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A green metrics assessment of phosgene and phosgene-free syntheses of industrially important commodity chemicals*

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Abstract: Synthesis plans for the following important industrial commodity chemicals using phosgene and phosgene-free chemistries have been analyzed and compared by green metrics to determine the most material-efficient routes so far developed (number of plans given in parentheses): dimethyl carbonate (DMC) (31), diphenyl carbonate (DPC) (40), diphenylurea (DPU) (23), methyl carbamate (MC) (8), methyl chloroformate (MCF) (6), methyl *N*-phenylcarbamate (MNPC) (25), methyl phenyl carbonate (MPC) (32), phenyl isocyanate (PI) (19), phenyl chloroformate (PCF) (10), and urea (13). Implications of these results are discussed.

Keywords: atom economy; carbamates; catalysis; chloroformates; dimethyl carbonate; E-factor; green metrics; isocyanates; optimization; phosgene; phosgene-free; reaction networks; synthesis strategy; ureas.

INTRODUCTION

Since its accidental discovery by John Davy, brother of the famous Sir Humphry Davy, nearly two centuries ago in 1812 [1], phosgene (carbonic acid dichloride, carbon oxychloride, carbonyl chloride) has been a cornerstone industrial commodity chemical used to synthesize other valuable chemical intermediates and end-products such as poly- and cyclic carbonates, isocyanates, diisocyanates, carbamoyl chlorides, chloroformate esters, and ureas [2–4]. In organic synthetic methodology, phosgene is a powerfully useful reagent for inserting the carbonyl functionality owing to its highly electrophilic center, which is susceptible to nucleophilic attack by species such as alcohols and amines. A survey of an extensive synthesis database [5] shows that it has been used to make various agrichemicals, dyestuffs, pharmaceuticals, and natural products: carbaryl [6], indoxacarb [7,8], crystal violet [9,10], indigo [11], Mischler's ketone [10], Schollköpf's reagent [12] in the synthesis of sitagliptin [13], suramin [14–16], cephalosporin C [17,18], (2*S*,4*R*)-hypoglycin A [19,20], (+)-longifolene [21,22], (+)-lysergic acid [23], (+)-paclitaxel [24–32], strychnine [33,34], (–)-vindoline [35,36], vitamin A [37,38], (±)-welwitindoline A [39,40], and biotin [41–58]. Other key chemical advantages for phosgenation reactions are that they are rapid and they generate desired products in high yields with no side reactions. Because phosgene is a gas, it is easy to separate from liquid or solid products. However, consistent with chemistry as a science of compromise, these advantages are outweighed by the high toxicity, hazards, and safety precautions associated with using this reagent [4]. More serious than these drawbacks is its notorious legacy as a chemical warfare agent in World War I (1914–1918) [59], known under the name White Star or the military code CG. It is claimed to have been responsible for at least 80 % of the deaths caused by chem-

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ical weapons in that conflict though other sources suggest that it was mustard gas [60–66]. Consequently, phosgene is now listed as a highly regulated substance in Schedule 3 of the Chemical Weapons Convention (CWC) approved in 1992 and ratified in 1997 by 188 countries [67–69]. Its manufacture, use, and distribution are tightly controlled. Any chemical plant producing this substance in excess of 30 metric tonnes per year must declare who they are, including the precise latitude and longitude coordinates of the plant site, the purpose of its manufacture, and also submit themselves to inspection at any time. Owing to its safety risks and restrictive trade, phosgene is typically made and used on site.

In order to circumvent the toxicity and hazard issues with phosgene, the liquid diphosgene (trichloromethyl chloroformate, TCF) [70–79] and solid triphosgene [bis(trichloromethyl)carbonate, BTC] [80–90] were the first-generation alternatives advanced as substitutes. These compounds are made by photochlorination of methyl chloroformate (MCF) [77] and dimethyl carbonate (DMC) [82,83], respectively. However, owing to the stigma and fear associated with the phosgene name, organic chemists only began using them in the 1970s well after their initial discoveries in 1887 and 1880, respectively. Representative examples of synthesis plans taken from the above-mentioned synthesis database [5] that have used these reagents include: *N*,*N*′-diethyl-*m*-toluamide (DEET) [91], (–)-epibatidine [92], (–)-paclitaxel [93–95], (±)-physostigmine [96], and thienamycin [97,98]. The combined modern concerns about national security and environmental stewardship and sustainability have further moved the chemical industry as a whole to seek nonchlorinated alternative reagents to manufacture the same chemical commodity products that were once made with phosgene. In this vein, DMC has gained considerable attention as an alternative under the green chemistry rubric and has been extensively discussed in the literature [99–108]. Though DMC satisfies a better safety and hazard profile it is far less reactive than phosgene, and, therefore, reactions in which it is used as a reagent require a catalyst to improve reaction performance. These catalysts are usually mineral substances such as zeolites or metal salts, which themselves require preparation from other precursors via calcination, a process that is energy-demanding because precatalysts need to be heated at elevated temperatures, typically 500 °C. Also, the possibility that reactions are reversible is much higher. Again, this is another compromise situation where kinetic and thermodynamic factors need to be overcome, but it is better than the former one. Table 1 summarizes various physical and toxicity properties for phosgene, diphosgene, triphosgene, and DMC.

Table 1 Summary of physical and toxicity properties of phosgene, diphosgene, triphosgene, and DMC.

Parameter	Phosgene	Diphosgene	Triphosgene	DMC
Formula	$COCl_2$	$C_2O_2Cl_4$	$C_3O_3Cl_6$	$C_2H_6O_3$
CAS number	[75-44-5]	[503-38-8]	[32315-10-9]	[616-38-6]
M_W (g/mol)	98.916	197.832	296.748	90.193
Phase at STP[a]	Gas	Liquid	Solid	Liquid
bp (°C)	7.4–8.2	128	203–206	90–91
mp (°C)	–128 to –118	–57	77–83	2–4
Density (g/cm^3)	1.338 (20 °C)	1.664 (15 °C)	1.629 (80 °C)	1.069 (20 °C)
Vapor pressure (mm Hg at 20 °C)	1170–1215	9.8–10.3	0.263 (25 °C)	40 to 42
LC_{50}, rat, inhalation, 4 h (mg/m^3 air)[b,c]	7.2	13.9	41.5	140 000

[a]STP = standard temperature and pressure (20 °C and 1 atm).
[b]See ref. [109] for phosgene, diphosgene, and triphosgene.
[c]See ref. [110] for DMC.

In this work, the specific material efficiency performances of syntheses of DMC, diphenyl carbonate (DPC), diphenylurea (DPU), methyl carbamate (MC), MCF, methyl *N*-phenylcarbamate (MNPC), methyl phenyl carbonate (MPC), phenyl isocyanate (PI), phenyl chloroformate (PCF), and urea were determined using the standard green metrics: percent reaction yield, percent atom economy (AE), and E-factor. For each of these compounds both phosgene- and non-phosgene-based syntheses were examined in order to gauge the progress that has been made in "greening up" their manufacture. All plans are ranked according to E-factor, and best plans are highlighted for each group.

GREEN METRICS ANALYSIS METHODOLOGY

Radial pentagon analysis was used for assessing reaction performance for individual reactions [111] using the relation for reaction mass efficiency (RME) and E-factor given by eq. 1

$$\text{RME} = \varepsilon(\text{AE})(1/\text{SF})(\text{MRP}) = 1/(1 + \text{E}) \tag{1}$$

where ε is the reaction yield with respect to limiting reagent, AE is atom economy, 1/SF is the inverse of the stoichiometric factor, which designates the consumption of excess reagents (SF = 1 means that no excess reagents are used, SF > 1 means that at least one reagent is used in excess), MRP is the material recovery parameter, which designates the consumption of all auxiliary materials other than reactants, and E is the total E-factor, which is the ratio of mass of overall waste to mass of desired product. In turn, the following expressions given by eqs. 2a–d were used to determine the contributions to the total E-factor from by-products, side-products, and unreacted starting materials (E-kernel), excess reagent consumption (E-excess), and auxiliary materials used in work-up and purification operations (E-aux).

$$\text{E-kernel} = [1/\varepsilon(\text{AE})] - 1 \tag{2a}$$

$$\text{E-excess} = [(\text{SF}) - 1] - 1/\varepsilon(\text{AE}) \tag{2b}$$

$$\text{E-aux} = [(\text{SF})/\varepsilon(\text{AE})][1/(\text{MRP}) - 1] \tag{2c}$$

$$\text{E-total} = \text{E-kernel} + \text{E-excess} + \text{E-aux} \tag{2d}$$

In this formalism, waste products designated as by-products are necessarily distinguishable from side-products. By-products arise as a mechanistic consequence of producing the intended target product in a reaction; whereas, side-products arise from an entirely different reaction pathway, and therefore a different mechanism, but beginning from the same set of starting materials. Such a side-reaction competes in parallel to the intended reaction. For syntheses involving more than a single reaction step, the algorithm to work out global E-factors and contributing E-factors described elsewhere was used [112]. In carrying out all of these computations, the best available experimental write-ups were selected from patents and journal articles that covered all of the major reaction routes used by industry to the target molecules. In cases when work-up and purification materials were not disclosed in experimental procedures, assumptions employed by the environmental assessment tool for organic synthesis (EATOS) were used [113–115]. For gaseous reagents, the ideal gas law was applied to determine molar and mass amounts of reagents as appropriate. Studies that dealt with catalyst optimization did not report percent yields per se, but typically reported instead percent conversion of starting materials to products and percent selectivities toward specified products as a function of catalyst type, amount, and other reaction conditions. For these cases, proper reaction yields were determined as the product of these two quantities as appropriate.

A simple tutorial exercise that illustrates nicely the tradeoff between toxicity, hazard, and material efficiency is a comparison of the AEs for the preparation of urea using phosgene, diphosgene, triphosgene, and DMC with ammonia as shown in Fig. 1. Since diphosgene and triphosgene effectively produce two and three molecules of phosgene respectively, AEs for reactions involving these reagents

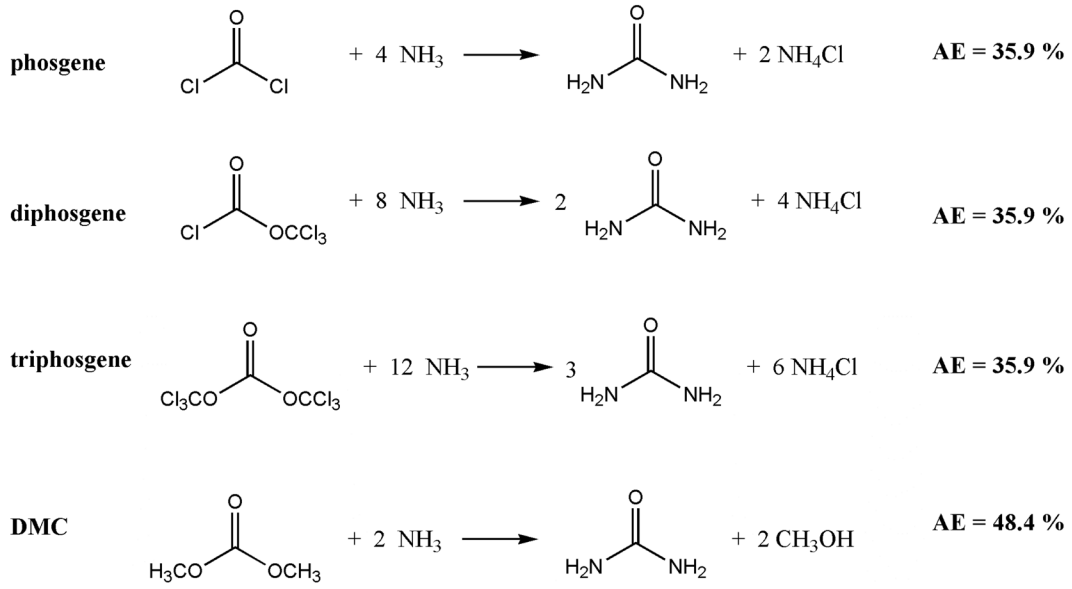

Fig. 1 Comparison of atom economies for production of urea.

are identical to that involving phosgene. Hence, the diphosgene reaction is equivalent to multiplying the parent phosgene reaction by a factor of two; similarly, for the triphosgene reaction the multiplying factor is three. All three reactions produce ammonium chloride as a by-product originating from the secondary neutralization reaction of hydrochloric acid. Reaction with DMC, on the other hand, results in a loss of two molecules of methanol and utilizes the least stoichiometric amount of ammonia, since all the ammonia ends up in the target urea. As an example calculation, the percent AE for the reaction using diphosgene is given by

$$\%\text{AE} = [2M_w(\text{urea})/[M_w(\text{diphosgene}) + 8M_w(\text{ammonia})]*100 = 35.9$$

The safest reagent among the phosgene series results in the same AE as the parent reaction but at the expense of utilizing greater quantities of ammonia; whereas, the safest reagent overall, DMC, results in the highest AE and utilizes the least quantity of ammonia.

A key illustration of the full scope of the material efficiency metrics highlighting the radial pentagon analysis is given in the following synthesis examples for PI and DPC. For each compound, the starting materials compared are phosgene, diphosgene, triphosgene, and DMC. Bottlenecks and advantages for each reaction are readily seen from the shapes of the radial pentagons. Tables 2 and 3 summarize the key metrics and reaction conditions. Figures 2 and 3 show the respective radial pentagons. These examples are the first head-to-head comparisons reported for material green metrics efficiency for such reactions and were selected as the best performers found in the literature for each reaction type.

Table 2 Summary of green metrics for various PI syntheses.

Reagent	% AE	% Yield	E-kernel	E-excess	E-aux	E-total	Comments
Phosgene[a]	52	90	1.1	0.005	7.7	8.8	Starting from aniline hydrochloride salt; reaction solvent is $O{=}PCl_3$; reaction T = 80 °C.
Diphosgene[b]	52	89	1.2	0.05	9.8	11.0	Starting from aniline hydrochloride salt; reaction solvent is 1,4-dioxane; reaction T = 60 °C.
Triphosgene[c]	62	76	1.1	0.001	12.0	13.1	Starting from aniline; reaction solvent is EtOAc; reaction T = 78 °C.
DMC[d]	65	42	2.6	14.9	22.3	39.8	Starting from aniline; 10 times excess DMC used; reaction T = 180 °C; reaction pressure = 1.5 MPa; PbO catalyst prepared by calcinating $PbNO_3$ on alumina at 500 °C; reaction solvent is THF.

[a]See ref. [116].
[b]See ref. [117].
[c]See ref. [118].
[d]See ref. [119].

Table 3 Summary of green metrics for various DPC syntheses.

Reagent	% AE	% Yield	E-kernel	E-excess	E-aux	E-total	Comments
Phosgene[a]	81	96	0.3	0.06	0.02	0.4	Starting from phenol; triphenylphosphite catalyst; reaction T = 170 °C.
Diphosgene[b]	44	94	1.4	0.03	61.1	62.6	Starting from phenol and triethylamine; reaction solvent is THF; reaction T = 67 °C; water work-up.
Triphosgene[c]	58	94	0.8	0.02	3.8	4.6	Starting from phenol and sodium hydroxide; reaction solvent is water; reaction T = room temperature (assumed).
DMC[d]	77	44	2.0	1.3	0.05	3.3	Starting from phenol; 1.2 times excess DMC used; reaction T = 120–180 °C; $Bu_2Sn{=}O$ catalyst.

[a]See ref. [120].
[b]See ref. [121].
[c]See ref. [122].
[d]See ref. [123].

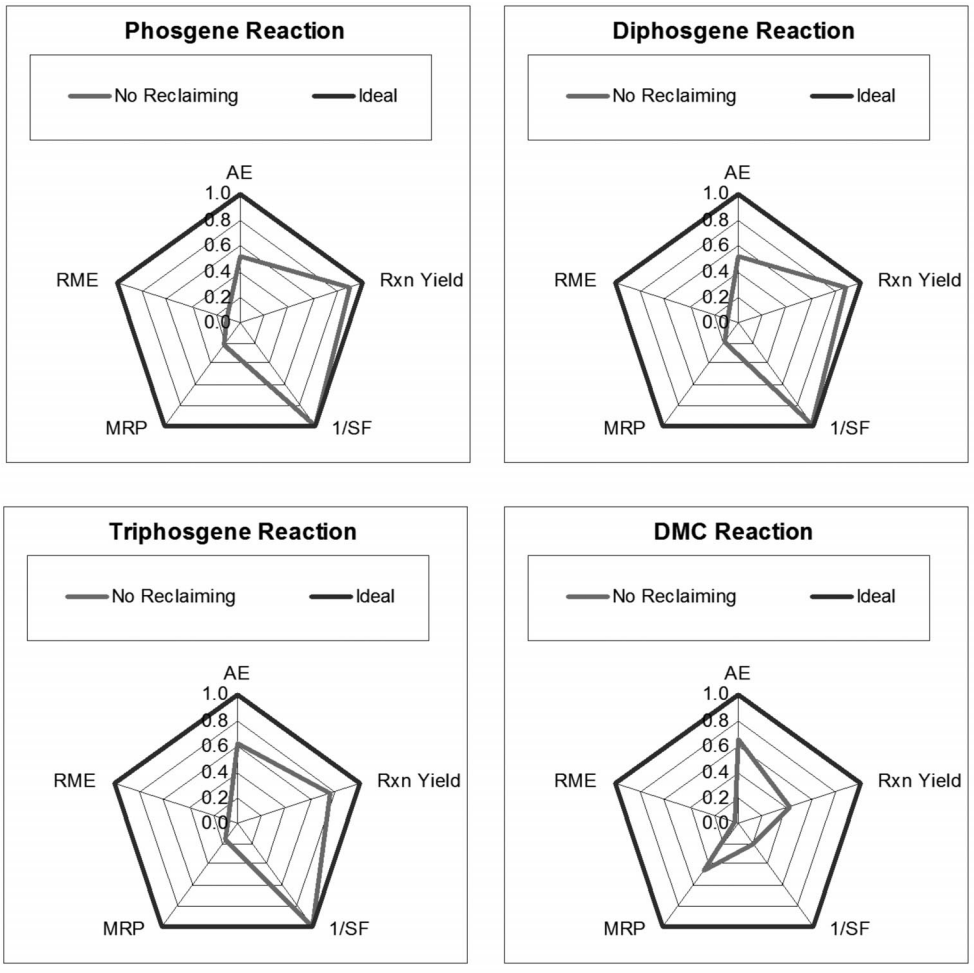

Fig. 2 Radial pentagons for syntheses of PI as given in Table 2.

For the PI syntheses we observe that

- the AEs are roughly the same, the phosgene and diphosgene cases have lower values than the triphosgene case because the latter begins from aniline rather than the hydrochloride salt of aniline;
- the reaction yield performance is best for phosgene and diphosgene;
- all phosgene-based reactions are run essentially under stoichiometric conditions, whereas, significant excess reagent consumption is employed for the DMC case since this is necessary to shift the equilibrium reaction toward product;
- all reactions require reaction solvent;
- the safest DMC reaction has the lowest reaction yield, uses a significant amount of excess reagent, is the only one requiring a catalyst to proceed which needs to be prepared by an energy-demanding calcination process, and has the highest reaction solvent demand; and
- all phosgene reactions have similarly shaped and sized pentagons, whereas the DMC case has the smallest and most distorted pentagon.

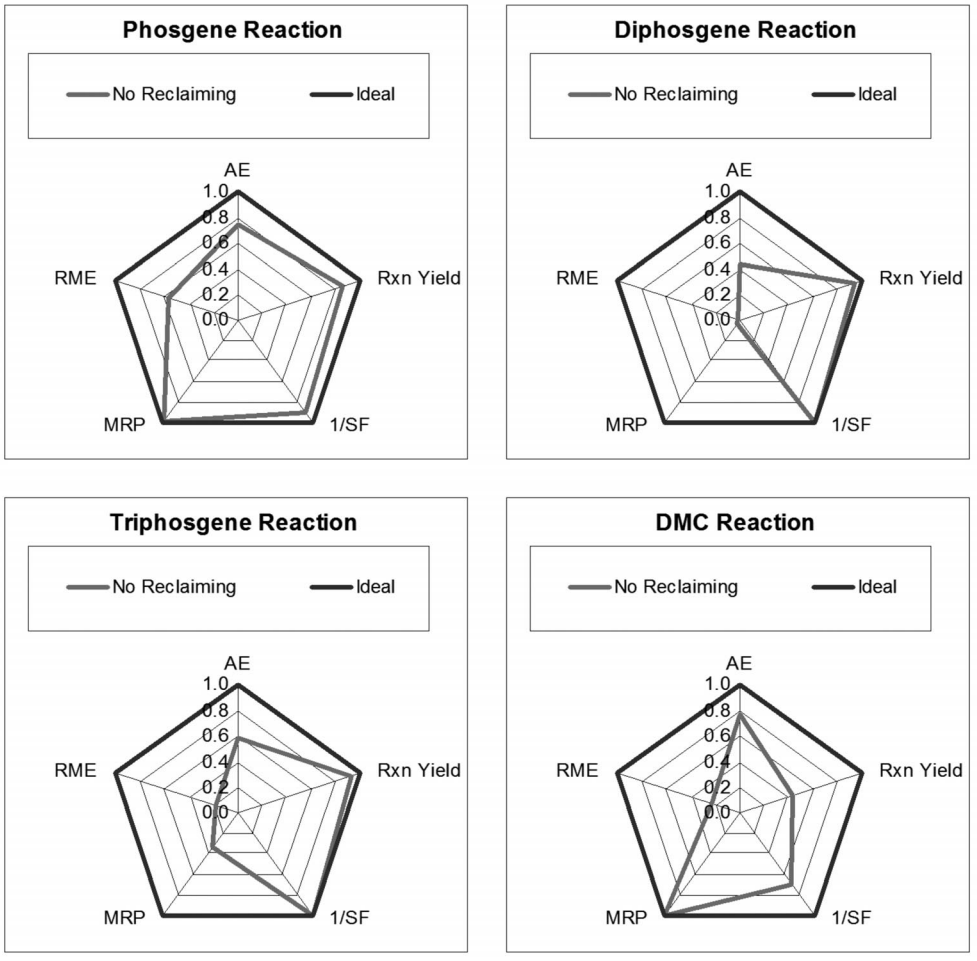

Fig. 3 Radial pentagons for syntheses of DPC as given in Table 3.

From these results it can be concluded that the most hazardous phosgene reaction is clearly the most material-efficient overall on all counts; whereas, the safest DMC reaction is the least material-efficient and likely the most energy-demanding. It can be argued that the excess DMC need not be destined for waste and therefore can be recovered and reused for further reaction with more aniline over several cycles until it is completely converted to PI product. The hope is that the catalyst will not need replacing and its turnover performance will not change significantly over the iterative reaction cycles. It should be noted that the excess DMC used also functions as a reaction solvent in this transformation.

For the DPC syntheses we observe that

- the radial pentagons show more variation in size and shape than in the PI cases;
- the phosgene and DMC cases have the highest AEs while the diphosgene and triphosgene cases have lower values because the latter pair involves bases as co-reagents whereas the former pair does not;
- again, the phosgene-based reactions have significantly higher yields than the DMC reaction;
- again, the phosgene-based reactions are run under stoichiometric conditions unlike DMC;
- the diphosgene case is unusually high in its solvent demand due to both reaction and work-up solvent usage, the phosgene and DMC reactions have almost no auxiliary solvent demand;

- the DMC excess reagent consumption is higher than the phosgene-based reactions but not to the same degree as for the PI examples; and
- the phosgene reaction has the largest radial pentagon, the diphosgene and triphosgene ones are similarly sized and shaped, and the DMC pentagon again shows the most distortion.

From these results, we can conclude once again that the most hazardous phosgene reaction is the clear winner for material efficiency on all counts; however, the safest DMC reaction performance comes in at second place slightly ahead of the triphosgene case. The diphosgene case is unusual in its high solvent demand, thus making it the worst all-round performer. In both examples, the tension in "greenness" performance between safety and toxicity vs. material efficiency vs. energy efficiency is clearly demonstrated.

SYNTHESIS PLANS TO INDUSTRIAL TARGETS

Green metrics material efficiency results for syntheses of DMC, DPC, DPU, MC, MCF, MNPC, MPC, PCF, PI, and urea are summarized in Tables 4–13. Schemes shown in Figs. 4–13 show the best-performing reactions for each reaction type. In each case, chemical equations are fully balanced, showing by-products produced and catalysts used. E-factors are given as well as the identities of the chemical companies or academic authors. Reactions in tables and schemes are listed in ascending order of E-factor. Reaction schemes involving phosgene are denoted with a boxed structural diagram.

Table 4 Summary of DMC syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Methanol carboxylation; cat = ZrO_2	1.6	83.3	87	124
Trimethylorthoacetate + CO_2; cat = $(MeO)_2SnBu_2$, $[nBu_4P]$+ I -	3.3	54.9	70	125
Methanol + EC transesterification; cat = PPh_3-stryene-divinylbenzene copolymer	4.8	59.2	51	126
Methanol + EC transesterification; cat = smectite (S-Mg-Ni-Na-K)	5.1	59.2	66	127
Methanol oxidative carbonylation; cat = CuCl	5.5	83.3	56	128
Methanol + EC transesterification (continuous method; tube reactor); cat = anion exchange resin	6.0	59.2	90	129
Methanol oxidative carbonylation; cat = CuCl	6.3	83.3	34	130
Methanol + urea; cat = ZnO	6.3	72.6	29	131
Methanol + methyl chloroformate; cat = none	6.4	54.1	79	132
Methanol + EC transesterification; cat = none	7.1	48.4	30	133
Methanol + urea; cat = polyphosphoric acid	8.5	72.6	67	134
Methanol oxidative carbonylation; cat = $PdCl_2(PPh_3)_2$, $Cu(OMe)_2$, $[Me_4N]Cl$	11.3	83.3	25	135
2MeONO + CO reaction; cat = $PdCl_2/CuCl_2$/charcoal	13.2	60.0	66	136
2MeONO + CO reaction; cat = Pd/C	14.1	60.0	39	137
Methanol oxidative carbonylation with $CuSO_4$; cat = LiOMe	16.8	21.9	75	138
Methanol oxidative carbonylation; cat = CuCl	17.1	83.3	95	139
2MeONO + CO reaction; cat = $PdCl_2/CuCl_2$/charcoal	23.4	60.0	31	140
Methanol oxidative carbonylation; cat = CuCl	23.4	83.3	48	141
Methanol + urea; cat = ZnO	29.2	72.6	26	142
Propylene oxide carboxylation - methanol transesterification; cat = KOH, 4A molecular sieves	32.3	54.2	17	143
MPC disproportionation; cat = $Pb(OAc)_2$ $2H_2O$	35.3	16.2	74	144
Methanol oxidative carbonylation with Br_2; cat = none	41.8	35.7	84	145
Methylcarbamate + MeOH: cat = MgO	43.3	84.1	18	146

(*continues on next page*)

Table 4 (*Continued*).

Synthesis methodology	E-factor	% AE	% Yield	Reference
Methanol + urea; cat = zinc stearate	52.0	72.6	29	147
Methanol + urea; cat = $ZnCl_2$-Et_3NHCl	54.3	72.6	26	148
$KHCO_3$ + methylchloride; cat = KBr/[nBu_4P]+ Br -	55.4	44.8	63	149
Methanol oxidative carbonylation; cat = Bpya/$CuCl_2$	69.1	83.3	42	150
Methanol oxidative carbonylation; cat = CuCl	76.0	83.3	29	151
2,2-Dimethoxypropane + CO_2; cat = $(MeO)_2SnBu_2$, 3A molecular sieves	108.6	60.8	30	152
Methanol oxidative carbonylation; cat = CuCl, pyridine	135.0	83.3	11	153
Cu(OMe)(Cl) + CO; cat = none	142.1	24.0	57	154

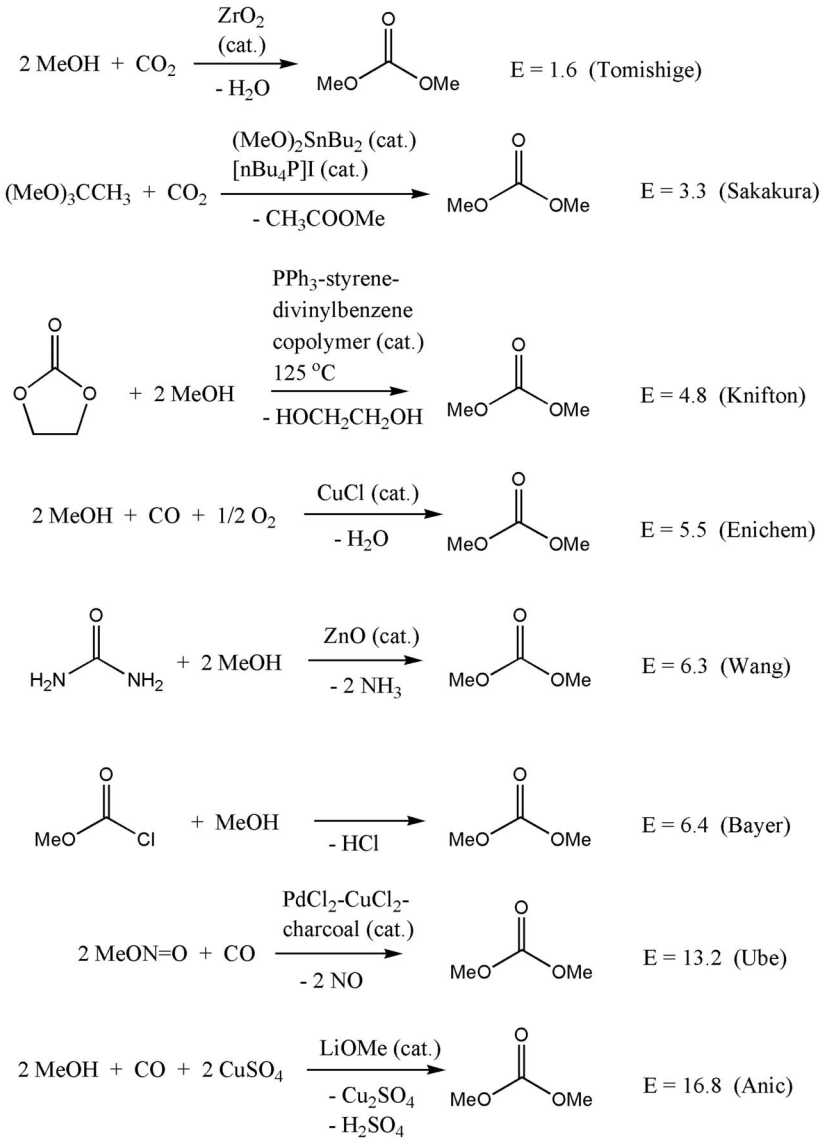

Fig. 4 DMC schemes (*continues on next page*).

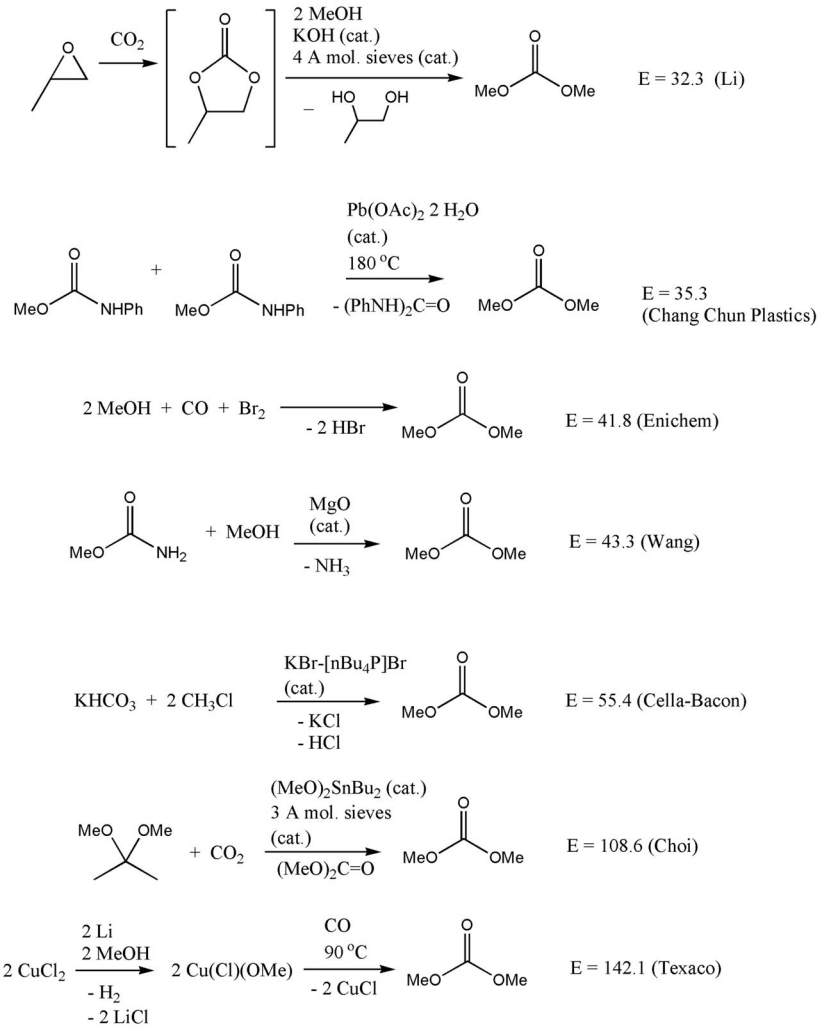

Fig. 4 (*Continued*).

Table 5 Summary of DPC syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Phenol + phenyl chloroformate; cat = Al_2O_3-507-C-I	0.2	85.4	98	155
Phenol + phenyl chloroformate; cat = TiO_2 (rutile)	0.2	85.4	99	156
Phenol + phenyl chloroformate; cat = Pb titanate	0.2	85.4	98	157
Phenol + phenyl chloroformate; cat = hydrotalcite (Mg/Al = 7:3)	0.2	85.4	98	158
Phenol + phenyl chloroformate; cat = ALPO-11	0.4	85.4	90	159
Phenol phosgenation; cat = triphenylphosphite	0.4	81.1	96	120
Phenol phosgenation; cat = imidazole	0.4	74.6	98	160
Phenol phosgenation; cat = pyridine	0.6	74.6	90	161
Phenol phosgenation; cat = triphenylphosphine oxide	0.6	81.1	92	162
Phenol phosgenation; cat = $AlCl_3$	0.7	74.6	81	163
Phenol phosgenation; cat = pyridine	0.7	74.6	88	164
MPC disproportionation; cat = PbO	0.8	70.4	90	165
Phenol phosgenation; cat = triphenylphosphite	0.8	74.6	86	166
Phenol phosgenation; cat = none	2.1	58.3	94	167
Ehenylchloroformate disproportionation; cat = $MgCO_3$	3.1	53.9	98	168
Ethyl phenyl carbonate disproportionation; cat = $Ti(OPh)_4$	3.3	64.5	38	169
Phenol + DMC transesterification; cat = $Bu_2Sn{=}O$	3.3	77.0	44	123
Phenol phosgenation; cat = $AlCl_3$	4.2	74.6	79	170
Phenol + DMC transesterification; cat = $Bu_2Sn{=}O$	4.4	82.6	22	171
Phenol oxidative carbonylation; cat = $PdBr_2$, iPr_2NEt, $Mn(acac)_3$-3A molecular sieves	4.5	92.2	70	172
Phenol + triphosgene + sodium hydroxide; cat = none	4.6	58.3	94	122
Phenol phosgenation; cat = none	4.7	58.3	100	173
Phenol phosgenation; cat = none	4.7	58.3	100	174
Phenol phosgenation; cat = Et_3N	4.8	58.3	97	175
Phenol + diisoamylcarbonate transesterification; cat = $Ti(OPh)_4$	8.9	54.9	19	176
Phenol + $(CF_3CH_2O)_2C{=}O$ transesterification; cat = NaOEt	9.1	51.7	85	177
Phenol phosgenation; cat = $[Me_4N]Cl$	9.8	74.6	80	178
Phenol phosgenation; cat = Et_3N	11.5	58.3	89	179
Phenylchloroformate disproportionation; cat = $MgCl_2$	15.9	68.3	99	180
Phenol oxidative carbonylation; cat = Pd/C-PbO-$[nBu_4]Br$	20.4	92.2	10	181
Phenol phosgenation; cat = none	26.9	58.3	100	182
Phenol + DMC transesterification; cat = $Pb(OPh)_2$	28.5	82.6	8	183
MPC disproportionation; cat = MoO_3/silica	58.2	58.2	9	184
2 Phenol + CCl_4; cat = $ZnCl_2$-ZnO	60.3	59.5	42	185
Phenol oxidative carbonylation; cat = $Pd(OAc)_2$, $Mn(acac)_3$	62.4	92.2	14	186
Phenol + diphosgene + Et_3N; cat = none	62.6	43.8	94	121
PPC disproportionation; cat = LiCl	102.0	31.5	21	187
Phenol + PC; cat = MgO, TiMCM-41	110.4	73.8	8	188
Phenol + DMC transesterification (reactive distillation method); cat = $Pb(OPh)_2$	3006	77.0	0.05	129
Phenol + DMC transesterification (batch operation); cat = $Pb(OPh)_2$	15036	77.0	0.01	129

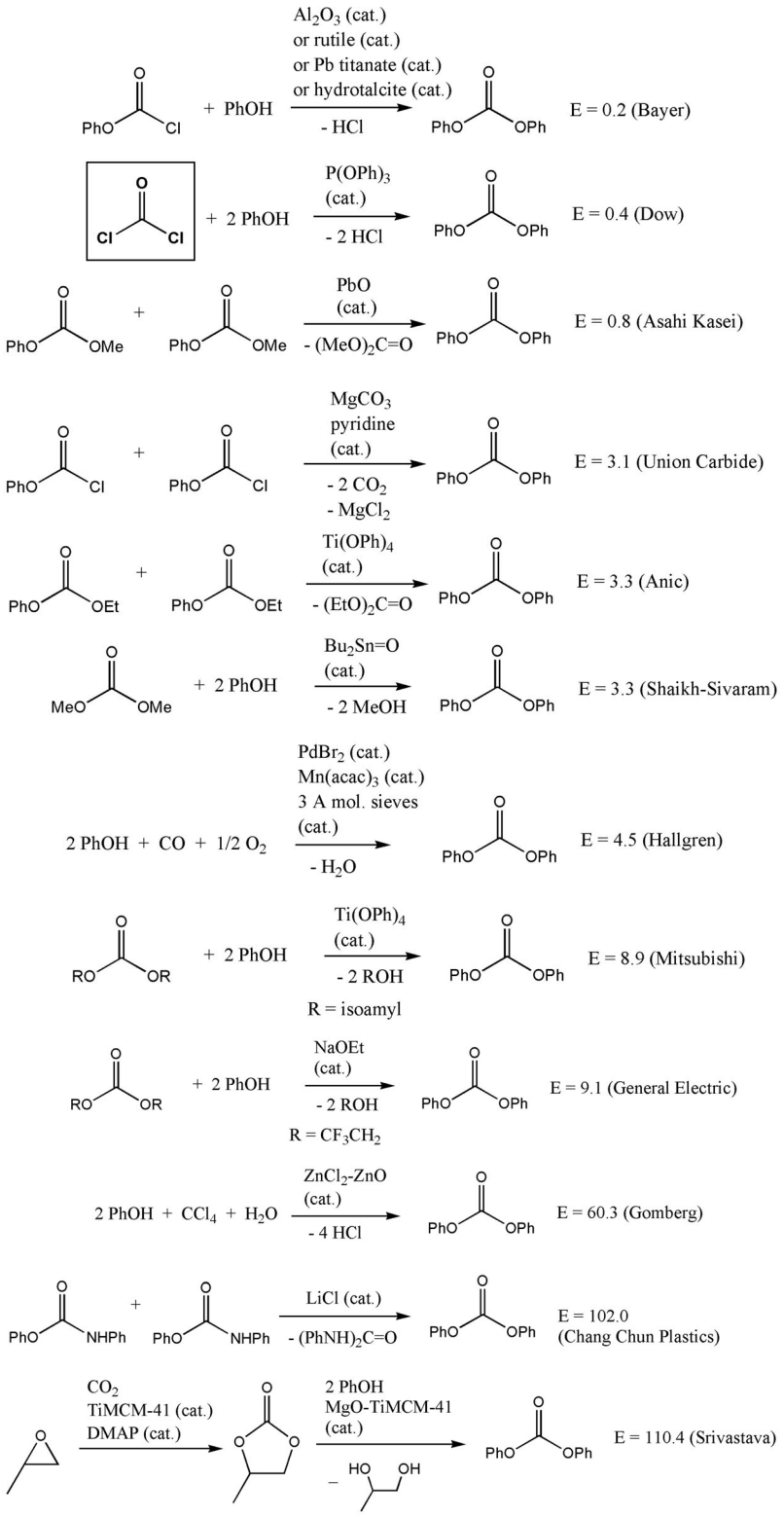

Fig. 5 DPC schemes.

Table 6 Summary of DPU syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Aniline + urea; cat = HOAc	0.1	86.2	100	189
Aniline + urea; cat = none	0.9	86.2	87	190
Aniline + urea; cat = $CeCl_3$ $7H_2O$, KI-PEG 400	2.2	86.2	96	191
Aniline + urea; cat = none	2.8	86.2	99	187
Aniline oxidative carbonylation; cat = Co(salphen)$(OH)_2$; 4-picoline	3.0	92.2	79	192
Aniline + NH_4SCN; cat = none	3.9	53.0	100	189
Aniline oxidative carbonylation; cat = $Pd(OAc)_2$; [bmim]iodide	4.1	92.2	98	193
Aniline + ethyl acetoacetate by microwaves; cat = none	5.0	67.1	62	194
Aniline phosgenation; cat = none	6.2	54.2	95	195
Nitrobenzene reductive carbonylation; cat = $Pd(OAc)_2$, PPh_3, $[Et_4N]Cl$	7.6	94.6	98	196
Aniline oxidative carbonylation; cat = $Pd(OAc)_2$(bipyDS); NaI	12.6	92.2	88	197
Aniline oxidative carbonylation; cat = $Pd(Cl)_2(PhNH_2)_2$	13.0	92.2	25	198
Aniline oxidative carbonylation; cat = [Co]; NaI	15.2	92.2	100	199
Aniline oxidative carbonylation; cat = $Pd(Cl)_2(PhNH_2)_2$; $CuCl_2(PhNH_2)_2$	16.7	92.2	47	198
Aniline carboxylation; cat = CsOH	17.6	92.2	27	200
Aniline carboxylation; cat = DBU/Me_3N/SO_3	21.0	92.2	64	201
Aniline oxidative carbonylation; cat = $Ru(CO)Cl(PPh_3)_2$; I_2	24.2	92.2	65	202
Aniline + triphosgene; cat = none	25.8	45.0	70	122
Aniline HCl + urea; cat = none	50.1	66.5	38	203
Benzenesulfenylchloride; cat = none	52.0	39.7	92	204
Aniline + bis(*p*-nitrophenyl)carbonate; cat = none	71.6	34.9	65	205
Aniline oxidative carbonylation; cat = *cis*-$Ru(CO)_2Cl_2(PPh_3)_3$	126.2	92.2	21	206
Aniline + ethyl acetoacetate; cat = HSZ zeolite	192.9	67.1	66	207

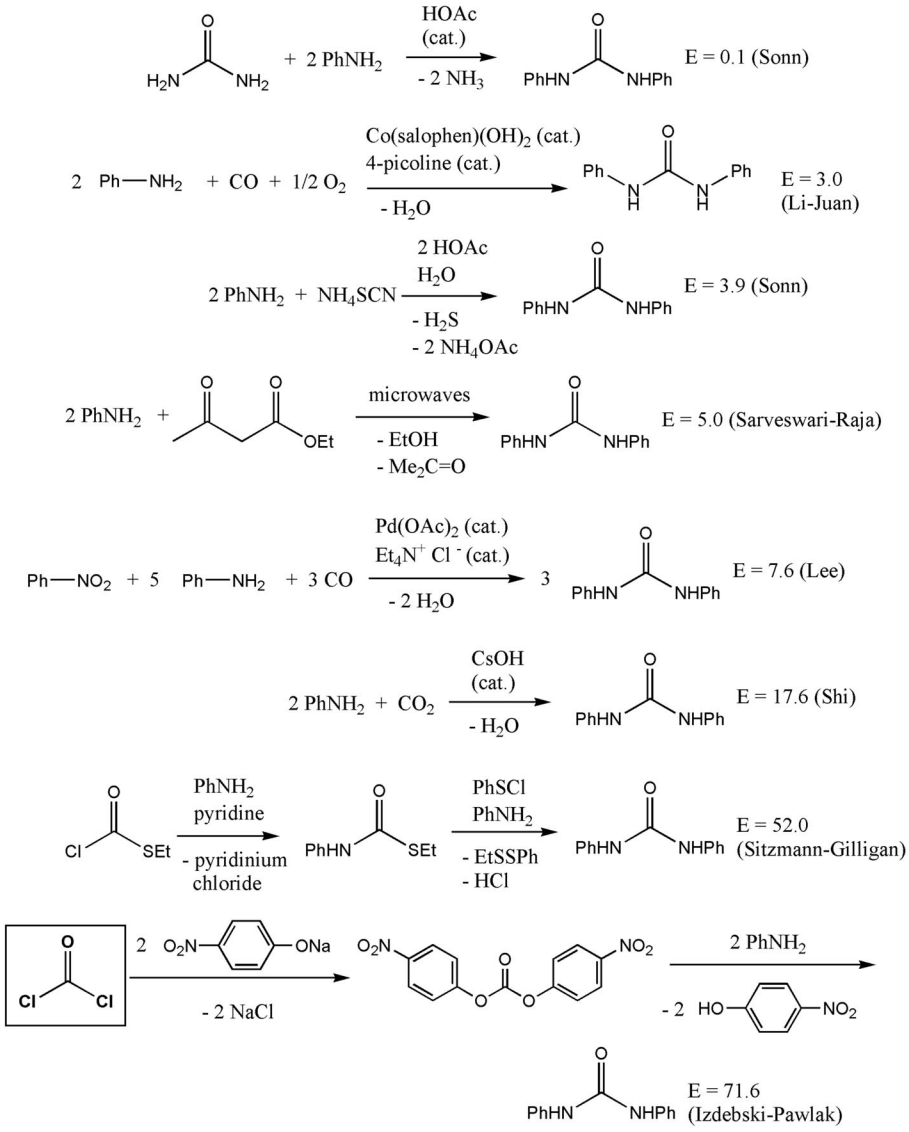

Fig. 6 DPU schemes.

Table 7 Summary of MC syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Urea + methanol; cat = none	1.7	81.5	94	208
Urea + methanol; cat = $Cu(OAc)_2$	2.1	81.5	42	209
DMC + ammonia; cat = none	2.7	70.1	99	210
Urea + methanol + H_3PO_4; cat = none	5.7	39.5	88	211
Formamide + methanol; cat = NaBr (electrochemical)	6.0	97.4	57	212
Urea + methanol + BF_3; cat = none	6.3	46.9	41	213
Urea + methanol; cat = none	9.0	81.5	98	214
Urea + methanol; cat = MgO	10.1	81.5	85	146

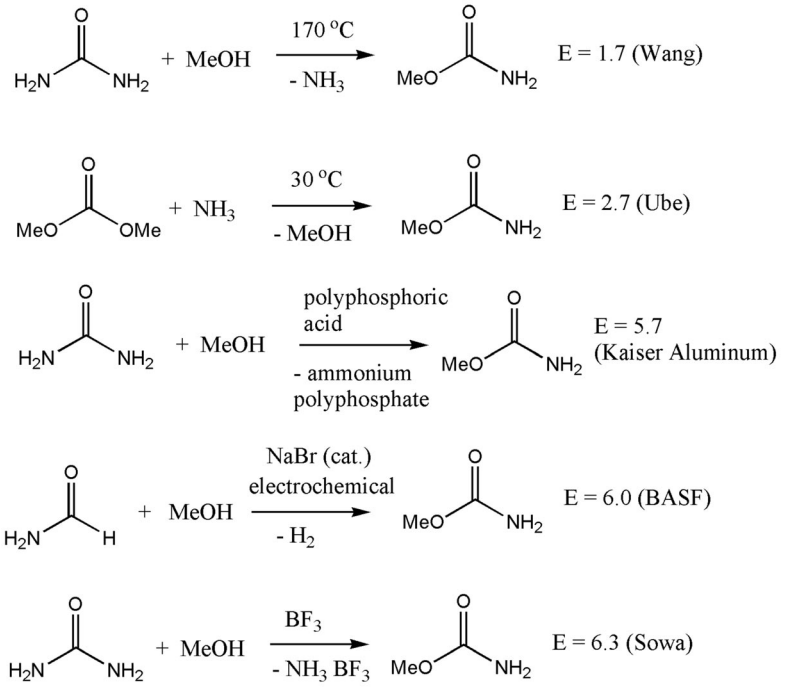

Fig. 7 MC schemes.

Table 8 Summary of MCF syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Methanol + phosgene; cat = none	0.4	72.2	99	215
Methanol + phosgene; cat = none	0.5	72.2	92	216
Methanol + phosgene; cat = none	0.6	72.2	95	217
2 MeONO + Cl_2 + 2 CO; cat = $PdCl_2$/alumina	19.8	75.9	80	218
2 MeONO + Cl_2 + 2 CO; cat = $PdCl_2$/alumina	27.1	75.9	59	219
$Pd(COOMe)_2(bipy)$ + 4 $CuCl_2$; cat = none	457.6	15.8	51	220

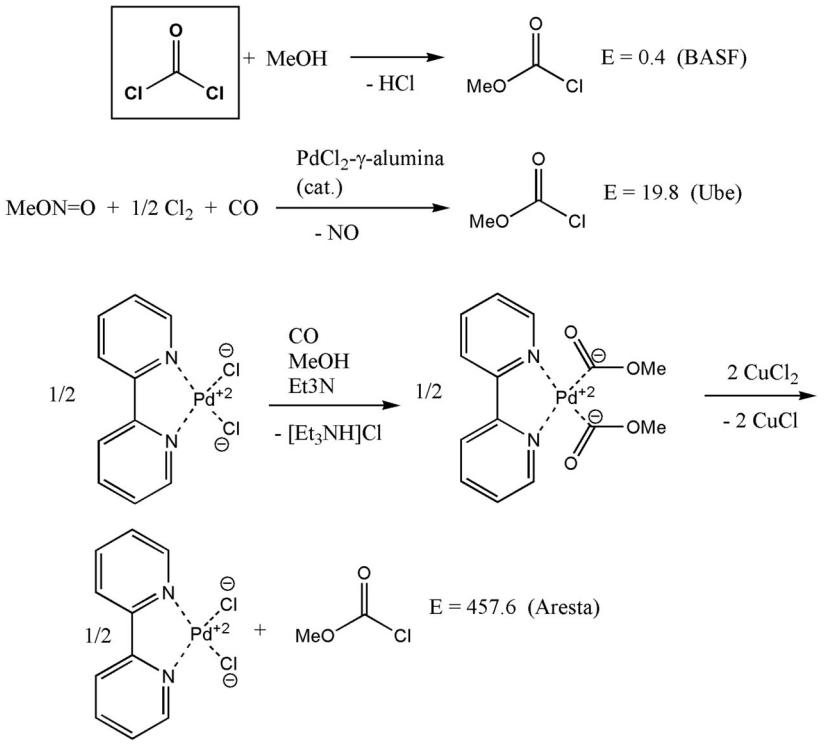

Fig. 8 MCF schemes.

Table 9 Summary of MNPC syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Aniline amidation with methylcarbamate; cat = $ZnCl_2$	1.7	89.9	82	221
Aniline amidation with DMC; cat = $ZnCO_3$, 2 [$Zn(OH)_2$ 2 H_2O]	2.9	82.5	95	222
Aniline amidation with DMC; cat = $Pb(OAc)_2$, Pb(OH)2	3.6	82.5	93	223
Nitrobenzene reductive carbonylation; cat = S/V_2O_5, NaOMe	3.7	63.2	85	224
Aniline amidation with methylcarbamate; cat = $ZnCl_2$	5.3	89.9	90	225
Diphenylurea transesterification with DMC; cat = 2 $PbCO_3$/$Pb(OH)_2$	6.1	100	97	226
Diphenylurea transesterification with DMC; cat = NaOMe	8.1	100	74	227
Aniline oxidative carbonylation; cat = Pd, CsI	8.9	89.3	95	228
Phenylurea esterification; cat = PHO	9.8	89.9	89	229
Phenylurea esterification; cat = P, PbO	10.6	89.9	81	230
Aniline oxidative carbonylation; cat = SeO_2, K_2CO_3	10.8	89.3	48	231
Aniline amidation with DMC; cat = Al-SBA-15	11.0	82.5	58	232
Aniline amidation with DMC; cat = ZrO_2, SiO_2	14.6	82.5	80	233
Phenylurea methanolysis; cat = SeO_2, K_2CO_3	15.7	89.9	47	234
Diphenylurea methanolysis; cat = NaOMe	17.5	57.6	30	235
Aniline oxidative carbonylation - esterification; cat = [Co]	18.0	51.4	95	236
Diphenylurea methanolysis; cat = none	19.4	54.3	30	144
Diphenylurea esterification; cat = H_2SO_4	34.5	61.9	87	237
Aniline oxidative carbonylation - esterification; cat = 1 % Pd-ZSM-5	37.3	51.4	98	206

(*continues on next page*)

Table 9 (*Continued*).

Synthesis methodology	E-factor	% AE	% Yield	Reference
Aniline oxidative carbonylation; cat = $PdCl_2$, HCl, $CuCl_2$	55.8	89.3	99	238
Aniline amidation with methylchloroformate; cat = In	59.0	80.6	82	239
Benzamide Lossen rearrangement; cat = none	200.2	16.1	64	240
Aniline oxidative carbonylation; cat = NaI, Pd-C (gas–solid heterogeneous batch method)	443.7	57.6	75	241
Aniline amidation with DMC; cat = $Yb(OTf)_3$	483.6	82.5	96	242
Aniline oxidative carbonylation; cat = NaI, Pd-C (slurry method)	807.6	57.6	82	241

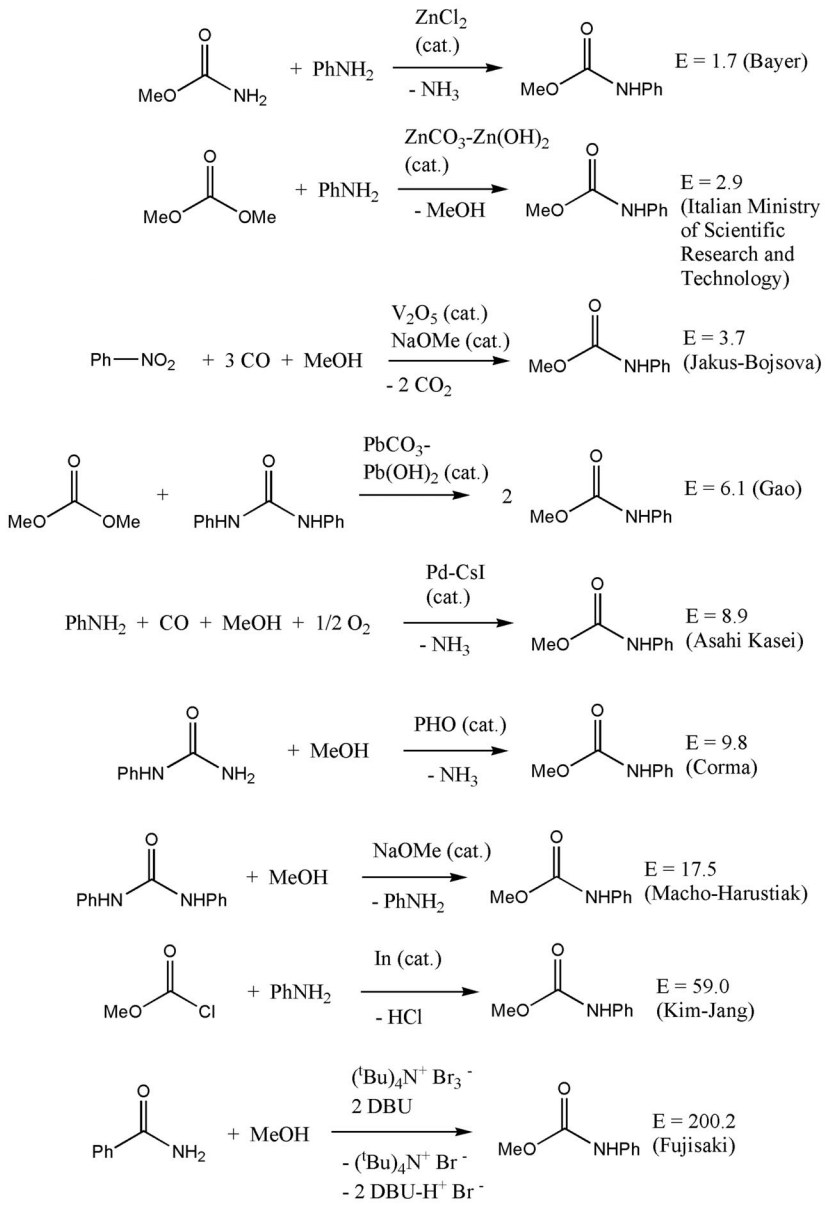

Fig. 9 MNPC schemes.

Table 10 Summary of MPC syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Phenylacetate + DMC; cat = $Bu_2Sn(OBu)_2$	2.3	67.3	64	243
Phenol + DMC; cat = MoO_3/SiMCM-41	3.6	82.6	26	244
Phenol + DMC; cat = Cp_2TiCl_2	3.6	82.6	40	245
Phenol + DMC; cat = BuSn=O(OH)/CuI	3.8	82.6	39	246
Phenol + DMC; cat = V_2O_5	4.6	82.6	22	247
Phenol + DMC; cat = MoO_3/CuO	4.9	82.6	21	248
Phenol + DMC; cat = poly(oxy(dibutyltin))	5.0	82.6	21	249
Phenol + DMC; cat = $HOSn(C_8H_{17})_2SnOSn(C_8H_{17})_2OH$	5.0	82.6	21	250
Phenol + DMC; cat = Cp_2TiCl_2	5.1	82.6	20	251
Phenol + DMC; cat = MgF_2	5.9	82.6	26	252
Phenol + DMC; cat = SmI_2	7.6	82.6	28	253
Phenol + DMC; cat = ZnPMo	7.7	82.6	14	254
Phenol + DMC; cat = $Ti(OPh)_4$	8.4	82.6	39	255
Phenol + DMC; cat = MPA/TiO_2	8.6	82.6	13	256
Phenol + DMC; cat = $ClSn(Bu)_2SnOSn(Bu)_2OH$	9.1	82.6	12	257
Phenol + DMC; cat = Bu_2Sn=O	9.3	82.6	12	258
Phenol + DMC; cat = $Ti(OBu)_4$	9.9	82.6	33	259
MeOH + DPC; cat = 1,5,7-Triazobicyclo[4.4.0]dec-5-ene	10.1	61.8	25	260
Phenol + DMC; cat = TiO_2/SiO_2	10.2	82.6	32	261
Phenylbenzoate + DMC; cat = $Ti(OiPr)_4$	12.0	52.8	83	262
Phenol + DMC; cat = $Ti(OiPr)_4$	14.5	82.6	8	263
Phenol + DMC; cat = $Ti(OPh)_4$	14.9	82.6	21	264
Phenol + DMC; cat = $Ti(OPh)_4$	15.9	82.6	20	265
Phenol + DMC; cat = $Ti(OPh)_4$	19.7	82.6	8	266
Phenol + CO + MeOH; cat = $PdBr_2$/$Mn(acac)_3$/ pentamethylpiperidine	19.8	98.7	15	267
Phenol + DMC; cat = MoO_3/SiO_2	20.2	82.6	17	184
Phenol + DMC; cat = TiO_2/SiO_2 (Si/Ti = 9)	28.5	82.6	13	268
Phenol + DMC; cat = TiO_2/silica	28.7	82.6	19	269
Phenol + DMC; cat = $(NH_4)_8Mo_{10}O_{34}$	43.3	82.6	8	270
Phenol + DMC; cat = $(NH_4)_8Mo_{10}O_{34}$	73.1	82.6	5	271
Phenol + CO + 2 $Cu(OMe)_2$; cat = none	231.6	40.7	9	272
MeOH + CO_2 + DBU + $(MeSO_2)_2O$ + phenol + pyridine; cat = none	552.2	26.4	26	273

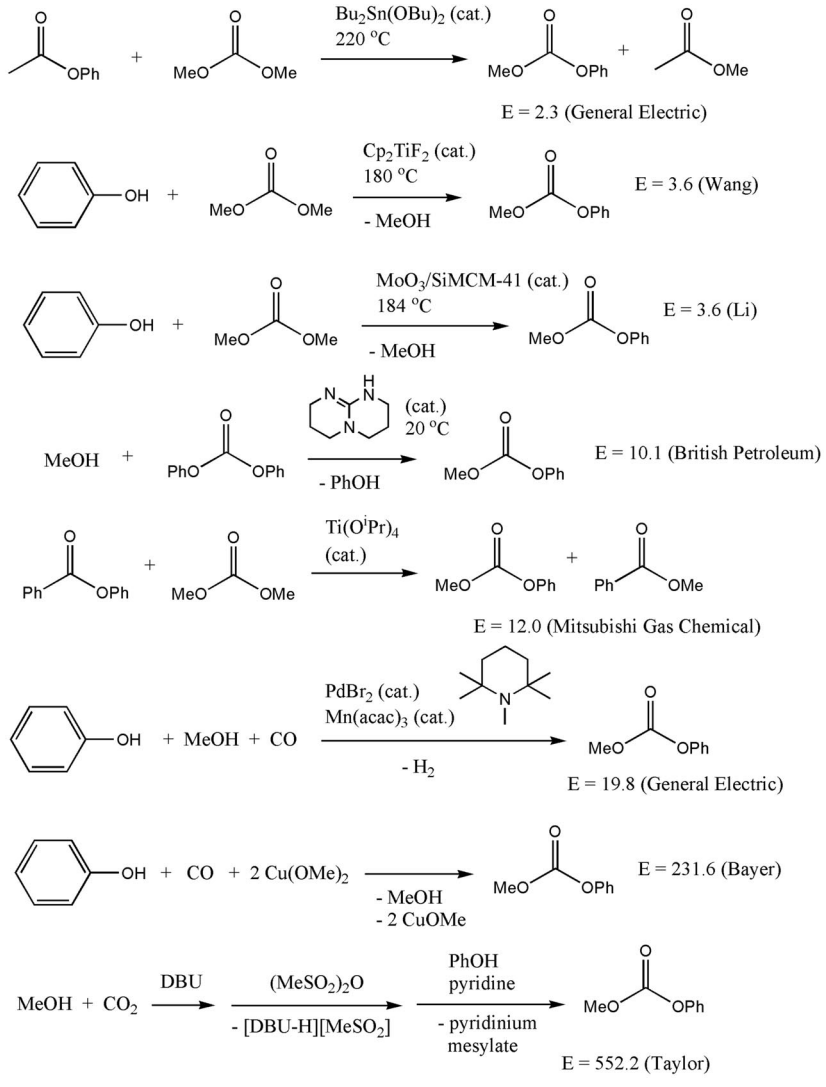

Fig. 10 MPC schemes.

Table 11 Summary of PCF syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Phenol phosgenation; cat = dimethylpropylurea	0.3	81.1	99	274
Phenol phosgenation; cat = $(PhO)_3P$	0.4	81.1	96	275
Phenol phosgenation; cat = DMF	0.5	81.1	92	276
Phenol phosgenation; cat = 2-undecylpyridine	0.5	81.1	89	277
Phenol phosgenation; cat = $[Ph_3PCH_2Ph]Cl$	0.6	81.1	82	278
Phenol phosgenation; cat = DMF	0.7	81.1	91	279
Phenol phosgenation; cat = $[Me_3NCH_2Ph]Cl$	1.1	81.1	70	280
Phenol phosgenation; cat = none	6.7	81.1	90	281
Phenol phosgenation; cat = none	13.7	67.2	80	282
Phenol phosgenation; cat = none	23.2	67.2	33	283

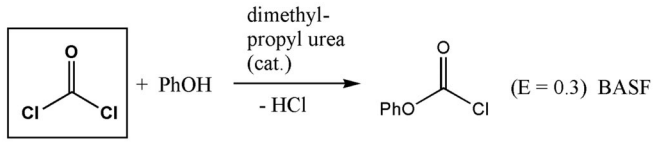

Fig. 11 PCF scheme.

Table 12 Summary of PI syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
Aniline phosgenation; cat = none	2.4	62.0	95	284
DPU phosgenation; cat = none	3.1	76.6	84	285
MPC ethanolysis; cat = none	3.9	35.1	59	286
Aniline phosgenation; cat = none	6.6	62.0	94	287
Aniline phosgenation; cat = none	7.9	62.0	96	288
Aniline HCl phosgenation; cat = none	8.8	52.1	90	116
Aniline phosgenation; cat = none	9.5	62.0	95	289
Aniline phosgenation; cat = none	9.5	62.0	95	290
Aniline phosgenation; cat = HCl (g)	10.7	62.0	83	291
Aniline HCl reaction + diphosgene; cat = none	11.0	52.1	89	117
Formanilide + DPC; cat = none	12.0	35.5	91	292
Aniline + triphosgene; cat = Et_3N	13.1	62	76	118
Aniline HCl phosgenation; cat = none	13.2	52.1	98	293
Aniline + triphosgene; cat = Et_3N	15.7	62.0	50	294
MPC methanolysis; cat = Bi_2O_3	27.1	78.8	70	295
Aniline + DMC; cat = PbO	39.8	65	42	119
Aniline phosgenation; cat = none	49.9	43.8	29	296
Carbonylation of Ph_3P=NPh; cat = none	158.5	28.0	83	297
N-Sulfinylaniline (PhN=S=O) phosgenation; cat = pyridine	5417	38.3	55	298

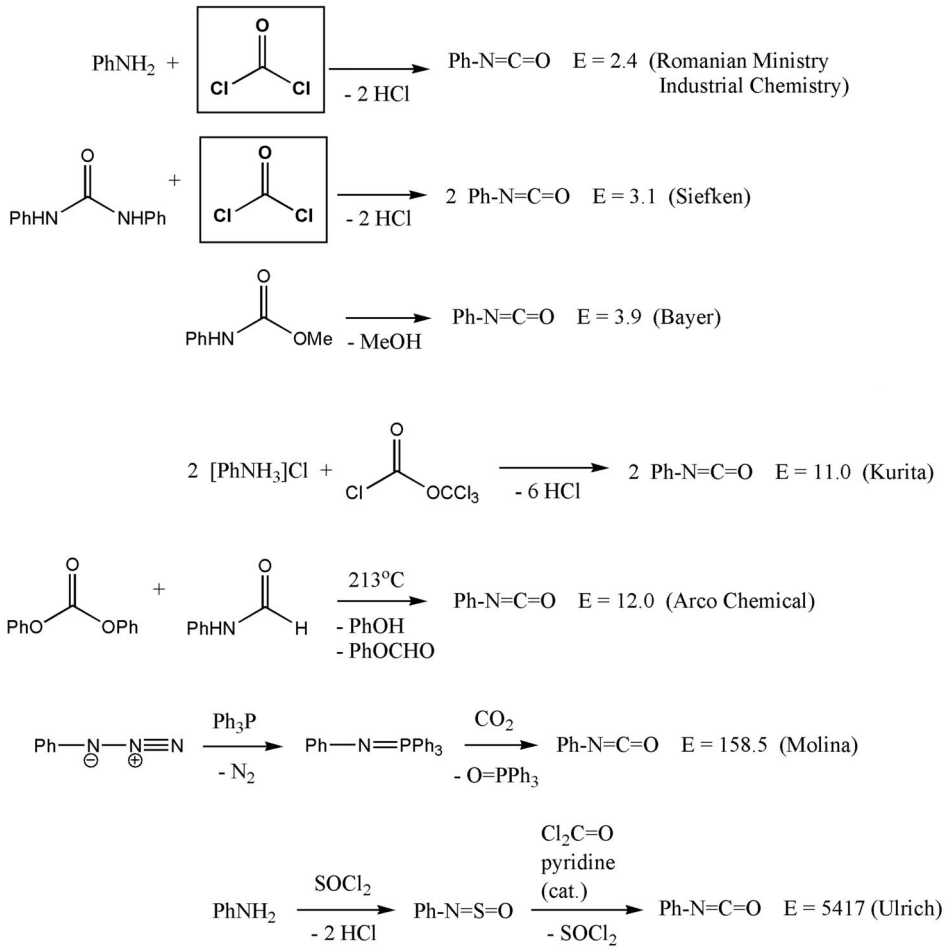

Fig. 12 PI schemes.

Table 13 Summary of urea syntheses.

Synthesis methodology	E-factor	% AE	% Yield	Reference
$2NH_3 + CO_2$; cat = none	1.8	76.9	65	299
$2NH_3 + CO_2$; cat = none	1.9	76.9	82	300
$(NH_4)(NH_2CO_2)$; cat = none	2.0	76.9	43	301
$2NH_3 + CO_2$; cat = none	2.3	76.9	40	302
$2NH_3 + CO$; cat = $Ni(CO)_4$	2.5	96.8	30	303
$2NH_3 + CO + S$; cat = none	4.5	63.8	74	304
$4NH_3 + COCl_2$; cat = none	6.7	35.9	70	305
$NaOCN + (NH_4)_2CO_3$; cat = none	20.9	30.5	70	306
$4NH_3 + Fe(CO)_5$; cat = none	25.6	22.7	99	307
$3NH_3 + CO + Mn(CO)_5Cl$; cat = none	38.6	19.4	94	308
$4NH_3 + [Mn(CO)_6]Cl$ HCl; cat = none	84.7	16.5	90	308
$4NH_3 + Fe_2(CO)_9$; cat = none	85.5	13.9	99	307
$Mn_2(CO)_{10} + 3NH_3 + Na[BPh_4] + 3CO$; cat = none	198.5	6.9	56	308

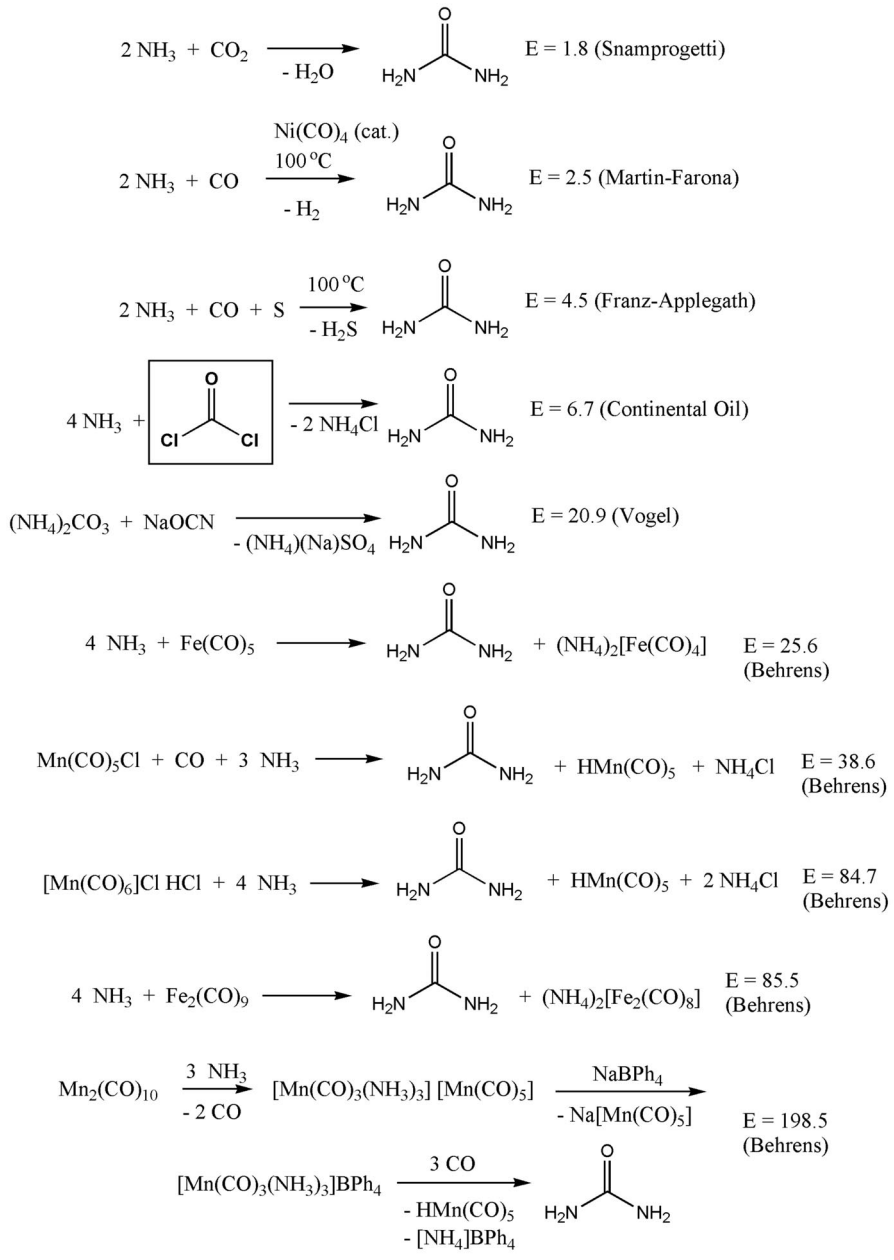

Fig. 13 Urea schemes.

REACTION NETWORKS

The various synthetic routes to the target commodity chemicals examined in this work may be conveniently displayed using a reaction network as shown in Fig. 14. From this diagram, the number of routes to each target compound covered by this study is as follows: PI (1067), DPU (116), urea (10), MNPC (229), MCF (2), PCF (1), DPC (1007), DMC (97), MC (108), and MPC (392). The total number of routes covered by this network is then 3029. Figures 15 and 16 show the best-performing reaction networks for phosgene- and non-phosgene-based routes, respectively. E-factors are highlighted in bold

text. In the simpler phosgene network, phosgene is the central starting material for all products and so it appears as a central node. By contrast, the non-phosgene network shows a greater degree of interconnectedness among the target nodes. The overall best-performance network is shown in Fig. 17. From this it can be seen that phosgenation is still the most material-efficient route to PI and MCF. Figure 18 shows an E-factor comparison of phosgene- and non-phosgene-based routes under weak and strong conditions. The overall aim is to have E-factor (non-phosgene route) < E-factor (phosgene route). When comparing best non-phosgene routes against worst phosgene routes (weaker criterion), greenness has been apparently achieved for PI, DPU, and DPC; but, marginally for PCF and definitely not for MCF. When comparing best non-phosgene routes against best phosgene routes (stronger criterion), greenness has been achieved convincingly for DPU, but marginally for PCF and DPC. The performance for PI

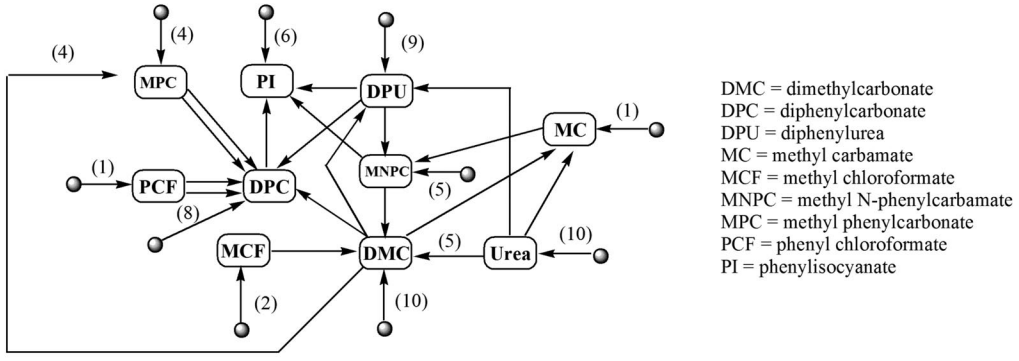

Fig. 14 Total reaction network connecting relevant industrial target molecules. Numbers in parentheses above arrows indicate the number of routes connecting the input and product nodes. Circles indicate starting materials.

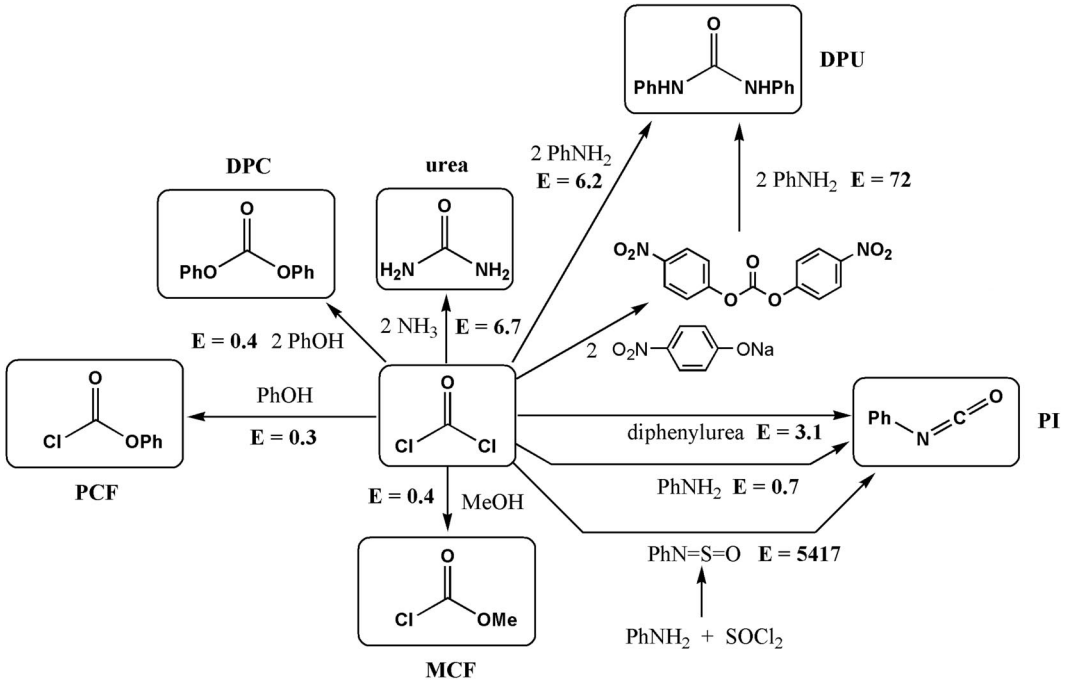

Fig. 15 Reaction network based on phosgene chemistry. Best E-factor values are given for each target molecule.

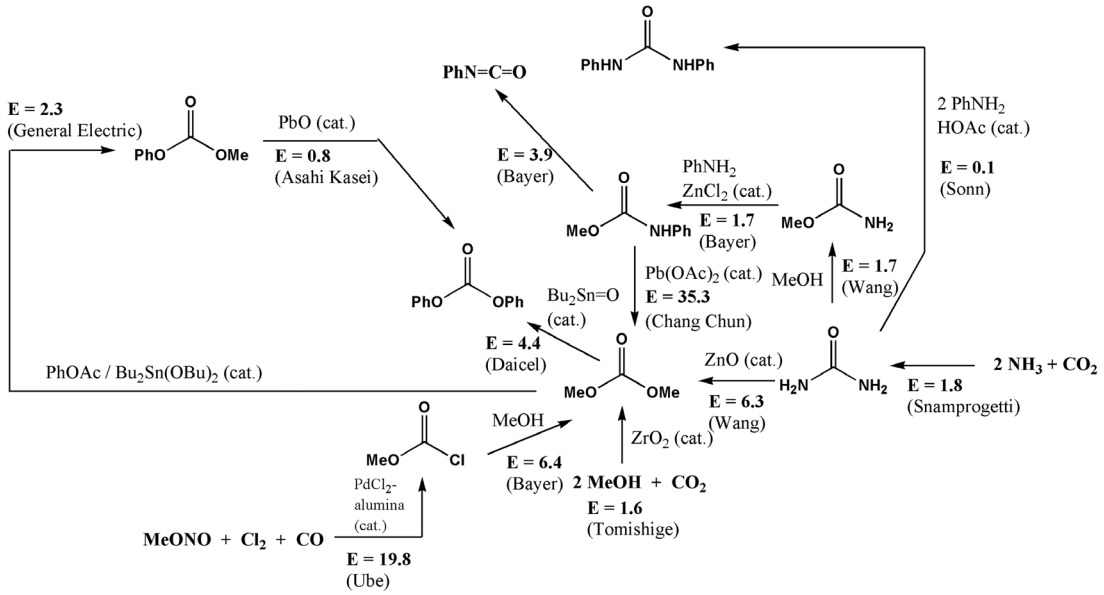

Fig. 16 Reaction network based on non-phosgene chemistry. Best E-factor values are given for each target molecule.

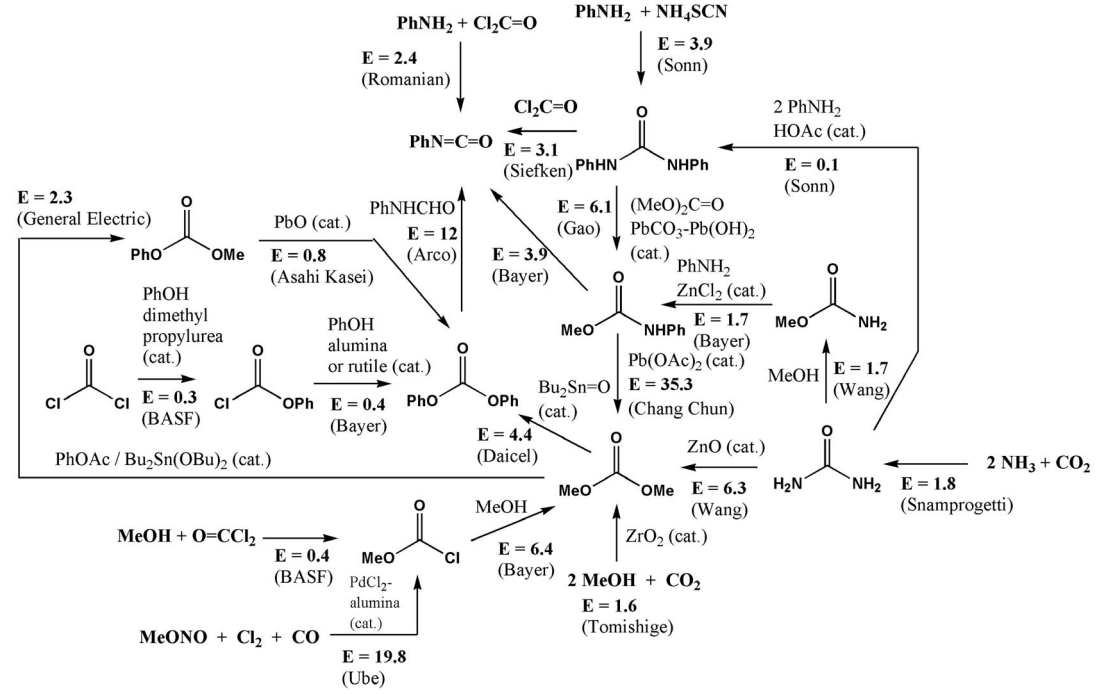

Fig. 17 Overall reaction network showing lowest E-factor routes to target molecules.

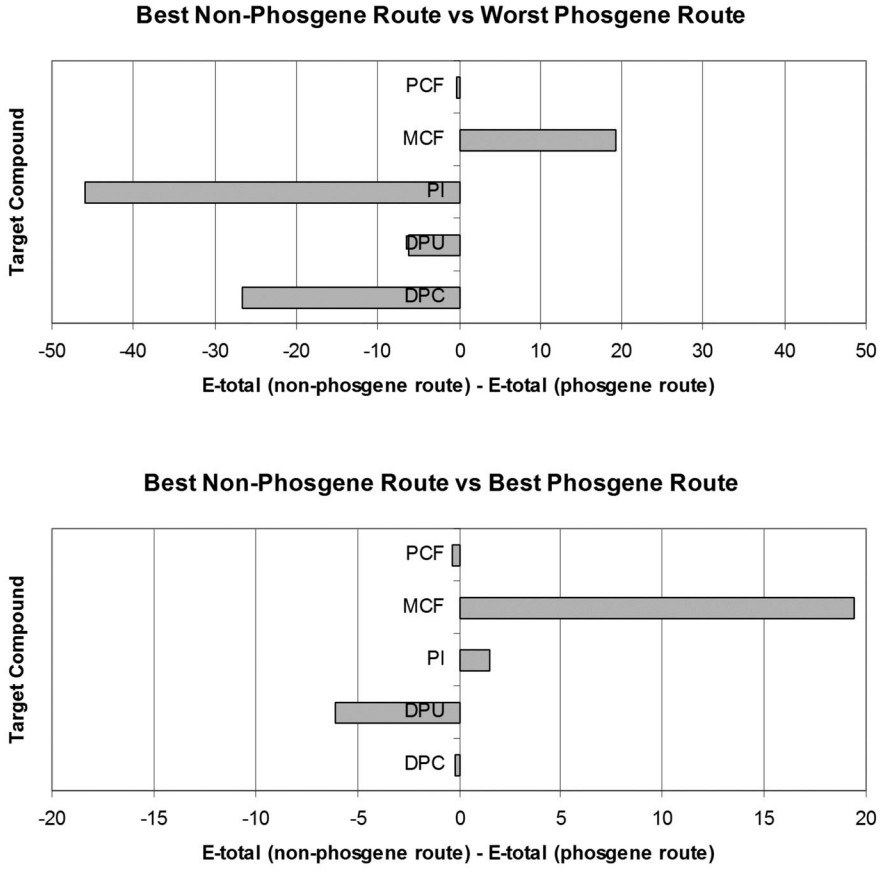

Fig. 18 Relative E-factor comparison of non-phosgene and phosgene routes according to weak (top) and strong (bottom) criteria.

shifts marginally in the direction of phosgene, and still MCF is better made using phosgene by the same E-factor difference as under the weaker criterion. It is clear that satisfying the E-factor inequality under the stronger criterion is more challenging. It is evident that MCF and to a lesser extent PI require further improvements with respect to E-factor reductions. Of these two, MCF is more challenging since it is a chlorine-containing compound and hence requires a chlorine-based precursor for its synthesis. The same thing may be said for PCF.

CONCLUDING REMARKS

Though phosgene is an extremely versatile reagent in organic synthesis for inserting carbonyl functionality from a kinetic and thermodynamic standpoint and in industry for the production of important commodity chemicals, its associated hazards, notorious reputation as a chemical weapon, and highly regulated manufacture, use, and distribution have unfortunately made it an overall taboo chemical. Great efforts have been made to reduce and avoid its use altogether as evidenced by a rigorous evaluation of material efficiency green metrics presented in this work. The radial pentagon and global E-factor metrics algorithms have proved to be effective in identifying best material-efficient routes, pinpointing bottlenecks, and giving direction for future optimization. However, they formally focus only on material consumption efficiency and do not include energy consumption efficiency, toxicity, and hazard assessment. Hence, it may be argued that even thorough E-factor evaluations alone do not tell

the whole story. The radial pentagon examples given for PI and DPC show that it is very difficult to satisfy a three-way optimization involving material efficiency, energy efficiency, and tolerable safety/toxicity profiles. When faced with a situation of deciding between using a hazardous reagent that results in lower waste production over using a safer one that does not, it is not always clear that safety/toxicity factors will always trump waste production. An important point that needs to be made is that most of the work done on DMC reactions is focused on finding the optimum reaction condition parameters such as catalyst choice, catalyst loading, reagent feed rate, temperature, pressure, solvent choice, and substrate-to-catalyst ratio. Reactions are carried out in pressurized autoclaves on a small scale, typically hundreds of millimoles, and final products are not actually isolated but determined from chromatographic product studies only. What has not been demonstrated convincingly, once such optimum conditions are found, is to scale up the reaction sufficiently to actually isolate products and gauge reaction performance as a function of scale. Claims of efficiency are essentially hinged on percent conversion of starting material to products and percent selectivity to the desired product. The observation that reactions involving DMC are energy-intensive has not been addressed. Additionally, all of the reported chemical literature suffers a serious drawback in that no explicit experimental data for energy consumption is ever reported as a standard protocol for any chemical reaction, though guesses can be made from reaction conditions such as temperature and pressure. Also, data necessary for a complete lifecycle analysis including rigorous and standard metrics for hazards, toxicity, and environmental impact are hard to locate, are unknown or unreliable, and/or are fragmented. This lack of readily available and reliable data makes it nearly impossible to do a complete unbiased evaluation of "greenness" that covers all aspects. It is also the main reason that will impede green chemistry from making headway in mainstream chemistry research and education in academia and industry if left unchecked. Mercer, Jessop, and Andraos have advanced a preliminary method of green metrics material and lifecycle analysis using various academic and industrial syntheses of aniline as an example [309] that represents a preliminary attempt to deal with this situation. A key aim in reaction optimization with respect to green chemistry principles is to achieve synergy between material and energy efficiency, minimum environmental impact, and maximum safety so that all of these attributes appear in the same reaction or synthesis plan in a relative sense, that is, when several routes to a given target are compared. An important caveat in implementing green chemistry principles is that it does not always result in an overall win–win situation on every metrics parameter in an absolute sense. Chemistry is an experimental science based on trial-and-error and often leads to compromises. Thermodynamics and cost of starting materials, whether market-driven or artificially fixed, are often the final arbitrators of feasibility and decision-making. Therefore, the ranking results presented in this work will change significantly when both material and energy efficiencies are considered, for example, and again when toxicity and hazard are included. This change of ranking is inevitable for non-phosgene chemistry where energy demand is known to be high owing to catalyst preparation and activation. It is hoped that these analyses will be used by chemists in industry as a stepping stone for future developments and improvements in greening up phosgene-based target molecules, and most especially in the complete reporting of their results to the wider chemical community.

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