed in the absorption process at room temperature.

interaction between complex **1** and FOMBLIN<sup>®</sup> (60 cSt), we can only assume at this stage of our investigations that it has to be related to the existence of the bromine atoms in the molecules; attempts to dissolve measurable amounts of other  $\text{Tp}^x\text{CuL}$  complexes being ineffective.

The extraction of complex **1** from this fluoruous medium was performed with various solvents. A series of samples of FOMBLIN<sup>®</sup> (4 mL), containing an exactly-determined amount of dissolved **1**, were treated with six different solvents: dichloromethane, THF, acetone, ethanol, cyclohexane and hexane. After 5 min of stirring, the organic solution was separated and the copper content determined by AAS. The results are shown in Fig. 3. With dichloromethane, THF or acetone, nearly 30% of the copper was removed from the fluoruous phase. Ethanol only retrieved 10%, whereas cyclohexane and hexane showed 1.5–2% of copper removal. Therefore, we have chosen hexane as the solvent for the separation of the products after the catalytic reaction, since there was no significant loss of catalyst due to it.

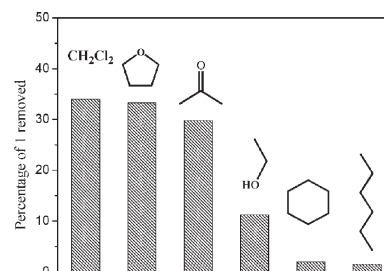
Once the fixation of complex **1** in a fluoruous phase was achieved, we moved on to study its catalytic use in a well-known probe reaction: styrene cyclopropanation with ethyl diazoacetate (EDA),<sup>9</sup> where two diastereomers, *cis* and *trans*, are formed (eqn. (1)). A *ca.*  $2.4 \times 10^{-3}$  M solution of **1** in FOMBLIN<sup>®</sup> 60 cSt (0.0095 mmol in 4 mL) was charged with 0.5 mmol of EDA and 2 mmol of styrene, and stirred for 1.5 h. After this time, 2 mL of hexane was added, the mixture stirred for 5 min and the organic phase separated. GC studies revealed the total consumption of diazo compound. 90% cyclopropanes were found, with a *cis* : *trans* ratio of 60 : 40 (Table 2, entry 1), the remaining 10%

corresponding to a mixture of diethyl fumarate and maleate. This diastereoselectivity was nearly identical, within experimental error, to that obtained when the experiment was carried out under homogeneous conditions in dichloromethane (*cis* : *trans*, 58 : 42). The amount of copper that leached into the hexane solution was determined to be 1.5% of the initial amount absorbed, therefore 98.5% of **1** remained in the fluoruous phase. In good accordance with this observation, a second cycle was run under identical conditions (Table 2, entry 2), with yields and diastereoselectivities very similar to those in the first test. The catalyst was recovered and recycled three more times (Table 2, entries 3–5) with the same behaviour; copper leaching being maintained within the 1–1.5% range.



The observation of catalyst leaching must unequivocally be related to some loss of activity, though not appreciably within the reaction time (1.5 h) shown in Table 2. To observe this, we monitored the evolution of nitrogen as a probe for the reaction rate.† Fig. 4 displays the variation of nitrogen evolution, at room temperature, during the recycling process, where a certain decrease is clearly observable in the reaction rate from one cycle to the next. This is in good accordance with the already mentioned detection of copper leaching. A very low concentration of **1** (*ca.*  $10^{-4}$  M) was employed to amplify the differences between the kinetic curves.

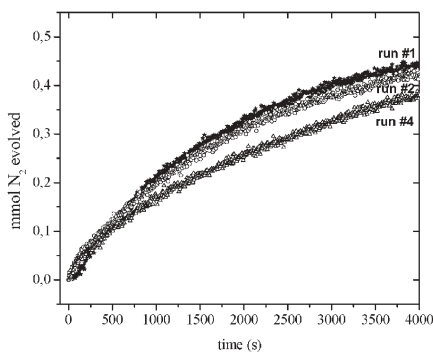
The results displayed in Table 2 demonstrate the catalytic capabilities of complex **1** in FOMBLIN<sup>®</sup> for the carbene transfer reaction, with the same catalytic activity and diastereoselectivity being repeated throughout the five cycles studied, and with minor leaching being observed after each run. This behaviour is identical to that observed under homogeneous conditions, *i.e.*, the change in



**Fig. 3** Effect of solvent on the washing, at room temperature, of the FOMBLIN<sup>®</sup> solutions of **1**. Initial [**1**]<sub>FOMBLIN<sup>®</sup></sub> =  $1.48 \times 10^{-3}$  M. Leaching determined by AAS.

**Table 2** Styrene cyclopropanation of EDA using  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  (**1**) as the catalyst in FOMBLIN<sup>®</sup> at room temperature

Entry	Cycle	Time/h	Yield (%)	<i>cis</i> : <i>trans</i>	Amount of Cu leached/mmol (%)
1	1	1.5	90	60 : 40	—
2	2	1.5	90	59 : 41	$1.40 \times 10^{-4}$ (1.5)
3	3	1.5	85	60 : 40	$1.07 \times 10^{-4}$ (1.15)
4	4	1.5	93	58 : 42	$1.24 \times 10^{-4}$ (1.35)
5	5	1.5	91	57 : 43	$1.23 \times 10^{-4}$ (1.35)



**Fig. 4** Nitrogen evolution in the reaction of EDA and styrene, catalyzed by **1** in FOMBLIN<sup>®</sup> at room temperature. Run #3 has been omitted for clarity.

reaction medium has not affected its catalytic properties. Overall, the use of this copper–FOMBLIN<sup>®</sup> system achieves the ultimate goal for when moving from a homogeneous catalyst towards heterogeneous conditions: to easily separate the catalyst and products while operating with the same activities and selectivities as those of purely homogeneous conditions. There are only a few examples of fluororous catalysis for the carbene transfer reaction from diazo compounds to organic substrates, these being based exclusively on rhodium<sup>10</sup> or copper.<sup>11</sup> In all cases, a fluororous ponytail-containing catalyst and a fluororous reaction medium were employed, with differing results to those presented herein, and using a fluororous medium with a non-fluororous catalyst. Another singularity in our case is that the already-reported copper-based systems for styrene cyclopropanation, under fluororous conditions, displayed a substantial decrease in yields when the catalyst was reused in successive cycles. This is not the case for this system, where yields and selectivities are maintained within a narrow interval. However, we wish to point out that it is possible that the catalytic reaction might occur in a homogeneous phase formed by styrene and EDA, and that the addition of hexane could force the catalyst to return to the fluororous phase. In any case, this would not affect the catalytic capabilities of this system in terms of recovery and reuse.

In conclusion, we have discovered that complex  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  (**1**) can be absorbed in perfluoropolyether  $\text{CF}_3\text{O}[-\text{CF}(\text{CF}_3)\text{CF}_2\text{O}]_x[-\text{CF}_2\text{O}]_y\text{CF}_3$ , FOMBLIN<sup>®</sup> (60 cSt), in spite of the lack of any fluorine atoms in the structure of the copper complex. The absorbed amounts of **1** can be employed to catalyze the styrene cyclopropanation reaction with ethyl diazoacetate, in a process that provides the expected cyclopropanes with constant yields and diastereoselectivities along five cycles of recovery and reuse of the catalyst-containing fluororous phase. We believe that this finding could open up a new area in designing non-fluorine-containing catalysts for use in certain fluororous reaction media.

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## Notes and references

† Experimental procedures, all performed at room temperature. (a) Fixation of **1** in FOMBLIN<sup>®</sup>, general procedure: A solution of 0.25 mmol of **1** in 4 mL of the solvent (dichloromethane or cyclohexane) was transferred into a Schlenk tube containing 4 mL of FOMBLIN<sup>®</sup> 60 cSt or 2 mL of FOMBLIN<sup>®</sup> 1400 cSt, purchased from Aldrich and employed without further purification. After the desired stirring time (from 8 to 45 h), the mixture was decanted and the upper, organic phase separated. The volatiles were removed under vacuum and the residue investigated by AAS, following standard protocols to determine the amount of copper not absorbed into the FOMBLIN<sup>®</sup>. (b) Washing with different solvents: A solution of **1** in FOMBLIN<sup>®</sup> (60 cSt), prepared as above and with a known content of **1**, was treated with 4 mL of a given solvent (dichloromethane, THF, acetone, ethanol or hexane). After 5 min of stirring, the upper phase was separated and investigated, as above, to measure the leaching of copper. (c) Styrene cyclopropanation: A solution of **1** in FOMBLIN<sup>®</sup> ( $2.4 \times 10^{-3}$  M, 4 mL of FOMBLIN<sup>®</sup>) was charged with 0.5 mmol (57 mg) of ethyl diazoacetate and 2 mmol (208 mg) of styrene. The mixture was stirred for 1.5 h, and then 4 mL of hexane added. After 5 min of stirring, the organic phase was separated and investigated by GC, as previously reported.<sup>6</sup> In addition, the amount of copper leached was also determined by AAS.

‡ The rate determining step in the metal-catalyzed diazo compound decomposition corresponds to the formation of a transient metallacarbene intermediate from the interaction of the catalyst and the diazo compound, and the concomitant formation of a molecule of  $\text{N}_2$ . See ref. 9.

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