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Dimethyl carbonate: a modern green reagent and solvent

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Contents

Abstract. The published data on dimethyl carbonate as a non-toxic reagent and solvent in organic synthesis are generalized and discussed. The methods for dimethyl carbonate production and its use as a methylating and methoxycarbonylating agent are considered. Special attention is paid to the eco-friendly processes that meet the 'Green chemistry' requirements. The bibliography includes 104 references.

I. Introduction

Green chemistry, as one of the primary methods of pollution prevention, is a fairly recent phenomenon. 'Green' organic syntheses must include some of the following requirements: avoid waste, be atom efficient, avoid the use and production of toxic and dangerous chemicals, avoid auxiliary substances (*e.g.*, solvents), use renewable materials, use catalysts rather than stoichiometric reagents.[1 – 5]

In particular, it is important to find a replacement for toxic and dangerous reagents produced by eco-unfriendly processes and that are responsible for producing expensive-to-dispose-of inorganic salts. Methyl halides (CH_3X, X = I, Br, Cl), dimethyl sulfate (DMS), and phosgene ($COCl_2$) are representative examples of undesirable reagents used for methylation and methoxycarbonylation reactions. All these reagents are toxic and corrosive chemicals. Moreover, the reactions require stoichiometric amount of bases and produce stoichiometric amounts of inorganic salts that need to be disposed of.

Dimethyl carbonate (DMC) is an environmentally benign substitute for phosgene, DMS and methyl halides since it is a well-known non-toxic reagent as compared to other carboxylating or alkylating agents (phosgene and methyl halides, respectively). Dimethyl carbonate does not produce inorganic salts. In fact, the leaving group, methyl carbonate, decomposes giving only methanol and CO_2 as by-products. Dimethyl carbonate is classified as a flammable liquid, smells like methanol and does not have irritating or mutagenic effects by either contact or inhalation. Therefore, it can be handled safely without the special precautions required for the poisonous and mutagenic methyl halides and DMS, and extremely toxic phosgene. Besides, DMC is widely studied also for its many potential applications.[6, 7] In fact, recent research indicate DMC as an oxygenated fuel additive of gasoline or diesel oil to replace *tert*-butyl methyl ether.[8] Dimethyl carbonate can reduce the surface tension of diesel boiling range fuels leading to an improved (diesel) fuel with better deinjection delivery and spray. An obvious advantage of DMC over other candidate as fuel additives is that it slowly decomposes to form CO_2 and methanol, which have no serious impact when released into the environment. This and other applications led to an enormous effort in the investigation of low-cost and not toxic synthesis of DMC.

II. Production of dimethyl carbonate

For a long time, DMC has been produced from phosgene and methanol. In this synthesis, HCl was an unwanted side product. However, since the mid-1980s, DMC is no longer produced from phosgene, but by oxidative carbonylation of methanol with oxygen through a process developed by Enichem (Italy):[9 – 12]

$$2\,MeOH + \frac{1}{2}\,O_2 + CO \xrightarrow{Cu\ salt} MeOCO_2Me + H_2O.$$

The most relevant features of this process are:

— low-cost and widely available raw materials with low toxicity;

— high production rates;

— non-toxic and easily disposable by-products (carbon dioxide and water);

— high quality product.

The new technology does not produce any by-products that are difficult to dispose of. The DMC obtained has also low toxicity and ecotoxicity (biodegradability > 90% at

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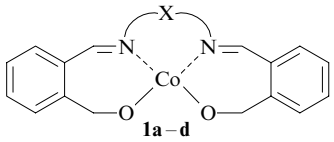
28 days, OECD 301C; acute toxicity for fish; no effect at 1000 mg litre^{-1}, OECD 203).

The oxidative carbonylation paved the way for industrial phosgene-free route to DMC. In fact, since 1984, when it was firstly patented, many new catalytic systems have been investigated for this process.[13–19] A very recent one includes the use of Co(II)–Schiff base complexes **1a–d**.[20]



1a–d

X = $(CH_2)_2$ (**a**), $(CH_2)_2NH(CH_2)_2$ (**b**), cyclohexane-1,2-diyl (**c**), *o*-phenylene (**d**).

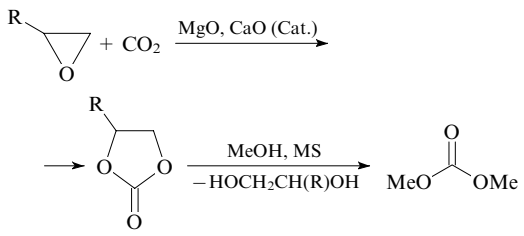
However, such complexes are prone to dimerization, which reduces the service-life of the catalysts. Incorporation of a complex into a cavity of zeolite substantially enhances its stability and prevents dimerization. In the study cited, zeolite-encapsulated Co(II)–Schiff base complexes with four spacer diamines have been prepared by a 'ship-in-a-bottle' approach.

The oxidative carbonylation proceeds within the zeolite cavity; the influx of the reagents and removal of the reaction products occur through the zeolite channels.

Catalyst **1d** manifested the highest reactivity with conversion of methanol and selectivity of DMC of 25.4% and 99.5%, respectively. This complex-catalyst can be reused up to five times without showing any loss of activity.

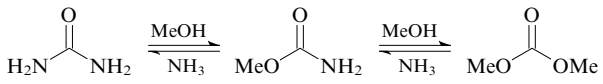
$$MeOH + CO_2 + O_2 \xrightarrow{\text{Cat. } \mathbf{1}} MeOCO_2Me + H_2O.$$

Another industrial procedure developed and recently industrialized in China is the cleavage of cyclic carbonates that are prepared by insertion of CO_2 to epoxides. Importantly, this synthesis does not use any chlorine-containing reagents.[21]



R = H, Me; MS is zeolites exchanged with alkali and/or earth metal ions.

High-yield synthesis of DMC can also be achieved by reaction of methanol and urea using a catalytic distillation process.



The reaction equilibrium involved in this synthesis is thermodynamically unfavorable. Besides, other major drawbacks of the procedure are the thermal decomposition of DMC and the reaction between the methyl carbamate and DMC, which reduce drastically the yield in batch process. In order to minimize the side reactions, Wang *et al.*[22] proposed to use catalytic distillation technique. As a result, it was possible to obtain DMC in 60%–70% yield by catalytic distillation over a Zn-based catalyst. The catalytic distillation process demonstrated a stable performance and a substantial improvement in DMC yield compared with batch results.[22]

III. Reactivity of dimethyl carbonate

Dimethyl carbonate is a well-known non-toxic reagent showing several main green-chemistry features[23] as compared to other carboxylating or alkylating reagents (phosgene and methyl halides, respectively).[24,25]

As has been mentioned, dimethyl carbonate does not produce inorganic salts in either acylation[26] or alkylation[27,28] reactions:

$$Nu^- + MeOCO_2Me \rightleftharpoons NuCO_2Me + MeO^-, \quad (1)$$

$$Nu^- + MeOCO_2Me \longrightarrow NuMe + MeOCO_2^-, \quad (2)$$

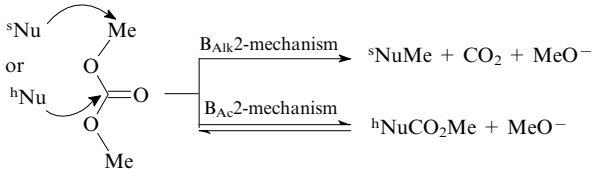
$$MeOCO_2^- \longrightarrow MeO^- + CO_2. \quad (3)$$

Nu is a nucleophile.

In fact, since the leaving group, methyl carbonate, decomposes (reaction 3), the base is restored and can be used in truly catalytic amounts. This feature allows utilization of continuous-flow procedures (*i.e.*, gas-liquid phase-transfer catalysis, GL PTC,[29,30] and a continuously fed-stirred tank reactor, CSTR[31]). Since reaction (1) is an equilibrium and reaction (2) is not, the product of the process can be controlled, temperature being the key factor. In fact, because methylation reactions involve higher Gibbs activation energies, low temperatures favour methoxycarbonylation, whereas high temperatures give methylated derivatives.[32] Moreover, when operating at 200–250 °C, no decomposition and polymerization products or tars are formed and usually clear reaction mixtures are obtained.

Dimethyl carbonate manifests a very selective behaviour in reactions with different nucleophiles (such as amines, CH acids, phenols, *etc.*) acting as an alkylating or carboxymethylating agent. This different reactivity of DMC with different nucleophiles may be rationalized by the principle of hard and soft acids and bases (HSAB principle),† according to which hard nucleophiles preferably react with hard electrophiles and *vice versa*.[38]

Dimethyl carbonate, as an electrophile, has three reactive centres that can react with nucleophiles: the carbonyl and two methyl groups. According to the HSAB principle, the carbonyl group is the harder electrophile as a result of partial positive charge on the carbon atom and its sp^2 hybridization; the two methyl groups represent softer electrophiles, thanks to their sp^3 orbital and their saturated carbon atom.



^{s}Nu and ^{h}Nu are soft and hard nucleophiles, respectively.

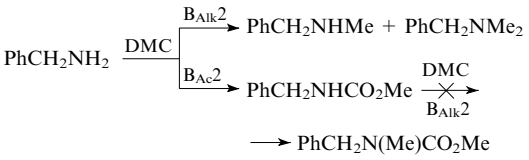
Many ambident nucleophiles are known, but few ambident electrophiles have been studied. Many investigations

† P Pearson introduced[33,34] the principle of hard and soft acids and bases (HSAB principle) in 1963. The fundamentals of the HSAB principle were further developed by Mendez[35] and Klopman.[36,37]

verified the compliance of reactivity of ambident nucleophiles and electrophiles with the HSAB principle. Among the ambident electrophiles, we can mention esters and particularly propiolactones,[39–42] α,β-unsaturated carbonyl compounds,[43] 3-chloro-1,2-benzoisothiazole[44] and trichlorocarboxylates.[45] Actually, alkyl halides are also included among the ambident electrophiles, as they react with nucleophiles yielding either products of substitution reactions (soft–soft reaction) or alkenes (hard–hard interaction).[46,47] At this regard, the reaction of 2-bromoethylarenes with different phenoxide anions is relevant: it yields different mixtures of ethers and alkenes, according to the nucleophilic nature of the anion species, which can modulate the reaction outcome.[48] Here the reactivity of some soft/hard mono- and bidentate nucleophiles with DMC is compared: nitrogen, oxygen, and sulfur nucleophiles are considered.

1. Dimethyl carbonate as a methoxycarbonylating agent (substitute of phosgene)

Dimethyl carbonate can be used efficiently as a methoxycarbonylating agent (as a phosgene substitute) for a wide string of nucleophiles. A relevant example of its versatility is the methoxycarbonylation of amines, which has great industrial relevance. In fact, carbamates are very useful compounds widely used in the synthesis of pesticides, fungicides and herbicides, pharmaceuticals, cosmetics and polyurethanes; in addition, this can be employed as a protecting group.[49–53] Industrially carbamates are synthesized predominantly through the reaction of the relevant amine with phosgene.[54–56] This process is highly toxic and produces large volumes of waste. In order to improve this synthetic procedure, many environmentally benign pathways have been investigated, *e.g.*, oxidative carbonylation, reductive carbonylation and methoxycarbonylation.[57–60] However, as previously reported, one of the most promising substitutes for phosgene as a carboxylating agent is DMC. In particular, when an aliphatic amine such as benzylamine reacts with DMC in the absence of a base, the reaction gives both alkylation and methoxycarbonylation products without any selectivity: 12% of benzyl(methyl)amine, 6% of benzyl(dimethyl)amine and 4% of N,O-disubstituted carbamate (urethane). Thus, both $B_{Ac}2$ and $B_{Alk}2$ mechanisms are followed demonstrating an intermediate character of the amine nitrogen towards DMC, in terms of hardness and softness.



Strong bases, such as potassium *tert*-butoxide or sodium methoxide, catalyze the methoxycarbonylation reaction of aliphatic and aromatic amines at 90 °C.

In fact, it is well known that bases significantly accelerate aminolysis and transamination reactions. It was suggested[61] that the direct participation of a base was the reason for the enhanced reactivity of nitrogen nucleophiles with the carbonyl. In accordance with other authors,[62] naked RNH^- is excluded from the mechanism; it looks like the role of the base is that of removing H^+ from the protonated nitrogen during or after the attack, increasing in any case the negative charge on the nitrogen atom. Whatever the exact mechanism may be, the presence of a base enhances the hardness of the nucleophile. Therefore, the reactivity with harder electrophiles (the carbonyl in this case) is raised and aminolysis reactions are highly favoured. Dimethyl carbonate represents a valid model molecule; its reactivity can explain the competition between the harder RNH^- (more or less naked) and the softer RNH_2, through the HSAB theory. The behaviour of amines in the presence and in the absence of a base confirms that since the hardness of the nucleophile is increased while operating in the presence of a base, the $B_{Ac}2$ rate is dramatically accelerated and methoxycarbonyl derivatives are selectively obtained. Once formed, the urethanes need the presence of a base to react further with DMC. In these conditions, their RN^-COOCH_3 anions, softer nucleophiles than RNH^-, undergo solely $B_{Alk}2$ reactions. This was proved by the fact that in neither case, $RN(COOCH_3)_2$ products derived from a $B_{Ac}2$ reaction mechanism were observed.

With aliphatic amines, high yields of carbamates are achieved in few minutes. Then, if the reaction is protracted, the already formed carbamates react again with DMC to give the corresponding *N*-methyl derivative (Table 1).[63,64]

$$PhCH_2NH_2 + MeOCO_2Me \overset{B}{\rightleftharpoons} PhCH_2NHCO_2Me + MeOH,$$

$$PhCH_2NHCO_2Me + MeOCO_2Me \xrightarrow{B} PhCH_2N(Me)CO_2Me + CO_2 + MeOH,$$

B is a base.

Table 1. Reaction of amines with dimethyl carbonate in the presence of potassium *tert*-butoxide.[63,64]

Amine	Reaction time /min	Yield (%)	
		carbamate	*N*-methylcarbamate
$PhCH_2NH_2$	1	100	0
$PhCH_2NH_2$	30	32	68
$PhNH_2$	1	100	0
$PhNH_2$	180	60	40
n-$C_{10}H_{21}NH_2$	1	100	0
n-$C_{10}H_{21}NH_2$	60	56	44

Note. Reflux in DMC (90 °C), molar ratio amine : DMC : base = 1.0 : 40 : 1.2

Due to the lower nucleophilicity, aromatic amines (*e.g.*, aniline) are less reactive, as in the absence of a base they do not react at the reflux temperature of DMC (90 °C) At the same time, aniline reacted with DMC in the absence of a base at 200 °C in an autoclave (DMC as a solvent); after 24 h, the conversion was 61% without selectivity: 15% monomethylation product, 37% dimethylated product and 9% carbamate were obtained.[64] Aromatic amines in the presence of a base follow the behaviour of aliphatic ones even if the formation of *N*-methylcarbamate requires longer reaction time (see Table 1).

When weaker bases like potassium carbonate are used as catalysts, the reactions have to be carried out at high temperatures in an autoclave in order to achieve high conversion of the starting material. Table 2 shows results obtained with aromatic and aliphatic amines. Aliphatic amines, which are harder nucleophiles, give mainly the

Table 2. Reaction products (%) of amines with dimethyl carbonate in the presence of K_2CO_3 after 22 h.[64]

Amine	MNM	DNM	CARB	NMC
$PhNH_2$	6.2	2.6	8.3	41.0
p-$ClC_6H_4NH_2$	6.3	2.1	5.7	47.5
p-$MeOC_6H_4NH_2$	1.3	13.4	1.8	83.0
n-$C_8H_{17}NH_2$	–	1.2	53.7	45.0
$Ph(CH_2)_2NH_2$	–	–	77.0	23.0

Note. Conditions: T = 180 °C, molar ratio amine : DMC : base = 1.0 : 40 : 3; MNM is mono-*N*-methylation; DNM is di-*N*-methylation; CARB is carbamate; NMC is *N*-methylcarbamate.

corresponding carbamates and methylcarbamates after 22 h, while aromatic amines react slower, and their softness is responsible for the formation of mono- and dimethylated products.

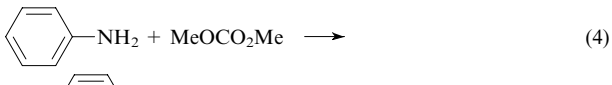
In contrast, with K_2CO_3 as a catalyst and under GL-PTC conditions at high temperature, monomethylation of aromatic amines occurs selectively (Table 3).[65] It is well known that the role of a phase transfer agent is to complex the alkaline metal cation thus enhancing the strength of the

Table 3. Reaction of aromatic amines with dimethyl carbonate under GL-PTC conditions.[65]

Substrate	Composition of the reaction mixture at the equilibrium (%)			
	amine	MNM	DNM	NMC
$PhNH_2$ (see [a])	54.3	40.8	1.6	3.3
o-$MeC_6H_4NH_2$ (see [b])	27.7	47.0	0.3	25.0
o-$ClC_6H_4NH_2$ (see [b])	14.6	62.7	0	22.7
p-$ClC_6H_4NH_2$ (see [b])	10.1	70.0	0	19.9

Note. Column V = 151 ml filled with 95 g of K_2CO_3 coated with 5 mass % of PEG-6000, T = 180 °C, flow rate = 24 ml h^{-1}.
[a] Molar ratio amine : DMC = 1 : 4; [b] molar ratio amine : DMC = 1 : 10.

naked anion as a base. The absence of carbamates in the equilibrium reaction mixture is noteworthy. The reaction between DMC and amines leading to carbamates is of strong interest for the industrial field, mainly as they represent precursors in a non-phosgene route to the production of isocyanates, in fact isocyanates can be produced by thermal decomposition of carbamates.



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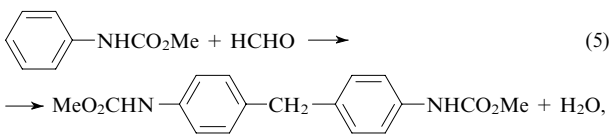

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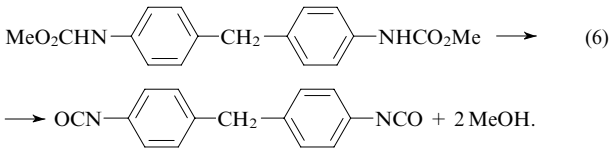


(6)

In addition to the production of isocyanate without phosgene, carbamates themselves are relevant industrial products because they can be applied in pharmaceutical and in crop protection sectors. Strong efforts have been done by industrial companies in order to discover new processes and find suitable catalysts for the methoxycarbonylation of amines, in particular aromatic, with dialkyl carbonates. There are many patents that report findings related to this topic, hereafter some of them are gathered.

In 1981, Bayer patented a process for the production of *N*,*O*-disubstituted carbamates (urethanes) by reacting primary aromatic amines with dialkyl carbonates in the presence of neutral or basic inorganic or organic compounds of lead, titanium, zinc or zirconium as catalysts.[66] Table 4 summarizes some of the most interesting examples reported.

Table 4. Process for the synthesis of *N*,*O*-disubstituted urethanes from aniline.

Dialkyl carbonate	Catalyst	T/°C	Time /h	Yield of urethane (%)
$(EtO)_2CO$	$Ti(OBu^n)_4$	130 – 140	6 – 7	96
$(Bu^nO)_2CO$	$Zn(OPr^n)_4$	190	5 – 6	89
$(EtO)_2CO$	$Pb(OAc)_2$	135 – 136	6	96
$(EtO)_2CO$	$Zn(O_2CC_{17}H_{35}\text{-n})_2$	132 – 135	9	97

In the same year also Dow reported a process for preparing carbamates from an organic carbonate and an aromatic amine in the presence of catalytic quantities of Zn, Sn or Co compounds.[67, 68] A wide screening of catalysts was reported including salts of organic and inorganic acids and other compounds having a pK_a value of more than 2.8 such as alkoxides, phenolates, acetylacetonates at a temperature of about 200 °C. The best results for the methoxycarbonylation of aniline with DMC, in terms of carbamate selectivity, were achieved with zinc (naphthenate, pivalate, benzoate, acrylate, hydroxyacetate, acetate, propionate, carbonate) and tin(II) catalysts (dibutyltin dilaurate, dibutyltin oxide polymer, dibutyltin maleate); the temperature optimum was 130 – 200 °C.

Other suitable catalysts for the methoxycarbonylation of aromatic amines are zinc or copper carbamates. A process for the preparation of carbamates from an aromatic amine and DMC in the presence of zinc and copper complexes with *N*,*N*-disubstituted carbamate was patented in 1997.[69] Table 5 summarizes the results reported in some of the patent examples, high selectivity was reported with aniline, while with 4,4-methylenedianiline (MDA) a considerable amount of *N*-methyl derivatives was found.

Yet another process for the synthesis of aromatic urethanes was based on the reaction of an organic carbonate, in particular DMC, with an aromatic diamine or polyamine in the presence of a Lewis acid catalyst;[70] the yield and selectivity are increased by partial removal of the alcohol

Table 5. Synthesis of aromatic urethanes.

Amine	Catalyst	Amount of the catalyst per mole of amine (%)	T/°C	Time /h	Conversion (%)	Selectivity (%) [a]
$PhNH_2$	Zn diethylcarbamate	1.0	170	2	⩾99	99
$PhNH_2$	Zn diethylcarbamate	1.5	130	11	96	98
MDA	Zn diethylcarbamate	1.5	160	3	99	63
$PhNH_2$	Cu diisopropylcarbamate	6.6	170	12	98	95

[a] Percentage of the urethane in the product.

co-produced during the reaction. In Table 6, some of the examples of reactions carried out with Zn acetate dihydrate as the catalyst are reported. Diurethanes obtained from MDA, 2,4- and 2,6-diaminotoluene (toluenediamine, TDA) (2,4-TDA : 2,6-TDA = 80 : 20) and polymeric MDA (a mixture of MDA and MDA oligomers) are key intermediates as their cracking can give the corresponding isocyanates: methylenediphenyl diisocyanate (MDI), toluene diisocyanate (TDI) and polymeric MDI that are fundamental raw materials for synthesizing polyurethane, which are widely used in manufacturing elastomer, elastic fibre, synthetic leather, and so forth.

Table 6. Process for the synthesis of aromatic urethanes using $Zn(OAc)_2 \cdot 2\,H_2O$ as a catalyst.

Amine	Amount of the catalyst [a]	T/°C	Time /h	Conversion (%)	Selectivity (%) [b]
MDA	4.0	140	1.5	⩾99	97
TDA	5.4	170	2.0	⩾99	93
Polymeric MDA	4.0	140	1.5	⩾99	96

[a] Mass % relative to amine; [b] percentage of the diurethane in the product.

At present, MDI is still produced in great amounts by the phosgene route. However, this procedure has several drawbacks, which include toxic feedstock, formation of hydrochloric acid as a by-product, and the contamination of the final product with the chloride anion. Nowadays, several phosgene-free routes have been developed. In general, they all consist of three main steps: synthesis of methyl *N*-phenylcarbamate (MPC), condensation of MPC with formaldehyde, and decomposition of the condensation product [reactions (4)–(6)]. The synthesis of MPC has been achieved by reductive carbonylation of nitrobenzene,[71] oxidative carbonylation of aniline [72] and reaction between aniline and alkyl carbonate.[73]

In the first process, only 30% of CO can be utilized effectively, and there exists difficulty in separation of CO and CO_2. In the second process, the formation of water lowers the atom utility of the reactants besides the safety issue due to the usage of oxygen. In addition, both processes require severe reaction conditions, such as high pressure, and a noble metal catalyst, such as palladium or rhodium. On the other hand, the synthesis of MPC from aniline and alkyl carbonates can proceed under mild conditions, and there exist no such problems as in the two above-mentioned processes, so it is a promising process for the manufacture of MDI. Some works have been published about the synthesis of MPC from aniline and DMC using zinc acetate [67] and lead acetate [74] catalysts. In general, metal acetates showed higher catalytic activity, but product separation and recovery of the homogeneous metal acetate catalyst is quite complicated. For the second step MDC was prepared in nitrobenzene as a solvent over $ZnCl_2$ catalyst in high yield and with high selectivity (around 80%).[75] However, MDC has not been separated from the reaction mixture. When zeolites were used as solid acid catalysts to synthesize MDC, MPC conversion was very low (38%).[76] Finally, the decomposition of MDC usually proceeds in the liquid phase over costly catalysts.[77]

Recently, the use of zinc acetate catalysts on different supports has been reported.[78] Supported zinc acetate catalyst on activated charcoal (AC) or α-Al_2O_3 shows good catalytic properties. In particular, the synthesis of MPC using $Zn(OAc)_2$/AC catalyst was very effective (78% yield and 98% selectivity). For the second step, zinc chloride was used as a catalyst and nitrobenzene as a solvent to afford MDC in 90% yield. In the third step, when zinc powder was employed as a catalyst, the yield of MDI was ~87%.

Full processes for the preparation of aromatic isocyanates using DMC were also patented. In particular, recently a patent has been published that claims an integrated process for the production of aromatic isocyanates without phosgene.[79] Successive phases of the process are reported starting form the reaction of the amine (TDA) with DMC to carbamate with zinc acetate dihydrate as a catalyst followed by passivation (removal of the remained catalyst) and gas-phase pyrolysis of the urethane.

Dimethyl carbonate is also used as an efficient methoxycarbonylating agent of alcohols. In general, the reaction of alcohols with DMC gives only transesterification products either under GL-PTC at 180 °C or under batch conditions.[80]

$$ROH + MeOCO_2Me \underset{}{\overset{PEG,\ K_2CO_3}{\rightleftharpoons}} ROCO_2Me + MeOH$$

PEG is poly(ethylene glycol).

At 200 °C, the reaction occurs at the carbonyl atom only. In fact, when octan-1-ol was used in reactions with DMC in the presence of K_2CO_3, no methyl octyl ether was observed, but methyl octyl carbonate and dioctyl carbonate were the only products formed.‡ Methylation of alcohols was reported [81] to occur also in the presence of tertiary amines [4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]-octane (DABCO)]. In this case, however, the catalyst modifies the hard–soft character of the two centres, thus

‡ The reaction of octan-1-ol (9.3 mmol) with DMC (40 ml, the reagent and solvent) in the presence of K_2CO_3 (11 mmol) was carried out in an autoclave at 200 °C.

Table 7. Reaction of phenols with DMC in the presence of K_2CO_3.[81]

Phenol	Conversion (%)	Yield (%)	
		ArOMe	$ArOCO_2Me$
p-$MeOC_6H_4OH$	7.0	23	77
p-MeC_6H_4OH	36.3	39	61
PhOH	27.7	72	28
p-ClC_6H_4OH	62.0	98	2
p-NCC_6H_4OH [a]	100.0	100	0

Note. DMC reflux temperature (90 °C); molar ratio phenol : DMC : K_2CO_3 = 1.0 : 40 : 1.2; conversions after 53 h.
[a] Conversion in the methylated derivative after 30 h was 82%.

allowing the nucleophilic substitution by the alkoxide to occur.

para-Substituted phenols were used in reactions with DMC at its reflux temperature in the presence of K_2CO_3. Under such conditions, the softer phenoxide anions could discriminate between the two centres of DMC and their substituent controlled the reaction outcome.

Table 7 reports the results and clearly shows that phenoxides undergo nucleophilic substitution on either the methyl or the carbonyl group.

$$ArOH + MeOCO_2Me \xrightarrow{K_2CO_3} \begin{cases} \rightarrow ArOMe + CO_2 + MeOH \\ \rightleftharpoons ArOCO_2Me + MeOH \end{cases}$$

The substituent in the aromatic ring clearly influences the reactivity: softer phenoxide anions give S_N2 displacement only, while harder ones allow both $B_{Ac}2$ and $B_{Alk}2$ reactions.

2. Dimethyl carbonate as a methylating agent (substitute of methyl halides and dimethyl sulfate)

In recent years, DMC has emerged as a methylating agent in organic synthesis. Even though its reactivity is lower than those of widely used methyl halides and dimethyl sulfate, it has the great advantage of being less toxic. In particular, DMC has successfully been used for the methylation of arylacetonitriles and methyl arylacetates at the α-position. In fact, the reaction of CH acids (such as arylacetonitriles, arylacetates, aryloxyacetates, sulfones, sulfoxides, and lactones) with DMC is highly selective, as it yields the sole monomethyl derivative.[82–86] Regardless of the high temperature and the great excess of the alkylating agent (DMC is also the solvent of the reactions), at complete conversion of the substrate selectivity for the monomethylated product is often > 99% (Table 8).

Table 8. Monomethylation of several CH acids.

Substrate	*T*/ °C	Product	Conversion (%)	Selectivity (%) [a]
$PhCH_2SO_2Me$	200	$PhCH(Me)SO_2Me$	98	100
$PhOCH_2CO_2H$	200	$PhOCH(Me)CO_2Me$	100	96
$PhCH_2CN$ [b]	180	PhCH(Me)CN	98	99
$PhCH_2CN$ [c]	180	PhCH(Me)CN	100	99.5

[a] Selectivity is defined as the ratio of monomethylated products : (monomethylated product + dimethylated product) (%); [b] GL-PTC; [c] batch process.

$$ArCH_2X + MeOCO_2Me \xrightarrow[180\ ^\circ C]{K_2CO_3} ArCH(Me)X + CO_2 + MeOH$$

X = CN, CO_2Me, SO_2R (R = Alk, Ar).

This reaction has an industrial relevance, since $ArCH(Me)CO_2H$ are well-known anti-inflammatory agents.[82]

The reasons for the selectivity of monomethylation of these compounds are not immediately evident. Isolation of intermediates and a detailed kinetic study showed that the reaction mechanism does not imply a simple nucleophilic substitution (7).[82–86]

$$\begin{array}{l} H \\ | \\ ArC^- \\ | \\ X \end{array} + MeOCO_2Me \not\rightarrow ArCH(Me)X + MeOCO_2^- . \qquad (7)$$

In fact, monomethylation derives from an unusual reaction pathway that involves the reactions of anion **An1** and anion **An2** according to two consecutive nucleophilic displacements: the first one follows a $B_{Ac}2$ mechanism, while the second occurs through a $B_{Alk}2$ mechanism [Eqns (8) and (9), respectively]:

$$\begin{array}{l} H \\ | \\ ArC^- \\ | \\ X \\ \textbf{An1} \end{array} + MeOCO_2Me \xrightarrow{B_{Ac}2} ArCH(CO_2Me)X + MeO^- , \qquad (8)$$

$$\begin{array}{l} CO_2Me \\ | \\ ArC^- \\ | \\ X \\ \textbf{An2} \end{array} + MeOCO_2Me \xrightarrow{B_{Alk}2} ArC(Me)(CO_2Me)X + MeOCO_2^- . \qquad (9)$$

Accordingly, the final product results from a series of consecutive pathways, all of them being very selective.

$$ArCH_2X + B \rightleftharpoons \underset{\textbf{An1}}{ArC^-HX} + BH^+ ,$$

$$\underset{\textbf{An1}}{ArC^-HX} + MeOCO_2Me \rightleftharpoons ArCH(CO_2Me)X + MeO^- ,$$

$$BH^+ + MeO^- \rightleftharpoons MeOH + B ,$$

$$ArCH(CO_2Me)X + B \rightleftharpoons \underset{\textbf{An2}}{ArC^-(CO_2Me)X} + BH^+ ,$$

$$\underset{\textbf{An2}}{ArC^-(CO_2Me)X} + MeOCO_2Me \longrightarrow$$

$$\longrightarrow ArC(Me)(CO_2Me)X + CO_2 + MeO^- ,$$

$$ArC(Me)(CO_2Me)X + MeO^- \rightleftharpoons ArC^-(Me)X + MeOCO_2Me ,$$

$$ArC^-(Me)X + BH^+ \rightleftharpoons ArCH(Me)X + B$$

Overall reaction: $ArCH_2X + MeOCO_2Me \longrightarrow ArCH(Me)X + CO_2 + MeOH$.

In summary, while anion $ArCH^-X$ does not give $ArC(Me)_2X$, also anion $ArC^-(CO_2Me)X$ does not allow the formation of $ArC(CO_2Me)_2X$.

We can assert that anions **An1** and **An2** give different compounds since they have different soft/hard character. The harder nucleophile **An1** attacks only the carbonyl group of DMC [Eqn (8)], while the anion **An2** is a softer nucleophile, thus it selectively produces the methyl derivative [Eqn (9)]. The change in hardness/softness of the anion,

due to the presence of the carboxymethyl group, is enough to significantly alter the reactivity of the DMC molecule.

The combination of the dual electrophilic character of DMC and its reaction products allows two consecutive steps to occur in a selective way in both the reaction sequence and yield: first, the hard–hard reaction occurs and produces only a soft anion; then a soft–soft nucleophilic displacement leads to the final product. Since hard–soft and soft–hard interactions are inhibited, neither double methylation, nor double methoxycarbonylation take place.

Dimethyl carbonate can also be used for the methylation of thiols.

$$RSH \xrightarrow{DMC} RSMe + CO_2 + MeOH.$$

In particular, when aliphatic and aromatic thiols reacted with DMC under comparable conditions, they produced only the methylated derivatives (Table 9). Benzenethiol was able to react in the absence of a base as well giving thioanisole. To rule completely out $RSCO_2Me$ as a possible intermediate in the reaction, n-$C_8H_{17}SCO_2Me$ was refluxed with DMC in the absence of potassium carbonate: no reaction was observed after 24 h, showing that $RSCO_2Me$ is not an intermediate in methylation reactions with thiolates.

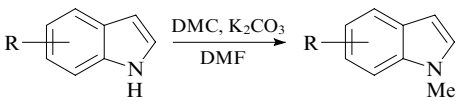
Table 9. Reactions of thiols with DMC in the presence and absence of K_2CO_3.[a]

Thiol	Base	Time /h	RSMe (%)
PhSH		1	27
PhSH	K_2CO_3	4	100
n-$C_8H_{17}SH$	K_2CO_3	24	34

[a] DMC reflux temperature (90 °C); molar ratio thiol : DMC : K_2CO_3 = 1.0 : 40 : 1.2.

It is well established that the RO^- and RS^- anions behave in an opposite way with electrophilic centres during nucleophilic substitutions.[87] Thus, the reaction of octan-1-ol with DMC affords only n-$C_8H_{17}OCO_2Me$ (65%). Under all of the investigated conditions, alkoxides show a $B_{Ac}2$ reaction mechanism, differently from thiolates, which react *via* a $B_{Alk}2$ type due to hardness of the O-nucleophile and softness of the S-nucleophile.

DMC has been also used for high-yielding methylation of indoles. N-Methylation of indoles with methyl iodide[88,89] and dimethyl sulfate[90] in the presence of a variety of bases, such as $NaNH_2$,[91] NaH,[92] KOH,[93] and NaOH,[93] is a classical method to form *N*-methylated indole derivatives. However, the use of this method for large-scale manufacturing has several disadvantages. Methyl iodide has a very low boiling point (40 °C), causing air emission problems, and it is a suspected carcinogen.[94] Dimethyl sulfate is also highly toxic. In addition, the by-products generated by these methylating agents can cause waste disposal problems. Methylation with DMC has been found to be a practical method to prepare *N*-methylated indole analogues in high yields and purity.[95]



This process provides a high selectivity of N-methylation over C-methylation of activated methylene compounds. This method also provides an efficient way to one-pot synthesis of methyl *N*-methylindolecarboxylate (N- and O-dimethylation) from indolecarboxylic acid.

This process was used in a ~1300-litre reactor train for N-methylation of 6-nitroindole (Table 10). Besides using the same approach, indoline and aniline were also methylated with DMC in high yield (> 90%). However, longer reaction time was required for indoline (9 h). For aniline, 20 h was required even in the presence of a phase-transfer catalyst (18-crown-6).

Table 10. N-Methylation of 6-nitroindole with DMC.

Molar ratio DMC : 6-nitroindole	Time /h	Yield (%)
0.8	8.0	50.0
1.1	3.0	96.5
1.6	2.5	96.7
2.0	2.0	95.8
2.2	1.5	96.4

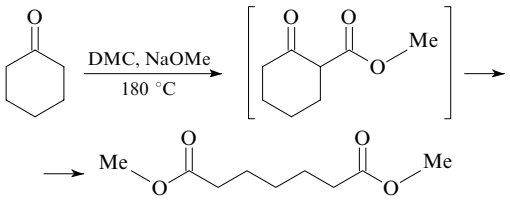
3. Reactions of dimethyl carbonate with ambident nucleophiles

Ambident nucleophiles are considered to be neutral molecules or anions containing two different nucleophilic centres.

In the literature, there are reactions of DMC with what would be considered ambident nucleophiles. For instance, indole is an ambident nucleophile. Using various organic chemistry procedures, reactions can either occur at the nitrogen or the carbon atom 3.[96,97] Thus it was possible to perform N-methylation selectively using DABCO as a catalyst in contrast to other systems (4-dimethylaminopyridine, 1,8-diazabicylo[5.4.0]undec-7-ene) that effected methoxycarbonylation at the same nucleophilic centre.[98]

X = Me or CO_2Me.

In addition, cyclic ketones successfully reacted with DMC to produce acyclic diesters upon methoxycarbonylation at the alpha carbon.[99]



In these examples, however, the ambidenticity of these systems toward DMC has not been shown. Only activation of one of the two centres has occurred.

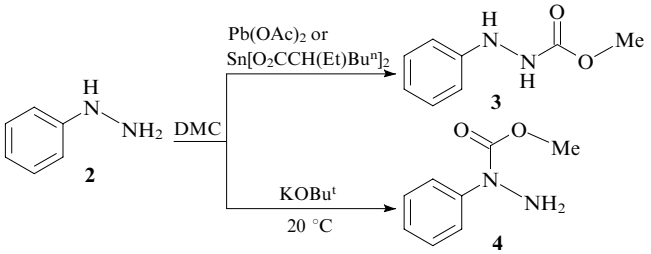
Lately, some investigations have been conducted regarding the reaction of yet another ambident nucleophile phenylhydrazine (**2**) with DMC.[100,101] Phenylhydrazine contains two non-equivalent nitrogen nucleophilic centres:

Table 11. Reaction of phenylhydrazine with DMC.[100]

Product	Base or catalyst	Quantity of base or catalyst /equiv.	Conditions	Time	Isolated yield (%)
3	$Pb(OAc)_2$	1	reflux	18 h	76
3	$Pb(OAc)_2$	0.2	"	20 h	70
3	$Sn[O_2CCH(Et)Bu^n]_2$	0.2	"	25 h 45 min	58
4	$KOBu^t$	1	room temperature	25 min	85
6	$KOBu^t$	1	reflux (removal of MeOH)	3 h 10 min	95
7	NaOMe	4	reflux with 3 equiv. NaOMe, then 1 equiv. of NaOMe and MeOH, reflux	5 h 40 min 3 h 30 min	79

that of the NH group [N(1)] is relatively more acidic due to the electron-withdrawing effect of the phenyl substituent, while the nitrogen atom of the NH_2 group [N(2)] possesses reactivity similar to that of an aliphatic amine.

Both of these centres were selectively carboxymethylated (hard–hard reaction). Classical metal catalysts such as $Pb(OAc)_2$ or $Sn[O_2CCH(Et)Bu^n]_2$ effected N(2) activation in refluxing DMC resulting in product **3**, whilst potassium *tert*-butoxide activated the centre N(1) at room temperature to yield compound **4** (Table 11).



It was reasoned that the reaction with a strong base was due to the deprotonation of N(1) creating an anion with hard nucleophilicity.[102, 103]

Under more forcing conditions using a base, cascade reactions involving methoxycarbonylation, methylation and methanolysis were observed (Scheme 1). The importance of the connectivity of the nitrogens to each other was shown. Thus second methoxycarbonylation occurred at N(2) due to the added electron-withdrawing carboxyl moiety at N(1), presumably lowering the pK_a of N(2). Consequently, N(2) of product **5** underwent methylation. Possessing a carboxyl moiety, electronic stabilization of N(2) makes it a soft nucleophilic centre. As a result, fully substituted hydrazine derivative **6** is obtained.

Methanol produced in the reaction also became a factor as it reacted with the fully substituted hydrazine compound **6**. Methanolysis tended to occur mainly at N(1). This allowed for selective production of either **6** or **7** by adding or removing methanol respectively, facilitating or circumventing the methanolysis process.

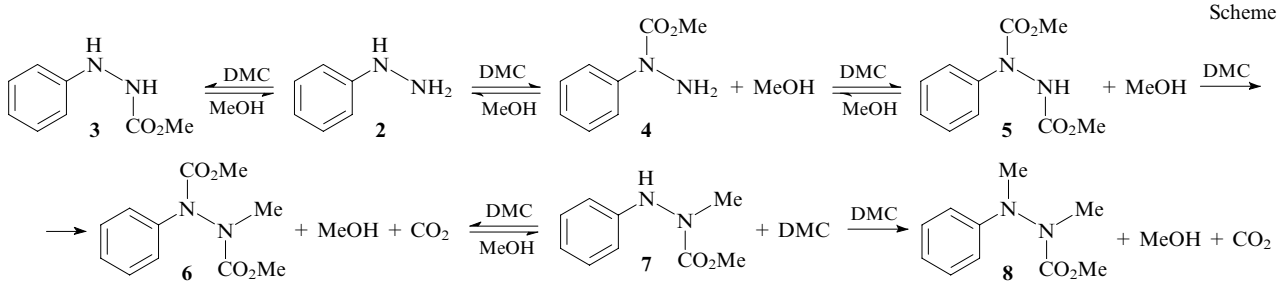
Once **7** was produced, N(1) was available to nucleophilic attack on DMC once more. Notably, both methylation and methoxycarbonylation occurred thereafter, signifying that N(1) of **7** possesses both soft and hard character. This was presumably attributable to both electron-donating and electron-withdrawing substitutents attached to the two nitrogen atoms.

Recently the reactions of DMC with several ambident nuclephiles such as *o*- and *p*-sulfanylphenols, *o*- and *p*-sulfanylbenzoic acids, *o*- and *p*-hydroxybenzoic acids, mandelic and phenyllactic acids in the presence of NaY faujasite under batch conditions have been investigated.[104] Highly chemoselective reactions can be performed at 150 °C. In the presence of catalytic amount of NaY faujasite, both sulfanylphenols and sulfanylbenzoic acids undergo only S-methylation reaction without affecting OH and CO_2H groups. Furthermore, at 165 °C, carboxylic acids bearing OH substituents form the corresponding methyl esters, while both their aromatic and aliphatic OH substituents are fully preserved from methylation and/or transesterification processes (Scheme 2).

Typical selectivities are of 90%–98% and isolated yields of products (*S*-methyl derivatives and methyl esters, respectively) are in the range of 85%–96% (Table 12). A comparative study of NaY faujasite and K_2CO_3 as catalysts was also reported. Although the base (K_2CO_3) turns out to be more active than the zeolite, the chemoselectivity is elusive.

K_2CO_3 and NaY allow a comparable selectivity only in the case of sulfanylphenols, where (methylsulfanyl)phenols are the only products in ~90% yields. The amphoteric nature of zeolite NaY suggests that two major points should account for such results: (i) the electrophilic activation of DMC over NaY and (ii) a possible nucleophilic activation that may take place through H-bonds with basic oxygen atoms of the framework of the aluminosilicate. Overall, the

Scheme 1



2 and **4** are hard nucleophiles, **5** is a soft nucleophile.

Scheme 2

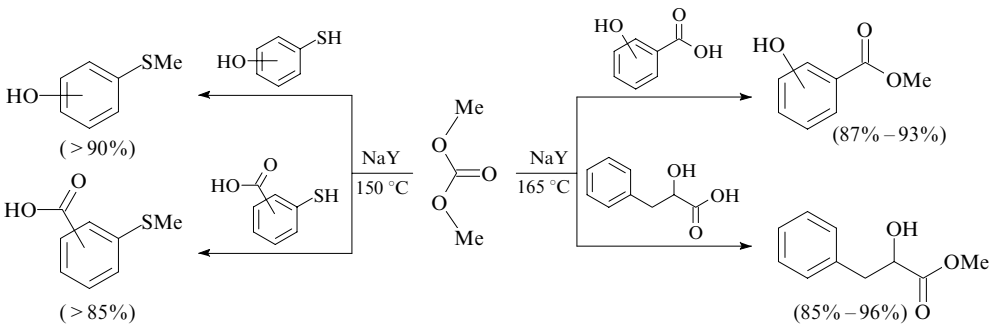


Table 12. Reaction of sulfanylphenols and sulfanyl- and hedroxybenzoic acids with DMC.[a]

Substrate[b]	Time /h	T/°C	Conversion (%)	Products[c]	
HO SH	13	150	100	HO SMe (94)	MeO SMe (0)
HO–SH	13	150	99	HO–SMe (90)	MeO–SMe (1)
HO_2C SH	15	150	93	HO_2C SMe (90)	MeO_2C SMe (2)
HO_2C–SH	26	150	100	HO_2C–SMe (90)	MeO_2C–SMe (10)
HO_2C–OH	24	165	100	MeO_2C–OH (100)	MeO_2C–OMe (0)
HO_2C OH	15	165	100	MeO_2C OH (98)	MeO_2C OMe (0)

[a] All reactions showed also the formation of small amount of disulfides; [b] the ratio NaY : substrate = 3 (mass %); [c] the product yields (in parentheses) are determined by GC (%).

combined use of a nontoxic reagent/solvent (DMC) and a safe promoter (NaY) imparts a genuine eco-friendly nature to the investigated synthesis.

IV. Conclusions

Since the 1960, Green Chemistry has fast gained more and more importance in organic synthesis leading to a new 'generation' of reactions that avoid the use of toxic and dangerous chemicals waste, use eco-compatible solvents, are more atom efficient, produce compounds that perform better or as well as the existing ones but that are biodegradable (renewable) and reduce energy requirements.

Dimethyl carbonate, as a 'green' solvent and reagent, incorporates several of these fundamental aspects of Green chemistry. In fact, since the mid-1980s it is synthesized by a green process using CO_2 as a building block. Dimethyl carbonate reacts selectively with a great variety of compounds as a methylating or carboxymethylating reagent, it requires only catalytic amount of a base and produces no waste (high atom economy). Several studies reported in this review show that DMC can also be used to control the selectivity of the methylation and/or methoxycarbonylation reaction both on simple (amines, alcohols, thiols, *etc.*) and more complex nucleophiles (hydrazines, sugars, amino acids, *etc.*). As a result, several industrial procedures already use DMC as a reagent (or a solvent) and many others are under investigation.

Ultimately, it must be stated that the exploitation of eco-sustainable reagents, such as DMC, is a fundamental issue for our ever-evolving society, since this will pave the way to a 'greener' future for the next generations.

References

1. P Tundo, A Perosa, F Zecchini *Methods and Reagents for Green Chemistry: An Introduction* (Hoboken, NJ: Wiley, 2007)
2. R A Sheldon *Pure Appl. Chem.* **72** 1233 (2000)
3. B M Trost *Science* **254** 1471 (1991)

4. P T Anastas, T Williamson, in *Green Chemistry: Designing Chemistry for the Environment (ACS Symp. Ser.)* Vol. 626 (Eds P T Anastas, T Williamson) (Washington, DC: American Chemical Society, 1996) p. 1
5. P Anastas, D Black, J Breen, T Collins, S Memoli, J Miyamoto, M Polyakoff, W Tumas *Pure Appl. Chem.* **72** 1207 (2000)
6. D Delledonne, F Rivetti, U Romano *Appl. Catal., A* **221** 241 (2001)
7. M A Pacheco, C L Marshall *Energy Fuels* **11** 2 (1997)
8. X C Lu, J G Yang, W G Zhang, Z Huang *Energy Fuels* **19** 1879 (2005)
9. US P. 4318862 (1982)
10. D Delledonne, F Rivetti, U Romano *J. Organomet. Chem.* **C15** 448 (1995)
11. F Rivetti, U Romano, D Delledonne, in *Green Chemistry: Designing Chemistry for the Environment (ACS Symp. Ser.)* Vol. 626 (Eds P T Anastas, T Williamson) (Washington, DC: American Chemical Society, 1996) p. 70
12. Eur. P. 425197 (1991)
13. C S Chin, D Shin, G Won, J Ryu, H S Kim, B G Lee *J. Mol. Catal. A: Chem.* **160** 315 (2000)
14. V Raab, M Merz, J Sundermeyer *J. Mol. Catal. A: Chem.* **175** 51 (2001)
15. J C Hu, Y Cao, P Yang, J F Deng, K N Fan *J. Mol. Catal. A: Chem.* **185** 1 (2002)
16. W L Mo, H Xiong, T Li, X C Guo, G X Li *J. Mol. Catal. A: Chem.* **247** 227 (2006)
17. W L Mo, H T Liu, H Xiong, M Li, G X Li *Appl. Catal., A* **333** 172 (2007)
18. S Yasushi, K Masahiro, S Yoshie *J. Mol. Catal. A: Chem.* **151** 79 (2000)
19. Y H Zhang, D N Briggs, E Smit, A T Bell *J. Catal.* **251** 443 (2007)
20. D Zhu, F Mei, L Chen, T Li, W Mo, G Li *Energy Fuels* **23** 2359 (2009)
21. *The Merck Index* (11th Ed.) (Ed. S Budavari) (Ralway, NJ: Merck and Co. Inc., 1989)
22. M Wang, H Wang, N Zhao, W Wei, Y Sun *Ind. Eng. Chem. Res.* **46** 2683 (2007)
23. P Anastas, J C Warner *Green Chemistry: Theory and Practice* (New York: Oxford University Press, 1998) p. 30
24. F Rivetti, in *Green Chemistry: Challenging Perspectives* (Eds P Tundo, P Anastas) (Oxford: Oxford University Press, 2000) p. 201
25. P Tundo, in *Continuous Flow Methods in Organic Synthesis* (Chichester: Horwood, 1991) p. 190
26. Eur. P. 0570071 (1993)
27. P Tundo, M Selva, A Bomben *Org. Synth.* **76** 169 (1999)
28. P Tundo, M Selva *Acc. Chem. Res.* **35** 706 (2002)
29. P Tundo *J. Org. Chem.* **44** 2048 (1979)
30. P Tundo, M Selva *Chem. Tech.* **25** 31 (1995)
31. A Bomben, M Selva, P Tundo, L Valli *Ind. Eng. Chem. Res.* **38** 2075 (1999)
32. P Tundo, M Selva, A Perosa, S Memoli *J. Org. Chem.* **67** 1071 (2002)
33. R G Pearson *J. Am. Chem. Soc.* **85** 3533 (1963)
34. R G Pearson, J Songstad *J. Am. Chem. Soc.* **89** 1827 (1967)
35. J L Gazquez, F J Mendez *J. Phys. Chem.* **98** 4591 (1994)
36. G Klopman *Chemical Reactivity and Reaction Paths* (New York: Wiley, 1974)
37. G Klopman *J. Am. Chem. Soc.* **90** 223 (1968)
38. H Tse-Lok *Chem. Rev.* **75** 1 (1975)
39. T L Gresham, J E Jansen, F W Shaver, J T Gregory, W L Beears *J. Am. Chem. Soc.* **70** 1004 (1948)
40. T L Gresham, J E Jansen, F W Shaver, M R Frederick, F T Fiedorek, R A Bankert, J T Gregory, W L Beears *J. Am. Chem. Soc.* **74** 1323 (1952)
41. T L Gresham, J E Jansen, F W Shaver, J T Gregory *J. Am. Chem. Soc.* **70** 999 (1948)
42. T L Gresham, J E Jansen, F W Shaver, R A Bankert *J. Am. Chem. Soc.* **71** 661 (1949)
43. R S Davidson, W H H Gunther, S M Waddington-Feather, B Lythgoe *J. Chem. Soc.* 4907 (1964)
44. D E L Carrington, K Clarke, R M Scrowston *J. Chem. Soc. C* 3262 (1971)
45. A C Pierce, M M Joulliè *J. Org. Chem.* **27** 3968 (1962)
46. F G Bordwell, in *Organic Chemistry* (New York: Macmillan, 1963) p. 218
47. A J Parke *Adv. Phys. Org. Chem.* **5** 173 (1967)
48. R F Hudson, G Klopman *J. Chem. Soc.* 5 (1964)
49. W Tai-Teh, J Huang, N Arrington, G Dill *J. Agric. Food Chem.* **35** 817 (1987)
50. US P. 4514339 (1985)
51. T Kato, K Suzuki, J Takahashi, K Kamoshita *J. Pesticide Sci.* **9** 489 (1984)
52. M Aresta, E Quaranta *Chem. Tech.* **27** 32 (1997)
53. T Greene, P Wuts *Protective Groups in Organic Synthesis* (3rd Ed.) (New York: Wiley, 1999)
54. H Babad, A Zieler *Chem. Rev.* **73** 75 (1973)
55. H Eckert, B Foster *Angew. Chem., Int. Ed. Engl.* **26** 894 (1987)
56. L Costarca, P Delogu, A Nardelli, V Sunjic *Synthesis* 533 (1996)
57. M Aresta, P Giannoccaro, I Tommasi *J. Organomet. Chem.* **476** 13 (1994)
58. V Valli, H Alper *J. Org. Chem.* **60** 257 (1995)
59. D Butler, H Alper *Chem. Commun.* 2575 (1998)
60. M Yoshida, N Hara, S Okuyama *Chem. Commun.* 151 (2000)
61. J F Bunnett, G T Davis *J. Am. Chem. Soc.* **82** 665 (1960)
62. W P Jencks, J Carriuolo *J. Am. Chem. Soc.* **82** 675 (1960)
63. P Tundo, L Rossi, A Loris *J. Org. Chem.* **70** 2219 (2005)
64. P Tundo, S Bressanello, A Loris, G Sathicq *Pure Appl. Chem.* **77** 1719 (2005)
65. F Trotta, P Tundo, G Moraglio *J. Org. Chem.* **52** 1300 (1987)
66. Eur. P. 483171 (1981)
67. US P. 4268683 (1981)
68. US P. 4268684 (1981)
69. US P. 5698731 (1997)
70. Eur. P. 0881213 (1998)
71. Eur. P. 029460 (1980)
72. Jpn. P. 59-172451 (1984)
73. WO 88/05430 (1988)
74. Z H Fu, Y Ono *J. Mol. Catal.* **91** 399 (1994)
75. Eur. P. 0410684 (1992)
76. US P. 5241119 (1993)
77. US P. 4388246 (1983)
78. X Zhao, Y Wang, S Wang, H Yang, J Zhang *Ind. Eng. Chem. Res.* **41** 5139 (2002)
79. US P. 6992214 (2006)
80. P Tundo, F Trotta, G Moraglio, F Logorati *Ind. Eng. Chem. Res.* **27** 1565(1988)
81. US P. 4770871 (1989)
82. M Selva, C A Marques, P Tundo *J. Chem. Soc., Perkin Trans. 1* 1323 (1994)
83. US P. 5278533 (1994)
84. A Bomben, C A Marques, M Selva, P Tundo *Tetrahedron* **51** 11573 (1995)
85. A Bomben, M Selva, P Tundo *J. Chem. Res. (S)* 448 (1997)
86. Ital. P. 20159A/90C (1990)
87. S Rahmathullah, J E Hall, B C Bender, D R McCurdy, R R Tidwell, D W Boykin *J. Med. Chem.* **42** 3994 (1999)
88. M G Reineeke, J F Sebastian, H W Johnson Jr, C Pyun *J. Org. Chem.* **37** 3066 (1972)
89. S Nunomoto, Y Kawakami, Y Yamashita, H Takeuchi, S Eguchi *J. Chem. Soc., Perkin Trans. 1* 111 (1990)
90. R S Stauton, A Topham *J. Chem. Soc.* 1889 (1953)
91. K T Potts, J E Saxton, in *Organic Syntheses* Vol. IV (New York: Wiley, 1973) p. 769
92. G Buchi, C P Mak *J. Org. Chem.* **42** 1784 (1977)
93. O Ottoni, R Cruz, R Alves *Tetrahedron* **54** 13915 (1998)
94. M Lissel, A R Rohani-Dezfuli, G J Vogt *J. Chem. Res. (S)* 312 (1989)
95. X Jiang, A Tiwari, M Thompson, Z Chen, T P Cleary, T B K Lee *Org. Process Res. Dev.* **5** 604 (2001)
96. J Bergman, L Venemalm *J. Org. Chem.* **57** 2495 (1992)
97. H Heaney, S V Ley *Org. Synth.* **54** 58 (1974)

98. W-C Shieh, S Dell, A Bach, O Repic, T J Blacklock *J. Org. Chem.* **68** 1954 (2003)
99. M Selva, C A Marques, P Tundo *Gazz. Chim. Ital.* **123** 515 (1993)
100. A E Rosamilia, F Aricó, P Tundo *J. Org. Chem.* **73** 1559 (2008)
101. A E Rosamilia, F Aricó, P Tundo *J. Phys. Chem. B* **112** 14525 (2008)
102. W N Olmstead, Z Margolin, F G Bordwell *J. Org. Chem.* **45** 3295 (1980)
103. Y Zhao, F G Bordwell, J-P Cheng, D Wang *J. Am. Chem. Soc.* **119** 9125 (1997)
104. M Selva, P Tundo *J. Org. Chem.* **71** 1465 (2006)