

Catalytic reactions with low environmental impact solvents and reagents

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Introduction

The design and implementation of eco-compatible synthetic methods finds its natural environment in *Green Chemistry (GC)* which today, has grown into an internationally recognized focus area of Chemical Sciences.¹ Not surprisingly, major targets of genuinely clean procedures are always encompassed within the leading twelve principles of *GC*.² Among them, the foremost need to realize catalytic rather than stoichiometric processes, and the use of innocuous solvents and reagents as well.

In this context, our group has a long standing interest in several fields including the utilization of supercritical carbon dioxide as a solvent,³ the investigation of the reactivity of organic carbonates as safe replacements of hazardous chemicals,⁴ and the setup of multiphase systems generated by ionic liquids, able to enhance the reaction productivity and the recovery of products.⁵ The presence of inorganic catalysts as well as organocatalysts represents the cornerstone of all these activities. Catalysis by itself, has been referred to as a “foundational pillar” of *GC*.⁶

In particular, this work reports on two different topics which may have a potential in the synthesis of fine chemicals: i) alkylation processes using safe organic carbonates in place of conventional alkylating agents (alkyl halides and sulfates). This section highlights the reactions of dimethyl carbonate (DMC) with several nucleophiles in the presence of basic and amphoteric catalysts of the class of alkaline carbonates and alkali metal exchanged faujasites, respectively; ii) C-C bond forming reactions in dense CO₂ as a solvent. This section is especially focused on the metathesis of alkenes catalyzed by heterogeneous systems, more specifically by Re-oxides supported on different aluminas and silicas.

Case by case, the nature of the catalysts and the experimental conditions are examined to discuss their effects on the reaction outcome (both on selectivity and yields) as well as to propose plausible mechanistic hypotheses.

Results and Discussion

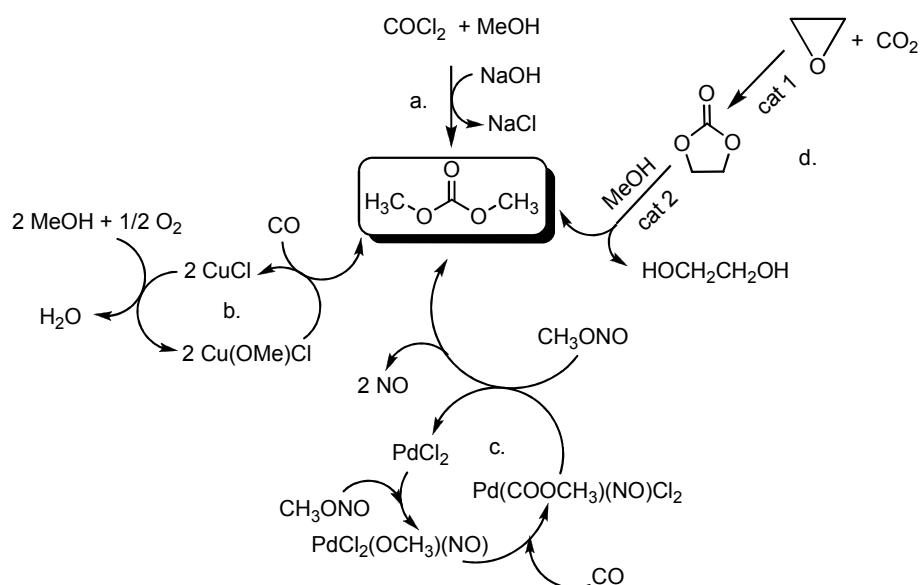
Dimethyl carbonate (MeOCO₂Me)

The industrial synthesis of dimethylcarbonate. The allure of DMC as a green reagent and solvent is readily recognized in several aspects which include not only its general reactivity and properties, but also its methods of industrial synthesis as well. Although the old phosgene route is still active in both SNPE and BASF plants (Scheme 1a),⁷ this process is highly undesirable from both safety and environmental standpoints: the toxicity/corrosivity of phosgene, the generation of contaminated salts, and careful waste-water treatments are major drawback. Today, alternative synthesis of DMC operate with clean technologies which are based on three different reactions (Schemes 1b–d).⁸

1. The oxycarbonylation of methanol catalyzed by copper salts (Scheme 1b), patented by Enichem in the early 1980s,⁹ whose key advantages are the high safety improvement with

respect to the phosgenation of MeOH, the high selectivity, and the sole formation of water as a by-product.

2. The carbonylation of methyl nitrite over a Pd-catalyst (Scheme 1c), developed by UBE Industries in 1993,¹⁰ in which methyl nitrite serves simultaneously as the substrate for the formation of DMC and as an efficient oxidant of the catalyst.
3. The two-stage process of insertion of CO₂ into an epoxide, followed by a transesterification reaction with MeOH (Scheme 1d).¹¹ This represents a recent breakthrough in the production of DMC, in which the building block is the safe and cheap carbon dioxide.



Scheme 1

Overall, thanks to the choice of raw materials, catalysts, conditions, etc., processes based on reactions 1–3 actually prevent pollution at the source.

The reactivity and other green features of DMC. In addition to its synthesis, the flexible reactivity of DMC is also a key feature to devise innovative synthetic strategies. DMC possesses two electrophilic centers (the carbonyl and methyl carbon atoms), which, in the presence of a generic nucleophile (NuH), may undergo two distinct reactions. In particular, a carboxymethylation or a methylation process may take place (Schemes 2a,b).⁴ In the first case (a), DMC serves as safe substitute for fosgene, while in the second one (b), DMC replaces highly noxious methyl halides or dimethylsulfate (DMS). The temperature and the nature of the catalyst used, may discriminate between paths (a) and (b). In the presence of basic catalysis, the carboxymethylation is favored at low temperatures (up to the reflux of DMC, 90 °C), while the methylation process predominates above 120 °C. Solvation phenomena plausibly account for this change in reactivity.¹² In the presence of neutral or weak acid catalysts (e.g., zeolites), methylation reactions takes place preferably. Whatever the reaction, the only co-products are MeOH which is, in principle, recyclable to the synthesis of DMC, and CO₂, which does not usually involve disposal problems.

Compared to phosgene and to conventional methylation agents (e.g, MeI and DMS), which are labeled as highly toxic compounds, DMC offers an advantageous toxicological profile (Table 1): it displays a very low (eco)toxicity, it has no irritating or mutagenic effects, and it is biodegradable.¹³ In addition, DMC is noncorrosive and air and moisture stable so that it can be handled safely, being classified as a flammable but non toxic chemical.

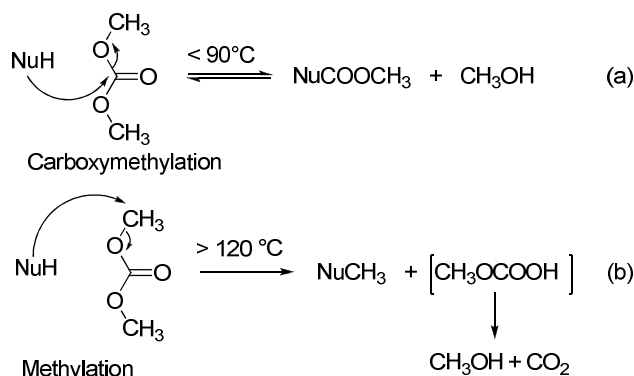


Table 1. Toxicological data and hazard of DMC in comparison to phosgene and DMS/MeI

Properties	DMC	Phosgene	DMS/MeI
Oral acute toxicity (rats)	LD ₅₀ 13.8 g / Kg		DMS: LD ₅₀ 440 mg / Kg MeI: LD ₅₀ 76 mg/kg
Acute toxicity per contact (cavy)	LD ₅₀ > 2.5 g / Kg		MeI: LD ₅₀ 110 mg/kg
Acute toxicity per inhalation (rats)	LC ₅₀ 140 mg / l; (4h)	LC ₅₀ 16 mg / m ³ ; (75 min)	DMS: LC ₅₀ 1.5 mg/l (4h)
Mutagenic properties	None		DMS: Mutagenic
Irritating properties (rabbits, eyes, skin)	None	Corrosive	DMS: causes burns MeI: irritating to skin
Reagent Hazard	No	Yes	Yes

Selective Mono-C-methylation of CH₂-active compounds with DMC. An emblematic example of highly selective methylation processes mediated by dimethyl carbonate is the reaction with methylene active compounds. In this context, good models as nucleophiles are arylacetonitriles (ArCH₂CN). In the presence of several organic and inorganic bases, these compounds can be α -methylated with conventional techniques involving methyl halides.¹⁴ However, a poor selectivity is usually observed due to the formation of mixtures of mono- and bis-C-methylation products: for example, in the reaction of phenylacetonitrile with MeI, the overall mono-C-methyl selectivity hardly exceeds 70 %, at a quantitative conversion. By contrast, in the presence of a weak base (e.g., K₂CO₃) as a catalyst, the same reaction proceeds with a mono-C-methyl selectivity >99 %, when DMC is used in place of methyl iodide.¹⁵ DMC totally inhibits the multiple substitution. This result is quite general: it can be extended not only to different arylacetonitriles, but also to several CH₂-active compounds such as arylacetoesters, aroxyacetic acid derivatives, and sulfones bearing α -methylene groups (Table 2).¹⁶ A noteworthy application of this method is the synthesis of precursors for nonsteroidal anti-inflammatory drugs (NSAIDs)

belonging to the class of hydratropic acids. Well-known cases are those of ibuprofen, ketoprofen, and naproxen, whose preparation can be scaled up to batches of 250 kg, with overall yields >95 % (Scheme 3).¹⁷

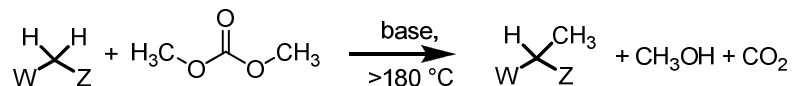
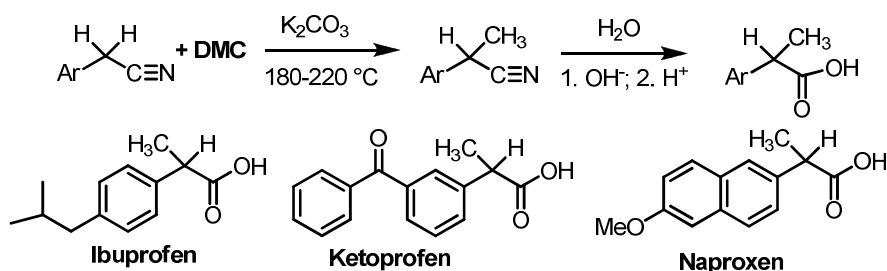


Table 2. Selective mono-C-methylation of CH₂-active substrates (WCH₂Z) with DMC

Entry	WCH ₂ Z		T (°C)	Product, WCH(CH ₃)Z (%, Selectivity)	Isolated Yield (%)
	W	Z			
1	<i>o</i> -MeOC ₆ H ₄	CN	180	>99	85
2	<i>p</i> -ClC ₆ H ₄	CN	180	>99	89
3	<i>p</i> -FC ₆ H ₄	CN	180	>99	81
4	C ₆ H ₅	CO ₂ CH ₃	200	92	80
5	(6-CH ₃ O)naphthyl	CO ₂ CH ₃	220	99	90
6	C ₆ H ₅ O	CO ₂ H	200	96	81
7	C ₆ H ₅ O	CO ₂ CH ₃	190	94	80
8	C ₆ H ₅	SO ₂ Ph	180	92	81
9	C ₆ H ₅	SO ₂ CH ₃	180	96	85

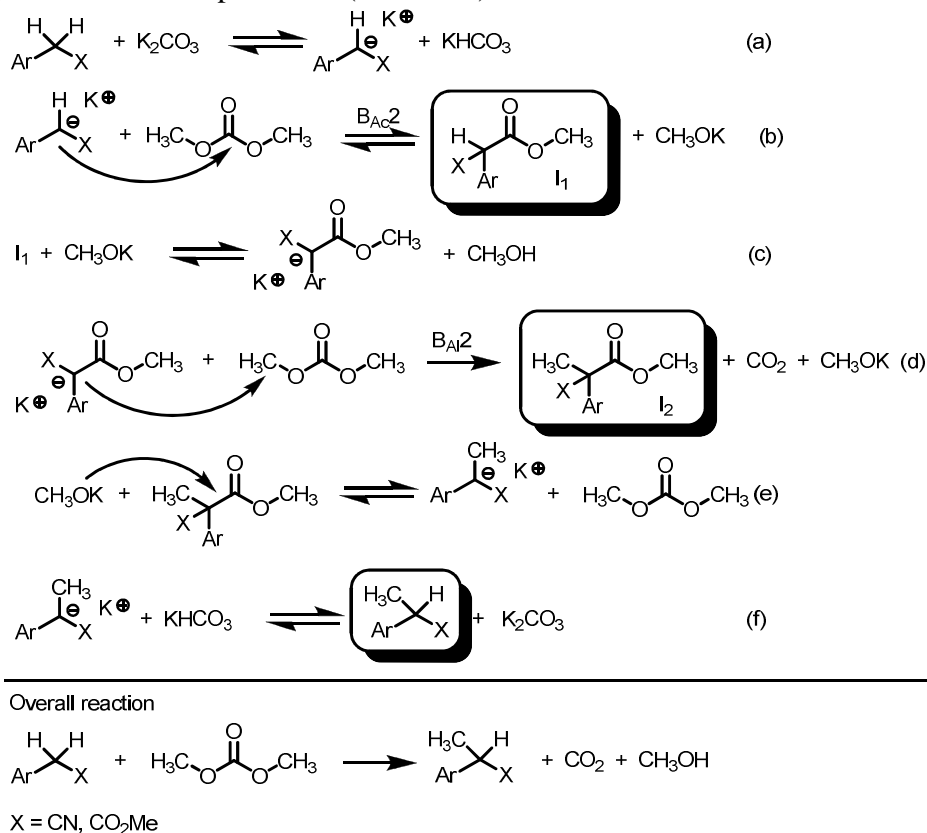


Scheme 3. The synthesis of some NSAIDs with DMC

A detailed investigation of these reactions has shown that the final mono-C-methyl product takes place via two intermediates (I₁ and I₂, Scheme 4). This observation along with a kinetic analysis of these processes supports the reaction mechanism outlined in Scheme 4 for the case of arylaceto-nitriles and -esters. The two nucleophilic anions generated by reactions (a) and (c) allow the formation of the intermediate I₁ and I₂, respectively. In these processes, DMC exhibits a dual reactivity: it behaves subsequently as a methoxycarbonylating and as a methylating agent through B_{Ac}2 and B_{Al}2 mechanisms [eqs. (b) and (d)]. Finally, I₂ is subjected to a demethoxycarbonylation reaction to the final product [ArCH(CH₃)X].

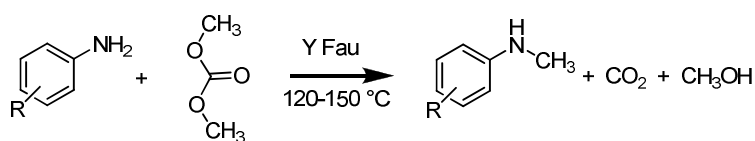
Selective Mono-N-methylation of primary aromatic amines with DMC. It is well known that conventional alkylation procedures of primary amines with alkyl halides are not usually feasible for the preparation of secondary amines: especially for methylation reactions, only mixtures of tertiary amines and quaternary ammonium salts are obtained. An elegant and very efficient synthetic solution comes from the combined use of DMC as the alkylation agent and of alkali metal-exchanged Y and X faujasites as catalysts (MY or MX; M = Li, Na, K). In the presence of these solids in fact, a number a primary aromatic amines even deactivated by both steric or

electronic effects, undergo mono-*N*-methylation reaction with an unprecedented high selectivity (93–98 %) at conversions up to 95 % (Scheme 5).¹⁸



Scheme 4. The mechanism for the mono-C-methylation of CH₂-active compounds with DMC

The result finds an even more notable application in the reaction of DMC with ambident primary amines such as anilines bearing functional groups susceptible to undergo themselves methylations or carboxymethylations with DMC.



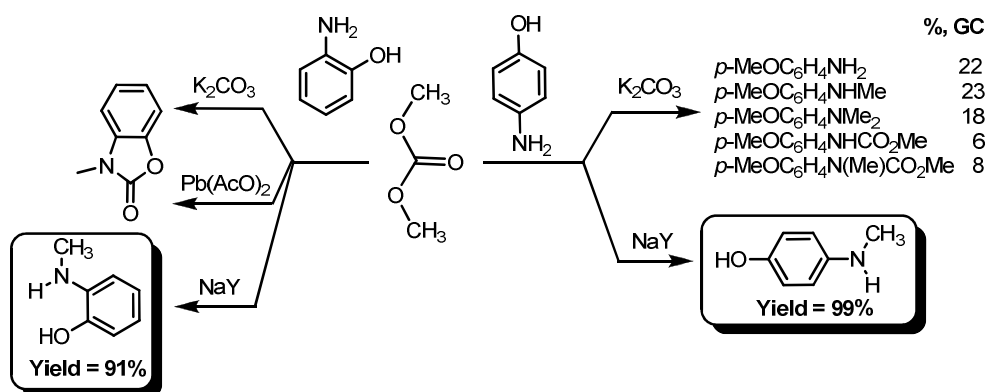
R	Catalyst	T (°C)	t (min)	Mono-N-methyl selectivity (%)	ArNHMe (%)
H	NaY	130	195	98	84
<i>p</i> -NO ₂	KY	150	600	93	79
<i>p</i> -CN	KY	150	270	98	83
<i>o</i> -CO ₂ Me	NaY	150	330	96	84
2,6(Me) ₂	NaY	150	300	94	76

Scheme 5. The mono-*N*-methylation of anilines with DMC

Scheme 6 clearly exemplifies the situation of aminophenols. In the presence of K₂CO₃ as a catalyst, the reaction of *p*-aminophenol with DMC proceeds through several competitive O- and N-methylation, and carboxymethylation processes (Scheme 6, top right). By contrast, when NaY

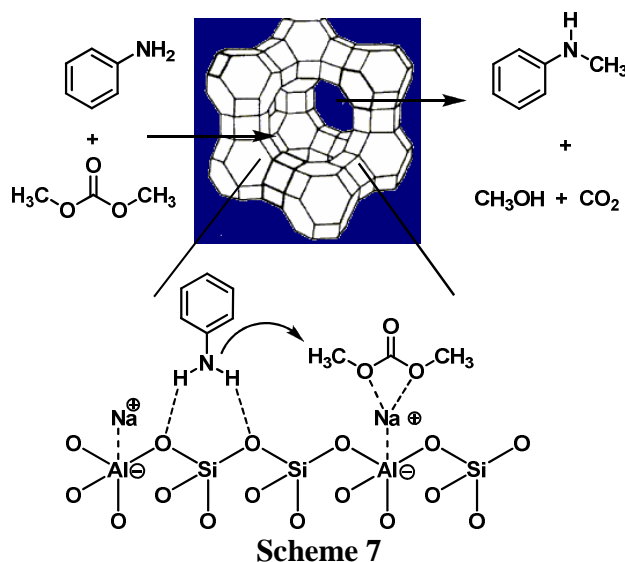
is used, the exclusive methylation at the N-atom is observed and, in particular, only the mono-*N*-methyl derivative is isolated in a substantially quantitative yield (99 %, bottom right).¹⁹

Likewise, when *o*-aminophenol and DMC react over a base (K_2CO_3) or even an acidic catalyst [$Pb(AcO)_2$], a *N*-methylbenzoxazolone is obtained via simultaneous methylation and carboxymethylation reactions at both the N- and O-terms (Scheme 6, top left). The NaY-catalyzed process affords solely *o*-(*N*-methyl)aminophenol in a 91 % yield (bottom left).



Scheme 6. The reaction of aminophenols with DMC over different catalysts.

Faujasite catalysts may therefore operate a fine tuning of the mono-*N*-methyl selectivity (Scheme 5) and of the methyl chemoselectivity (Scheme 6) as well. The investigation of adsorption phenomena of reagents (anilines and DMC) on faujasites supports the fact that both the mono- and the chemo-selectivity are controlled by the steric and the acid-base requisites of the catalyst. A pictorial description is offered in scheme 7 for the model case of aniline.



Once the amine and DMC diffuse into the supercages of the NaY catalyst, they may approach each other only according to the steric requisites of their adsorption patterns. The reaction proceeds via a S_N2 displacement of aniline on DMC. The product, mono-*N*-methyl aniline (PhNHMe), is more nucleophilic than aniline; nonetheless, the NHMe group may force the

molecule farther from the catalytic surface in a fashion less suitable to meet DMC and react with it. This behavior can account for the mono-*N*-methyl selectivity observed.

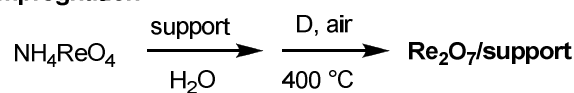
The reaction chemoselectivity instead, is discussed according to the principle of hard and soft acids and bases:²⁰ in fact, the methylation takes place exclusively via the attack of the less electronegative atom (the aminic N-atom) of anilines to the soft electrophilic center of DMC (i.e., the methyl carbon). This is true however, only on condition that reactant amines are “solvated” by their adsorption within the zeolite cage.

The self-metathesis of 1-olefins in scCO₂

The olefin metathesis is among the most powerful and elegant means of constructing complex carbon frameworks.²¹ Since its discovery in the 1950s, the reaction has undergone a tremendous development thanks to the preparation of new homogeneous catalysts able to operate under milder conditions, to improve the reaction selectivity, and to extend the synthetic scope of the process.²² The metathesis also represents the archetype green chemistry reaction for clean syntheses with reduced emissions of hazardous wastes to the environment.²³ In this context, a largely unexplored area is the use of alternative *greener* solvents able to replace conventional media, typically hydrocarbons or light chlorinated compounds. Only a few recent patents and papers report on the application of dense CO₂ or ionic liquids as solvents for metathesis reactions, using metal complexes (Grubbs catalysts) or transition metal salts.²⁴ Compressed CO₂ as a solvent seems perfectly suited to this purpose especially when combined to heterogeneous catalysts. In fact, thanks to its low viscosity (η) and high diffusivity (D), dense carbon dioxide is very efficient at penetrating meso- and micro-porous supports used for solid catalysts.²⁵ Yet, only very recently, we have investigated for the first time, the metathesis of α -olefins over heterogeneous catalysts in the presence of scCO₂ as a solvent.²⁶

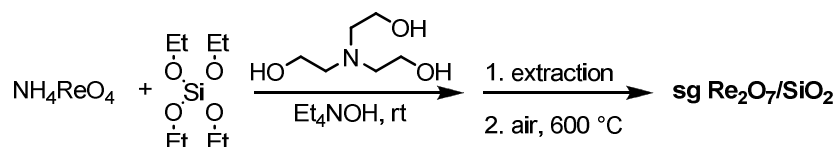
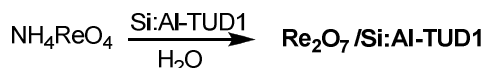
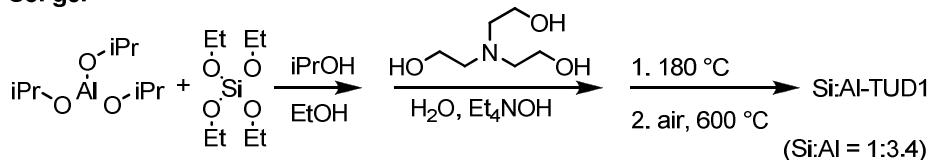
The self-methathesis of 1-octene. The best studied and effective heterogeneous catalysts for the metathesis of alkenes are based on Re-oxides supported on refractory solids, most often alumina and silica.²¹ Accordingly, such systems have been prepared via either a conventional wet impregnation, or sol-gel techniques (Scheme 8).²⁶⁻²⁷

Wet impregnation



support: g-Al₂O₃, mesoporous-Al₂O₃, SiO₂

Sol-gel



Scheme 8

The self-metathesis of 1-octene has been chosen as a model reaction. Based on a preliminary solubility screening, the experiments have been carried out in batch mode (autoclave) operating at 35 °C and at a CO₂ pressure of 90 bar. Under these conditions, scCO₂ is not only an efficient solvent for the reaction, but it allows even faster reactions with respect to conventional solvents (Table 3).

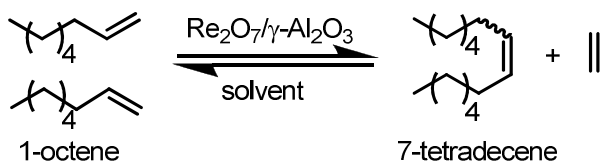


Table 3. The self-metathesis of 1-octene in scCO₂ and conventional liquid solvents

Solvent	Octene ^a (Xi x 10 ⁻²)	T (°C)	P (atm)	t (h)	Conv (%)	Selectivity (%)	Yield (%) ^b
<i>n</i> -heptane	1.1	35	1	2	40	95	38
Toluene			1		36	95	
scCO ₂			90		71	97	67

^a Molar fraction of 1 octene; ^b Isolated yield of 7-tetradecene

In the presence of Re₂O₇/γ-Al₂O₃, the conversion of 1-octene in the self-metathesis product 7-tetradecene, is 30% higher on average, in scCO₂ than in liquid solvents such as toluene or *n*-heptane. The increase of the mass transfer promoted by dense CO₂ as well as local density enhancement effects, likely account for the result.

Under the same reaction conditions, in scCO₂ as a solvent, other terminal olefins such as 1-hexene and 1-heptene, show a reactivity similar to 1-octene: they both undergo the self-metathesis reaction to the corresponding 5-decene and 6-dodecene, with a conversion of 61 and 63%, respectively.

The influence of the catalysts. The nature of the catalytic support affects the outcome of the self-metathesis of 1-octene. Table 4 reports the results obtained in scCO₂ at 35 °C and 90 bar.

Table 4. The conversion/selectivity of the self-metathesis of 1-octene over different catalysts

Catalyst (Re content, %)	S _A (m ² /g)	Conversion (%)	Selectivity (%)
Re ₂ O ₇ /γ-Al ₂ O ₃ (6.8)	250	74	96
Re ₂ O ₇ /γ-Al ₂ O ₃ (7.0)	200	37	86
Re ₂ O ₇ /meso-Al ₂ O ₃ (11.8)	362	33	96
Re ₂ O ₇ /Si:Al-TUD1 (7.7)	298	<1	-
Re ₂ O ₇ /SiO ₂ (6.7)	550	<1	-
sg Re ₂ O ₇ /SiO ₂ (2.7)	696	<1	-

Only those catalysts supported on Al₂O₃ (both γ-phase and mesoporous solids), show appreciable activities. Though, the conversion drops by decreasing the surface area of the support or by varying its morphology going from γ- to meso-Al₂O₃. Other catalysts supported on an alumin-

silicate (TUD) or on silica as such, are not active at all. A plausible explanation is based on the stabilization of monomeric tetrahedral structures of ReO_4^- - thought to be the active specie - over the surface of the support: accordingly, both the acidity and the surface area of different supports can play a role to affect the metal centre.

Continuous-flow(c.-f.) metathesis of alkenes in scCO₂. The last frontier in the use of dense CO₂ as a solvent for the metathesis of alkenes, has been the setup of the reaction of 1-octene in a plug-flow reactor filled with a bed of $\text{Re}_2\text{O}_7/\gamma\text{-Al}_2\text{O}_3$ (7%) and continuously fed by a solution of the olefin in scCO₂.²⁸ C.-f. conditions reproduce the trend observed during batch experiments (Table 5): the reaction conversion is higher in scCO₂, 53%, than in a conventional solvent such as n-hexane, 36%.

Table 5. The continuous flow self-metathesis of 1-octene in scCO₂ and n-hexane as solvents

Solvent	X (1-octene)	Flow rate 1-octene [mL min ⁻¹]	T (°C)/ P (bar)	t [min]	Conv'n	C ₁₄ product (self-met, %)	Sel [%]	Yield [%]
CO ₂	2.8 x 10 ⁻²	0.1	100/90	10	53	46	86	57
n-hexane		0.1	100	10	-	-	-	-
n-hexane		0.02	100	10	36	28	77	27

Not only. In the presence of n-hexane, the reaction takes place only at a flow rate about one-fifth lower than that used in scCO₂. Overall, the use of the supercritical solvent allows a great improvement of the reaction productivity.

Acknowledgements. I wish to express special thanks to the group I work with at the Dipartimento di Scienze Ambientali dell'Università Ca' Foscari. In particular, Dr. Alvise Perosa, and PhD students Massimo Fabris and Marco Noè are gratefully acknowledged.

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