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Carbenoid transfer in competing reactions catalyzed by ruthenium complexes

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Aiming at improving catalyst activity, ten ruthenium promoters have been investigated in carbenoid transfer from ethyl diazoacetate to styrene as a model substrate. Optimal selectivity in cyclopropanation has been attained with the new NHC–Ru complex 10, as well as with the Fischer carbene 7. The surprising non-metathetical behavior of the Grubbs' first-generation catalyst in this multifaceted process is highlighted. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: ruthenium; carbene; cyclopropanation; metathesis; dimerization

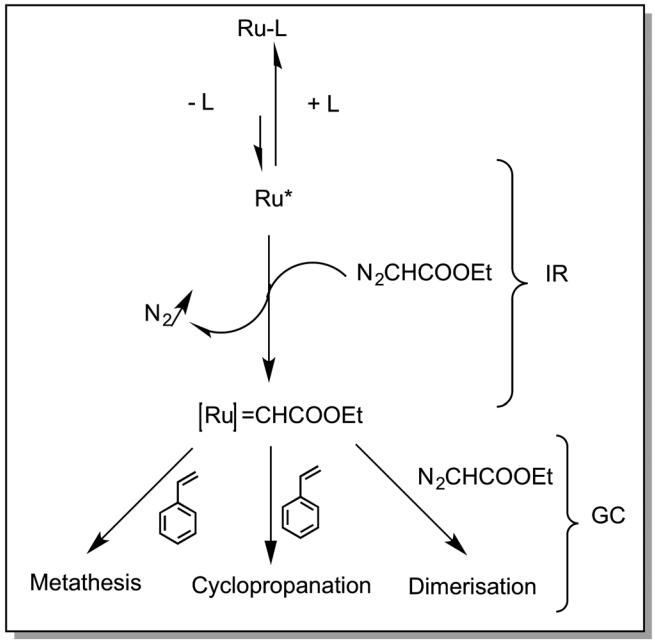
Introduction

A diversity of therapeutic agents and natural or unnatural compounds endowed with biological activity include cyclopropane as a basic structural unit.[1] The ability of cyclopropane to induce substantial conformation constraints promotes incorporation of this highly strained and reactive carbocycle in complex structures in need of a particular stereoconfiguration. In this context, a high-yielding and stereocontrolled construction of the cyclopropane motif by metal-free[2] or metal-catalyzed intermolecular cyclopropanation[3] has for years been a challenging task for organic chemists.[4] A leading pathway to access cyclopropane-containing derivatives is carbenoid cyclopropanation catalyzed by transition metal promoters, among which ruthenium complexes recently enjoy a renewed recognition.[5] It should be kept in mind, however, that in ruthenium-induced cyclopropanation several concurrent C–C coupling transformations, such as metathesis and homocoupling, frequently intervene. Advocating present trends for environmentally benign and cost-effective processes, use of more selective catalysts for cyclopropanation may have far-reaching consequences, in particular for the drug industry.

Results and Discussion

Here we report for the first time on the performance of a creative selection of structurally diverse ruthenium catalysts screened for concurrent cyclopropanation and metathesis, under identical reaction conditions. The high-yield valorization of the commercial first-generation Grubbs catalyst in the stand-alone cyclopropanation of styrene with diazoacetate is also showcased.

Progress of the reaction between styrene and ethyl diazoacetate (EDA), generally accepted as the standard system for cyclopropanation, was examined using complementary techniques (Scheme 1) and as proceeding under the promotion of ten ruthenium pre-catalysts, including the new complexes **4** and **10** (Scheme 2). As a certain control on undesired processes accompanying cyclopropanation can be exerted by modulating reaction



Scheme 1. Monitoring the reaction of styrene with ethyl diazoacetate induced by ruthenium catalysts (IR spectra for decomposition of $N_2CHCOOEt$ versus time; GC and NMR for product identification).

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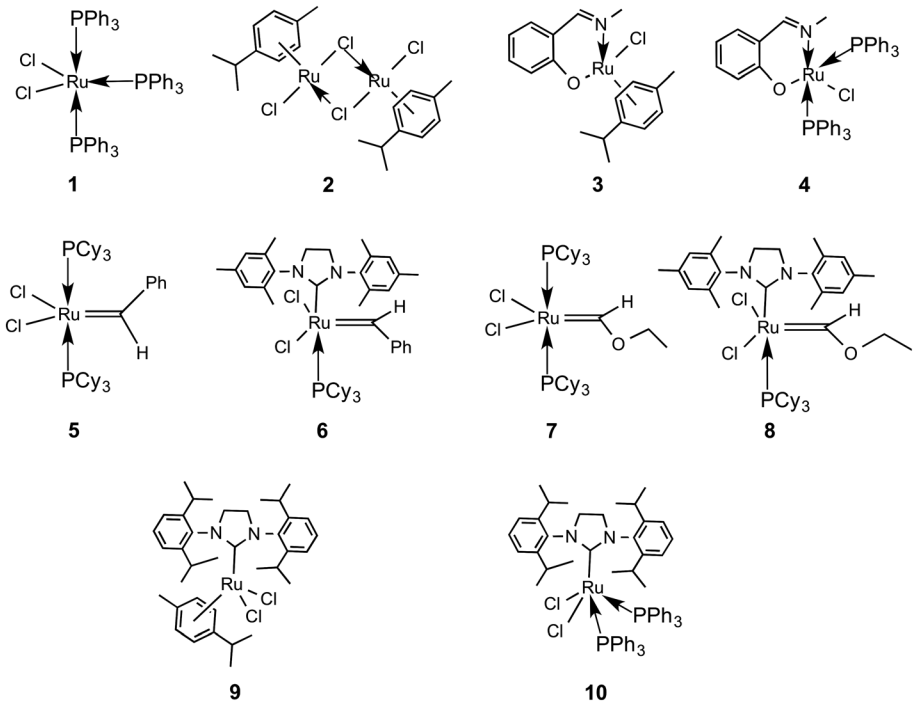


Scheme 2. Ruthenium catalysts employed in reaction of styrene with EDA.[6–9]

conditions, we decided to enhance cyclopropanation and minimize EDA homocoupling (dimerization) by slowly adding a diluted solution of the diazo compound to the mixture of excess styrene and catalyst. Working under such low catalyst loadings, metathesis is also expected to diminish, to the benefit of cyclopropanation.

It should be remarked that Ru complexes **4**, **7**, **8** and **10** have not been previously reported for cyclopropanation. Results obtained in this study are compiled in Table 1. For all of the catalysts, selectivity in cyclopropanation and metathesis is highlighted in Figs 1 and 2.

Table 1. Product distribution in the reaction of styrene with EDA (in toluene, at 60°C)[a]

		Reaction selectivity			
Entry	Catalyst	Cyclopropanation (%)	*trans*/*cis*	Metathesis (%)	Dimerization (%)
1	**1**	77	1.81	12	11
2	**2**	58	1.49	13	29
3	**3**	73	2.30	8	19
4	**4**	72	2.70	21	7
5	**5**	35	1.02	59	6
6	**6**	0	—	100	0
7	**7**	84	0.98	8	8
8	**8**	50	1.38	33	17
9	**9**	44	1.21	13	43
10	**10**	85	1.47	5	10

[a]Based on EDA; determined by GC by comparison with authentic samples (internal standard diethyl adipate). Ratio of dimerization products: diethylmaleate/diethylfumarate ~2/1. *cis*- and *trans*-ethylcinnamate were found only in trace amounts.

[b]Molar ratios: catalyst/EDA/styrene = 1/125/2500; toluene/styrene = 10.

[c]Based on EDA; EDA was totally consumed.

Among the catalysts examined in reactions performed under high dilution in toluene, at 60°C and with a molar ratio of catalyst:EDA:styrene = 1:125:2500, the best chemoselectivity for asymmetric intermolecular cyclopropanation was observed for the novel *IPr*-containing promoter **10** and the ethoxy Ru-carbene **7**, yielding 1-carbethoxy-2-phenylcyclopropane with 85% and 84% selectivity, respectively (Table 1). Moreover, cyclopropanation is still the major reaction pathway (72–77%) in the case of catalysts **1**, **3** and **4**; the latter catalyst, a new complex bearing an O, N-bidentate Schiff base and two PPh_3 ligands, showed excellent activity in cyclopropanation (91.1% yield).

Importantly, data on application of catalysts **5** and **6** as initiators in the ubiquitous cyclopropanation of styrene with diazo compounds are, to our knowledge, quite scarce and therefore we investigated in more detail the behavior of these catalysts in this process (see below). The first generation Grubbs catalyst **5** displays 35% selectivity for cyclopropanation, with metathesis prevailing as expected, while the second-generation Grubbs catalyst **6** gives neither cyclopropanation nor dimerization (diazocoupling), performing only metathesis (Table 1, entries 5 and 6). For catalyst **6** everything seems to depend, however, on molar ratios and reaction conditions, as disclosed in a related investigation where, for a molar ratio of catalyst:EDA:styrene = 1:200:5200 in chlorobenzene, at 60°C for 24 h, 1-carbethoxy-2-phenylcyclopropane was predominantly formed and only <1% metathesis was observed. [5]

If we consider now the competing side processes, an exceptionally sharp increase in dimerization was evidenced for catalyst **9** (43%), quite close to the extent to which cyclopropanation occurs. Though also a non-carbenic complex, the Schiff base bidentate-Ru catalyst **4**, as well as the ethoxy Ru-carbene **8**, largely favor metathesis over dimerization. The distinct behavior of **4** versus **1** (showing dimerization/metathesis = 1) is likely due to a longer lifetime of the metathesis-active species stabilized by the Schiff base, relative to that arising from **1**, in spite of the fact that in both cases activation involves decoordination of the same phosphine (PPh_3).

To our satisfaction, runs carried out with catalyst **5** at a still lower catalyst loading, in excess styrene, were successes by all accounts, leading to higher selectivities in cyclopropanation (Table 2). This is the more rewarding as, in an earlier report,[10] a tandem enyne cyclopropanation was accomplished with as much as 10 mol% of catalyst **5**, and at a more elevated temperature (75°C). We were consequently encouraged to explore the influence of temperature on cyclopropanation and the concurrent processes under promotion by catalyst **5**. In the range 30–50°C

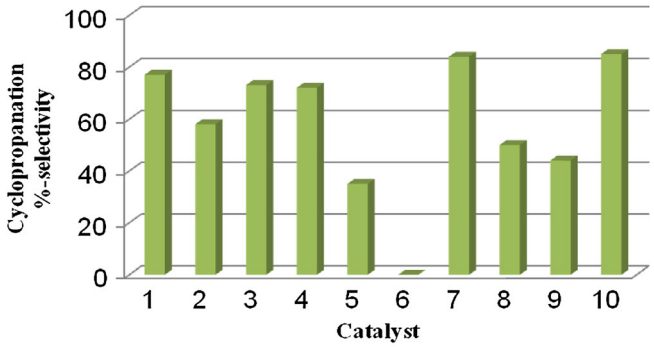


Figure 1. Varying selectivity in cyclopropanation products by change of the Ru complex (**1** to **10**).

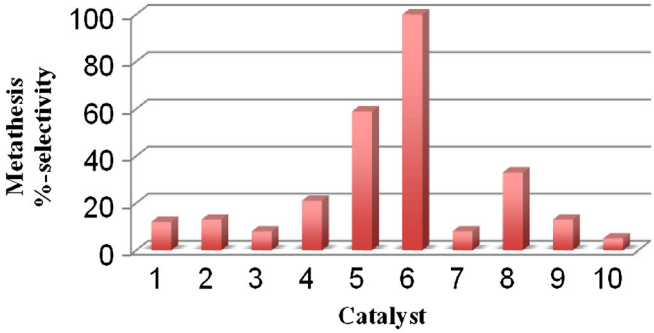


Figure 2. Selectivity for the metathesis products, in the presence of Ru complexes **1–10**.

we found that selectivity in the desired cyclopropanation products increased to 82.0%, while yields (based on EDA) increased from 72.7% to 90.6%, with dimerization and metathesis diminishing accordingly (Table 2).[11,12] An enhancement of cyclopropanation within the same temperature domain has been previously communicated for the catalyst **1**.[13]

The first- and second-generation Grubbs catalysts (**5** and **6**), commonly applied in a variety of metathesis processes,[14] appear as particular cases in cyclopropanation. Although these catalysts have been employed in tandem metathesis/cyclopropanation reactions,[10,15] it is well documented that in the presence of diazo esters catalyst **6** promotes mainly metathesis.[10,16] Of special interest here also is that, in the presence of catalyst **5**, the effect of reaction temperature on cyclopropanation is totally different from that on the dimerization and metathesis processes: lower temperatures restrain cyclopropanation to the advantage of dimerization and metathesis, while higher temperatures act in the opposite direction (Table 2). Our data demonstrate that dimerization is more sensitive to temperature changes, diminishing from 23.5% to 8.5% while metathesis abates only from 14.0% to 9.5%. It is noteworthy that variation of temperature in this range has no significant effect on the *trans*:*cis* ratio of the cyclopropanated products, which oscillates around a value of 2, in agreement with literature reports.[10]

Distribution between cyclopropanation, metathesis and dimerization products observed in this work testifies to the complexity of the chemical processes occurring simultaneously when adding EDA to the mixture of styrene and catalyst, thus complying with the generally accepted intervention of competitive mechanistic pathways as illustrated in Scheme 3.

Experimental

General Information

^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument (in $CDCl_3$ solution with tetramethylsilane as internal standard), infrared and Raman spectra were run on a Bruker FT-Raman/FT-IR spectrometer, while capillary GC measurements were performed using a Varian CDS 401. All materials were of analytical grade and used without further purification. Catalysts **1**, **2**, **5** and **6** are commercially available and were used without further purification. The ruthenium complexes **3**,[7,19,20] **7**,[8] **8**[8] and **9** (*in situ*)[9] were synthesized according to literature procedures. The new catalysts **4** and **10** were obtained by treatment of complex **1** with the corresponding Schiff base and NHC, respectively.[19–22] Details on **4** and **10** will be published elsewhere.

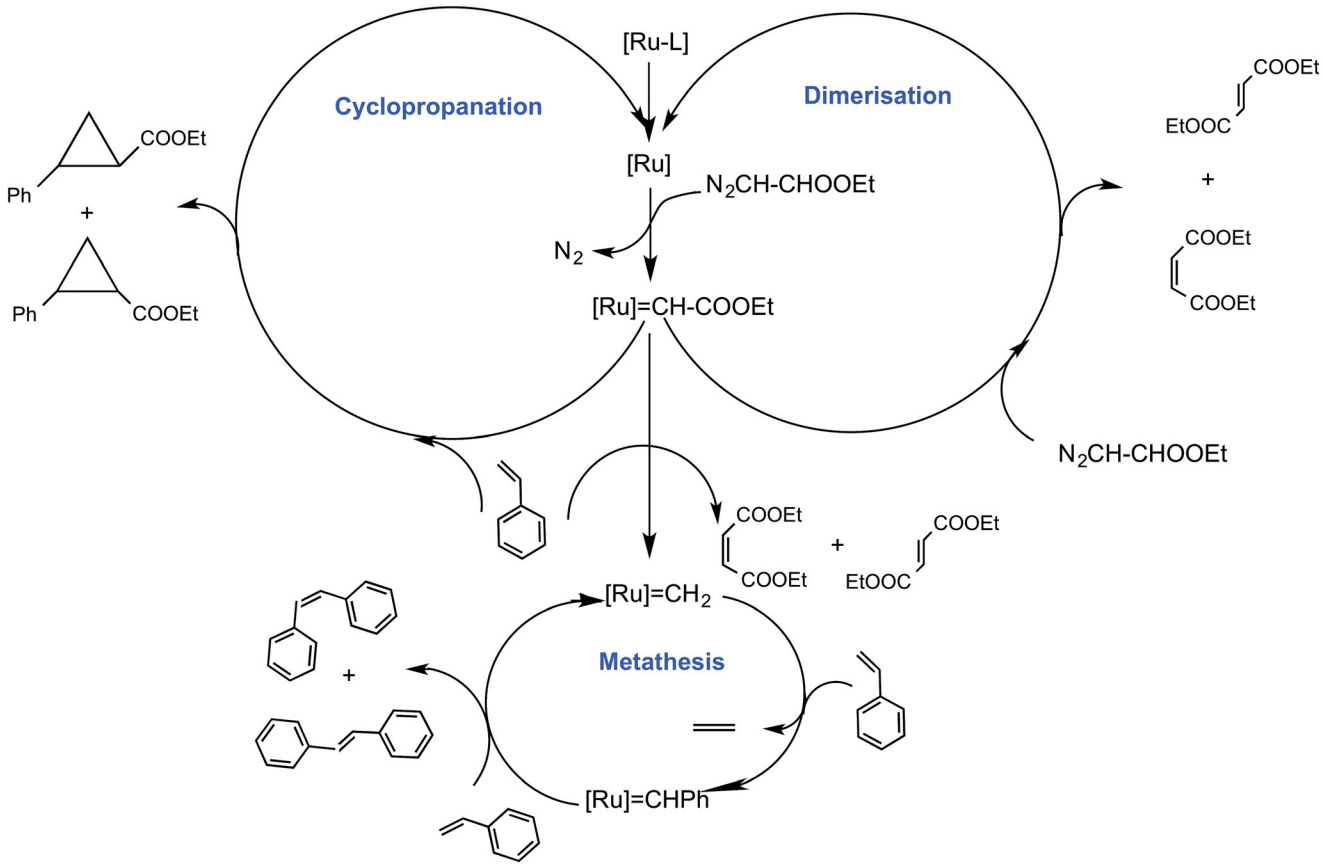
Conclusions

In this communication the application profiles of ten ruthenium pre-catalysts were explored to find an optimal choice for the asymmetric cyclopropanation of styrene by carbene transfer from EDA. It was found that the outcome depends considerably on the nature and combination of ligands present in the coordination sphere of ruthenium. Indeed, catalysts **1**, **4**, **7** and **10**, bearing at least two phosphines, exhibit great a propensity for cyclopropanation. Our new NHC–Ru promoter **10** and the Fischer carbene **7** were clearly shown to be superior in cyclopropanation, even under low catalyst loading. Catalysts **2** and **9**, which are triggered into action by loss of a *p*-cymene unit, form a second group with similar behavior, yet they appear as poorer promoters of cyclopropanation; in comparison, the considerably higher

Table 2. Influence of temperature on cyclopropanation, metathesis and dimerization in the reaction of styrene with EDA, in the presence of Grubbs' catalyst **5**[a]

		Reaction selectivity			
Entry	Temperature (°C)	Cyclopropanation (%)	*trans*/*cis*	Metathesis (%)	Dimerization (%)
1	30	62.5	2.2	14.0	23.5
2	35	71.0	1.9	11.0	18.0
3	40	73.0	1.8	9.0	18.0
4	45	77.0	1.9	8.5	14.5
5	50	82.0	2.0	9.5	8.5

[a]In excess styrene. Molar ratios: catalyst/EDA/styrene = 1/400/8000.



Scheme 3. Competitive routes for metathesis and cyclopropanation in the reaction of styrene with EDA under Ru pre-catalyst promotion.

selectivity manifested by **3** was assigned to stabilization of its active species by the Schiff base. Because of their predilection for metathesis, Grubbs' catalysts are the exception. Nevertheless, this work demonstrates that utilization of catalyst **5** can be manipulated for achieving prevailingly cyclopropanation. The latter conclusion could be helpful for medicinal chemists less familiar with these well-known, commercially available metathesis catalysts.

Acknowledgments

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