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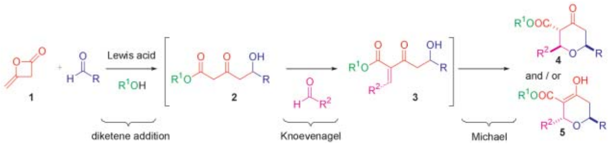
Combining pot, atom and step economy (PASE) in organic synthesis. Synthesis of tetrahydropyran-4-ones

Paul A. Clarke, Soraia Santos and William H. C. Martin

Applications of principles 1, 2, 5 and 8 of the twelve principles of green chemistry to the synthesis of highly functionalised tetrahydropyran-4-ones has led to a significantly 'greener' synthesis of these molecules.



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Combining pot, atom and step economy (PASE) in organic synthesis. Synthesis of tetrahydropyran-4-ones†

Paul A. Clarke,*[a] Soraia Santos[a] and William H. C. Martin[b]

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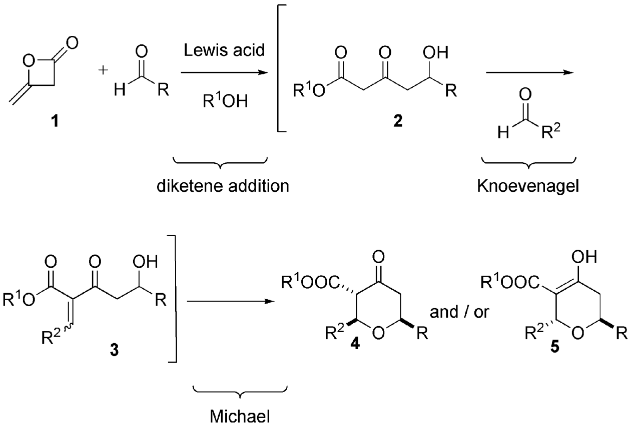
The combination of pot, atom and step economy (PASE) in the synthesis of organic molecules of medium complexity can lead to a significant 'greening' of a synthetic route. This is demonstrated by the synthesis of highly substituted tetrahydropyran-4-ones and is quantified by a series of recognised metrics, which demonstrate the efficiency of combining PASE over conventional synthetic strategies.

For several years synthetic chemists have been familiar with the concept of step economy,[1] which is the drive to increase the brevity and efficiency of a synthesis by a reduction in the number of synthetic steps. Traditionally, this has manifested itself in the attempt to limit the use of protecting group manipulations. A step economic synthesis has the potential to reduce the number and amount of reagents employed by reducing the number of synthetic steps. This should also lead to an increase in chemical yield of the desired product. Trost has introduced synthetic chemists to the idea of atom economy,[2] which is the concept that every atom of each reagent being used is included in the desired product of the reaction. While this concept does address the issue of waste in the form of reaction by-products, it does not address the fundamental problem of how to eliminate the solvent and the waste generated by any work-up or product isolation and purification procedure. These factors are addressed by the concept of pot economy, which is the drive to complete as many sequential synthetic transformations in the same reaction vessel without the need for work-up and product isolation between successive synthetic steps. The ultimate aim would be to complete an entire multi-step, multi-reaction synthesis in a single pot. A pot economic synthesis would, therefore, reduce dramatically the amount of solvents used in the synthesis, solvents used in work-up and product isolation, solvents used in product purification, silica gel or related substances used in chromatographic purification, contaminated aqueous waste generated from cleaning equipment and glassware, *etc*. While individually each of these strategies have the potential to 'green' organic synthesis, a more significant reduction in waste (and cost) could be achieved by combining all three of these concepts to produce a pot, atom and step economic (PASE) synthetic route. A PASE synthesis has the potential to (i) reduce the number and amount of reagents employed by reducing the number of synthetic steps, (ii) reduce the waste inherent in the generation of reaction by-products and (iii) to reduce the solvent and associated waste caused by many work-up and product isolation procedures along the synthetic route. Indeed, process chemists in industry have been striving for such sustainable routes to desired molecules for several years, on the basis of cost. Interestingly, this commercial drive for increased efficiency (and lower costs) by adoption of PASE synthesis embodies principles 1, 2, 5 and 8 of the twelve principles of green chemistry.[3]

However, it is a fact that even though process chemists in industry are seeking to adopt more sustainable synthetic routes, organic chemists in academia have been very slow to embrace these ideas. After discussions with process chemists, we were interested by the possibility of applying these ideas to our own work. The area which was highlighted by these discussions was our syntheses of highly substituted tetrahydropyran-4-ones (THPs), as these are present in a vast number of biologically and pharmaceutically important molecules. We have had prior experience in the construction of THP rings and THP containing natural products.[4] However, in this previous work we were not concerned with issues of sustainability and a redcuction of the environmental impact. For example, we regularly used two equivalents of *bis*-silylenol ethers in our syntheses. This obviously led to the generation of 4 equivalents of silanol waste and the need to separate this from the product. In order to circumvent this we developed an alternative strategy for the synthesis of THP units, still incorporating our original ideas, but now taking account of the principles of pot, atom and step economy as exemplied in the principles of green chemistry.



Scheme 1 PASE Synthesis of THP rings.

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† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data and HPLC data. See DOI: 10.1039/b700923b

Our new 'greener' strategy is outlined in Scheme 1. In practice, for PASE to be realised it was important that the three individual reactions, Lewis acid promoted addition of diketene to an aldehyde,[5] Knoevenagel condensation and intramolecular Michael reaction, all follow on from each other in one pot—thus achieving pot and step economy. Atom economy is achieved as all of the atoms of the reagents (with the exception of one equiv. of H_2O and the Lewis acid catalyst) are all included in the desired THP product.

In our initial investigations, we chose to use $TiCl_4$ as the Lewis acid as it had been shown to promote both the addition of diketene to aldehydes,[5] as well as the Knoevenagel and Michael reactions.[4] As this initial reaction (**1** → **2**) would generate the acyl chloride of the δ-hydroxy-β-ketoester, we opted to add an alcohol (MeOH) to the reaction mixture in order to form the ester and also introduce another potential site of diversity. We rationalised that after promoting the addition of diketene to the first aldehyde, the Lewis acid would be capable of promoting the Knoevenagel reaction of a second, different, aldehyde to the α-position of the β-ketoester, followed by an intramolecular Michael reaction. To our delight, when the above sequence of events was carried out, THP products were formed as a mixture of 2,6-*cis* (**4**) and 2,6-*trans* (**5**) diastereomers in good to excellent yields (Table 1).

We were somewhat disappointed by the low diastereoselectivity of the reaction. Previous experience in THP synthesis *via* an intramolecular oxy-Michael reaction had taught us that the isomerisation of the double bond was very facile, and that the Michael reaction was reversible and under thermodynamic control when $TiCl_4$ was employed as a Lewis acid.[4] Unfortunately, a number of other Lewis acids investigated failed to promote the reaction at all. We therefore decided to buffer the second stage of the reaction in an attempt to prevent the Lewis acid catalysed retro-Michael reaction. The buffer of choice was found to be pyridine, which suppressed the retro-Michael reaction and led predominantly to the formation of the 2,6-*cis* diastereomer **4** (Table 2).

Table 1 Formation of THP rings: PASE synthesis method A General method for the PASE synthesis of THPs **4a–i** and **5a–i**. Method A. To a stirred solution of diketene (0.1 ml, 1.30 mmol) and aldehyde (0.72 mmol) in CH_2Cl_2 (2 ml) at −78 °C, was added $TiCl_4$ (80 µl, 0.72 mmol). After 5 min, dry methanol (117 µl, 2.88 mmol) was added to the dark red mixture. The reaction was stirred for 30 min at −30 to −20 °C before it was again cooled to −78 °C, when the second aldehyde (0.87 mmol) was added. The reaction mixture was warmed back to −20 °C and stirred at this temperature for 16 h. After dilution with ether, the mixture was washed with a 20% (w/v) aqueous solution of citric acid (3 × 30 ml), brine (2 × 40 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash chromatography (Petrol–EtOAc–Pyridine: 200 : 1 : 2 to 100 : 4 : 2) gave the tetrahydropyran products. Full experimental procedures, spectroscopic data and HPLC data are included in the ESI.

Compound	R	R^2	Ratio (**4** : **5**)[a]	Yield [b](%)
a	Ph	*i*Pr	1.5 : 1	87
b	*i*Pr	Pr	2.1 : 1	72
c	*i*Pr	Ph	0.6 : 1	70
d	Cyhex	Ph	0.6 : 1	73
e	Ph	Ph	1 : 1	79
f	Ph	*p*-$MeOC_6H_4$	1 : 1	78
g	C_8H_{17}	Ph	1 : 1	96
h	Pr	CH_2OBn	4.2 : 1	58
i	*i*Pr	$(CH_2)_2CH{=}CH_2$	1.2 : 1	77

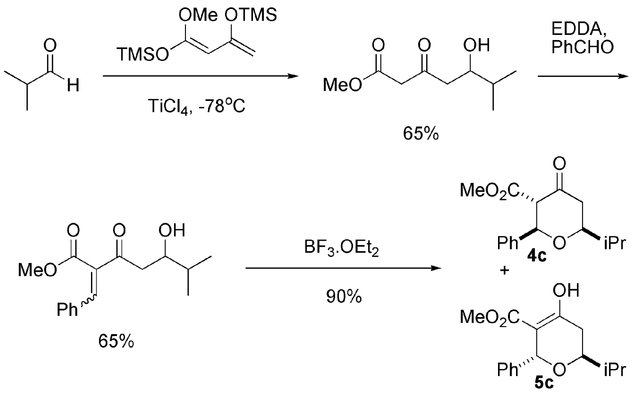
[a] As determined by 400 MHz ^1H NMR of the crude reaction mixture. [b] After flash column chromatography.

Table 2 Formation of THP rings: PASE synthesis: method B

Compound	R	R^{2a}	Ratio (**4** : **5**)[b]	Yield [c](%)
a	Ph	*i*Pr	5.7 : 1	81
b	*i*Pr	Pr	4.7 : 1	81
c	*i*Pr	Ph	2 : 1	84
d	Cyhex	Ph	1.6 : 1	83
e	Ph	Ph	1.7 : 1	89
f	Ph	*p*-$MeOC_6H_4$	3 : 1	39
g	C_8H_{17}	Ph	1.5 : 1	47
h	Pr	CH_2OBn	4.8 : 1	76[d]
i	*i*Pr	$(CH_2)_2CH{=}CH_2$	4.2 : 1	83

[a] Pyridine (1 eq.) added at the introduction of the second aldehyde. [b] As determined by 400 MHz ^1H NMR of the crude reaction mixture. [c] After flash column chromatography. [d] 2.4 eq. of benzyloxyacetaldehyde used.

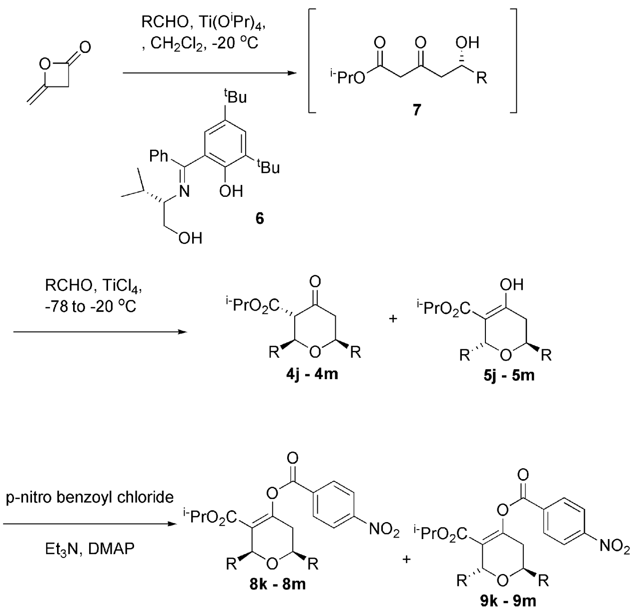
In order to assess the increased efficiency of our new PASE synthesis of these THPs over their traditional stepwise synthesis, we conducted a stepwise synthesis of **4c**/**5c** according to Scheme 2, and compared two sets of recognised and relevant metrics,[6] namely the mass intensity[7] and the atom economy[2] of the traditional route to the PASE route. These data are shown in Table 3. The mass intensity (MI) is defined as the total mass used/mass of product (kg kg^{-1}) and the atom economy is defined as (FW product/FW of all reagents used) × 100%. The mass intensity of the traditional route is therefore calculated to be 1.0790 kg/2.45 × 10^{-4} kg = 4404 kg kg^{-1}, while the traditional synthesis is 29% atom economic. While the mass intensity of the PASE route is only 0.38 kg/4.17 × 10^{-4} kg = 911 kg kg^{-1}, and the atom economy has



Scheme 2 A traditional synthesis of THP rings **4c**/**5c**.

Table 3 Comparison of traditional *vs.* PASE synthesis

Metric	Traditional	PASE
Steps	3	2
Pots	3	1
Yield (%)	38	70
Reaction solvent/mL	54	6
Work-up solvent/mL	260	70
Aqueous/mL	280	80
Drying agent/g	6	3.9
Silica gel/g	19	15
Chromatography solvent/mL	450	315
Reagents/mmol	19.2	19.8



Scheme 3 Asymmetric PASE synthesis of THP rings.

risen significantly to 90%. This clearly shows that combining pot, atom and step economy in general academic organic synthesis can lead to a reduced environmental impact and increased efficiency of a synthesis.

However, one area of waste which has yet to be addressed is that of enantiomeric waste. An increasing number of potential drug candidates are now required as single enantiomers, and the use of a racemic synthesis, no mater how pot, atom and step economic, inevitably leads to 50% of the final product mass being an unwanted by-product, and therefore classified as waste. It is possible to envisage solving this problem with the development of a catalytic asymmetric reaction. Our preliminary studies in this area focused on adapting the Ti(O^{i}Pr)$_4$ promoted asymmetric addition of diketene to aldehydes developed by Oguni and Hayashi.[8]

As we had previously demonstrated that the chiral centre installed in the aldol reaction is configurationally stable under cyclisation conditions,[4] we were confident that if we could form the aldol adducts in enantioenriched form then we would be able to form THPs with at least that level of enantioselectivity. A set of aldehydes were submitted to the conditions reported by Hayashi in the presence of enantiopure Schiff's base **6**. Before the addition of the second aldehyde, an aliquot was removed to determine the % e.e. of the adduct. The remainder of the reaction mixture was treated with a further equivalent of aldehyde and TiCl$_4$ at −78 °C and allowed to cyclise to form the THP products (Scheme 3, Table 4).

As conditions could not be found to assay the % e.e. of **4k–m** and **5k–m** directly due to the lack of chromophores, these pyrans had to be converted into the corresponding enol *p*-nitrobenzoates **8k–m** and **9k–m**. As can be seen from Table 4, the % e.e. of the products ranged from moderate (**9l**) through to excellent (**4j** and **5j**), and there is no appreciable erosion of the enantioselectivity in the Lewis acid promoted Knoevenagel—Michael reaction.

Table 4 Asymmetric PASE synthesis of THP rings

Compound	R	% e.e (7)[a]	Ratio (4 : 5)[b]	% e.e. pyran[c]
j	Ph	82	1 : 2	92 (**4j**)[a,d] >95 (**5j**)[d]
k	Pr	62	1 : 1	59 (**9k**)[e]
l	Cyhex	n/d[f]	1 : 0.4	47 (**9l**)[e]
m	*i*Pr	59	1 : 0.3	59 (**9m**)[e]

[a] Determined by 400 MHz ^{1}H NMR doped with chiral shift reagent (see ESI for full details). [b] As determined by 400 MHz ^{1}H NMR of the crude reaction mixture. [c] Determined by HPLC analysis on CHIRACEL OD–H coulmn (see ESI for full details). [d] These pyrans were crystaline and the difference in % e.e. between them and **7j** is attributed to enrichment of the major enantiomer during crystalisation. [e] % e.e. of the diastereomers **8k–8m** could not be assessed by either 400 MHz ^{1}H NMR doped with chiral shift reagent or HPLC analysis. Precedent suggests (ref. 4) that the % e.e. of these diastereomers is the same as that of **9k–9m** [f] Could not be determined by 400 MHz ^{1}H NMR doped with chiral shift reagents.

In conclusion, we have successfully applied the principles of green chemistry, specifically those of pot, atom and step economy to redesign a synthetic route to highly substituted THPs. The increased sustainability of this route has been quantified by the use of metrics such as mass intensity and atom economy, and it was shown to be significanly 'greener' than our original synthetic route. In addition to this, we have applied these same principles to develop an asymmetric variation of our pot, atom and step economic synthesis of THPs, which formed the desired products in moderate to excellent % e.e. Work is now underway at increasing the environmental benefits of this approach even further and applying these ideas to the synthesis of other molecular families.

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