Organic & Biomolecular Chemistry

Accepted Manuscript

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Subtle Mitsunobu couplings in super-heating: The role of high-throughput continuous flow and microwave strategies

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Abstract

Non-conventional heating techniques, high-throughput microwave-assisted synthesis and continuous flow penetrate almost every scientific field. Mitsunobu coupling is a ubiquitous choice for the dehydrative redox condensation of primary or secondary alcohols with (pro)nucleophiles. The aim of this review is to showcase the ease of subtle Mitsunobu coupling in super-heating. Surprisingly, this strategy is rather non-trivial; considering the sensitivity of reagents, Mitsunobu chemistry is typically performed at lower temperatures or under ambient conditions. In view of the absence of any previous work focusing on this topic, the current review considers the utility of super-heating in fragile Mitsunobu reactions. Therefore, we are anticipating that this review will also bridge some of the apparent gaps in the extant literature by specifically describing the advances made by non-conventional heating assisted by microwave or continuous flow in one of the most powerful stereochemical transformations.

Keywords: Continuous flow/microreactors, microwaves, HTS, Mitsunobu reaction, Fukuyama–Mitsunobu reaction

1. Introduction

Since the first application of microwave-assisted heating to accelerate organic transformations by Gedye and Giguere/Majetich in 1986, this non-conventional heating technique has become an established piece in the synthetic chemist's toolbox.[1] The power of this state-of-the-art technology can be gauged from the preponderance of publications, reviews and books published in the last ~27 years on this subject.[2] The merits of this front-line technique have been shown to be dramatically reduced reaction times (up to seconds), neat reaction profiles, improved reproducibility and minimal waste generation, thereby enhancing the product purities as compared to conductive or convective heating.[3] Arguably, the prevalent utility of this extremely efficient technique is resulting in its application in emerging areas including medicinal

chemistry and drug discovery,[4] polymer sciences,[5] peptide research,[6] material science,[7] nanotechnology,[8] biochemical processes, etc.[9] A dedicated microwave reactor for synthetic chemistry purposes with an operating frequency of 2.45 GHz is commercially available today with a different degree of sophistication with respect to automation that overcomes the controllability, safety and reproducibility issues related to the less desirable household microwave oven.[10] Dedicated microwave synthesisers are designed to irradiate either single reaction vessels (mono- or single-mode) or multiple vessels (multi-mode) simultaneously.[11] The features of specialised microwave reactors are the precise monitoring of reaction pressure and temperature, the accessibility of stirring with simultaneous cooling by compressed air or even by cooling while heating, control over pressure of the reaction, etc. Furthermore, the collective features of multi-mode and mono-mode microwave synthesisers are also commercially available nowadays.[12]

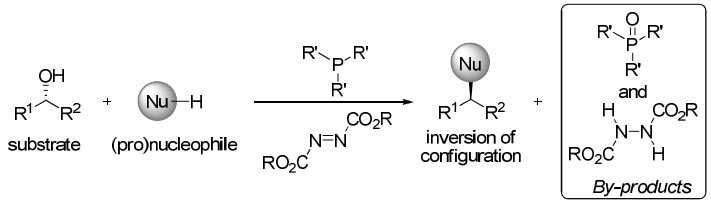
Despite the potential benefits of microwave flash heating in the area of organic chemistry, one severe drawback is the difficulty in scaling up this technology to the multi-kilogram scale, especially to the semi-plant scale. Nevertheless, during the past few years, remarkable progress has been made in translating milligram microwave chemistry to the multi-gram format. However, genuine production-scale volumes of the reaction are extremely difficult to accomplish in the case of microwaves due to the inadequate penetration depth of microwaves into the absorbing materials. Moving from smaller to larger batch sizes, the potential benefits of small-scale microwaves are in fact lost.[13a] A particular fact worth noting is that the rapid heating and cooling profiles obtained in small-scale microwave reactors can often not be duplicated at a large scale due to increased processing times.[13b]

To address these apparent scalability issues, recent studies have focused on translating high-temperature and pressure-batch microwave reactions to scalable continuous flow synthesis.[14] The potential advantage of the continuous processing technique is that it makes scaling up (in fact, 'scaling out') easier without the need for any further re-optimisation via multiple systems in parallel or multi-step single-flow formats.[15] In addition, high temperature and pressure in a flow reactor can be attained by using a fitted back pressure regulator (BPR) unit, which allows the complete replication of the microwave batch experiments.[16] Compared to batch processes (e.g. flasks), flow offers several distinct benefits, including efficient mixing, precisely controlled reaction parameters, software-controlled automated reaction processes, the ability to perform reactions at high temperatures and pressures, easy scaling up, etc.[17] Many previously hazardous reactions can now be safely conducted in flow.[18] Moreover, continuous flow methods can be combined with other enabling technologies to improve productivity significantly. Among them, one of the most innovative developments is the micro-flow device due to its several merits over the traditional flak method.[19] Higher surface-to-volume ratios and shorter diffusion distances compared to flasks can substantially improve heat transfer and reduce mixing times; thus, hot spots are removed and the side reactions are minimised considerably. Materials with very high thermal conductivity, for instance glass, stainless steel, silicone, metal, ceramic, polymer, etc., have been utilised to construct microreactors.[20] These allow extremely rapid heating and cooling rates, therefore eliminating the need to apply the microwave dielectric heating principle.

It should be emphasised that in the literature covered in this review, dedicated microwave equipment was utilised. Undoubtedly, debating the specific or non-thermal microwave effects is not advisable due to inadequate evidence for their existence/non-existence.[21] In the current

outline, rather than providing an exhaustive narration on microwave or flow apparatus, instrumental design, theory, processing techniques, etc., attention has been paid to their merits over classical thermal heating in performing temperature-sensitive Mitsunobu reactions. Furthermore, instances of the super-heating of the most common Mitsunobu chemistry solvent (i.e. THF) in the presence of microwave and continuous flow can be viewed frequently throughout the review. However, the literature on Mitsunobu coupling in the presence of high-temperature continuous flow / microreactors is underdeveloped; the available synthetic application will be discussed in a later section of this review.

2. Mitsunobu reactions



Scheme 1.

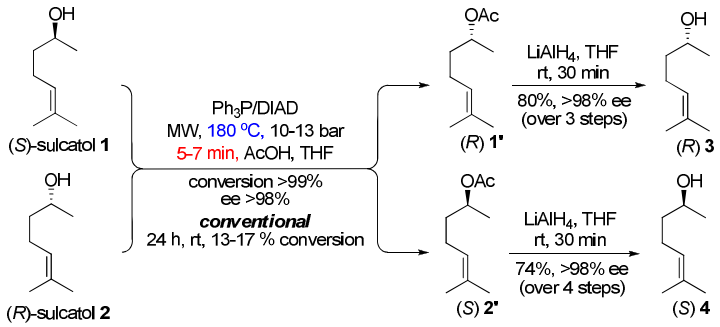
The dehydrative coupling of an alcohol with an acid (pro)nucleophile in the presence of stoichiometric quantities of redox duet, trialkylphosphine and dialkyl azodicarboxylate under mild and virtually neutral reaction conditions is commonly referred to as a Mitsunobu reaction **(Scheme 1).**[22] Since its pioneering discovery (Oyo Mitsunobu, 1967), this reaction has become a standard tool for a plethora of organic transformations due to its stereospecificity, mild reaction parameters and tremendous scope.[23] A straightforward mechanism of this reaction involves the activation of an alcohol from Morrison–Brunn–Huisgen betaine and the subsequent C-O bond cleavage caused by an attacking carboxylate anion to produce the ester with a complete Walden inversion of the alcohol stereocentre. For the most recent detailed discussion on its mechanisms, readers are referred elsewhere.[24] Practically, a wide range of functional groups (for instance, esters, azides, ethers, amines, thioesters, thioethers, cyanides and thiocyanides) can be efficiently

installed by this highly efficient methodology. Thus, this reaction permits C-C, C-N, C-O and C-S bond formation by the condensation of (pro)nucleophile, which is generally acidic (p*K*a 11-13), with primary or secondary alcohols.[25] Despite this ample scope, a severe drawback of this reaction is the use of stoichiometric quantities of redox reagents (e.g. diethyl azodicarboxylate, DEAD and triphenylphosphine (TPP)); therefore, the generation of the corresponding phosphine oxide and hydrazidedicarboxylate by-products often makes the isolation of the desired products cumbersome. However, intense research has been directed towards investigating the modified reagents and the separation strategies that can be used to resolve the copious purification issues.

The merits and limitations of the modified Mitsunobu reagents and emerging separation techniques have been recently highlighted.[26] Remarkably, the catalytic Mitsunobu reaction has also been investigated in one study in which DEAD was employed as a catalytic oxidant in the presence of iodosobenzene diacetate, $PhI(OAc)_2$, as a stoichiometric oxidant, which reduces the role of DEAD to that of the catalyst. By virtue of this strategy, the isolation of the products is streamlined by the required quantity of reagents, reducing the corresponding by-products.[27]

The power of Mitsunobu coupling in the arsenal of organic synthesis, natural products, peptides, purines, nucleosides, nucleotides and many emerging areas can be gauged by the general and specific reviews that have been published over time.[28] The aim of this review is to provide a meaningful insight into the potential of super-heating for this temperature-sensitive transformation. As mentioned, this tactic is rather unconventional for subtle Mitsunobu reactions, as these reactions are preferably conducted at ambient temperatures. Since 2001, when a seminal report was published on microwave-assisted Mitsunobu reactions, a small but growing number of contributions have been unveiled on this enabling technology. Thus, for the sake of brevity, the literature from 2001 to August 2014 has been scrutinised. To the best of our knowledge, this

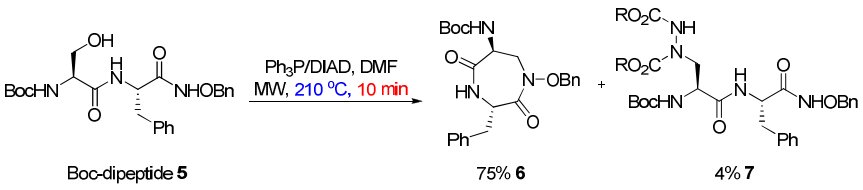
will be the first report to highlight the benefits of super-heating assisted by microwave or continuous flow in the myriad of high-throughput Mitsunobu and Fukuyama–Mitsunobu reactions. A discussion of the power of microwave heating in Mitsunobu couplings has been presented in the following subsections.



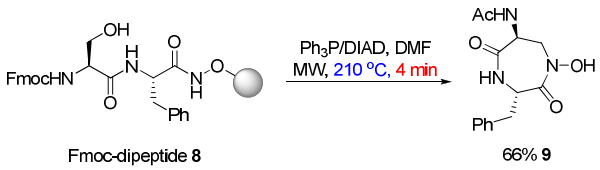
Scheme 2.

2.1 High-temperature stereoselective transformation: (±)-Sulcatol is the male-produced aggregation pheromone of the ambrosia beetles *Gnathotrichus sulcatus* and *Gnathotrichus retusus*. Numerous synthetic methodologies have been pursued for the preparation of either *(R)*- or *(S)*-sulcatol, for instance kinetic resolution by lipase, asymmetric reduction with baker's yeast, alcohol dehydrogenases, synthesis from chiral precursors, etc. Most of them involve multi-step transformations and provide only one of the desired enantiomers, albeit in lower yields. In a pioneering work on microwave-assisted enantio-convergent Mitsunobu inversions, Kappe and coworkers[29] accomplished a temperature-sensitive Mitsunobu reaction, delivering racemisation-free *(R)*- and *(S)*-sulcatols. The optimal condition involved the microwave heating of *(R)*- and *(S)*-sulcatols **1** and **2** utilising Ph_3P/DIAD (DIAD = diisopropyl azodicarboxylate) and acetic acid in a sealed-vial mono-mode reactor in the presence of the most commonly used solvent for Mitsunobu reactions (THF) at 180 °C (10–13 bar) for 5–7 min, to afford the corresponding sulcatyl acetates **1'** and **2'** with a clean S_N2 inversion (99% conversions by GC, 98% *ee*)

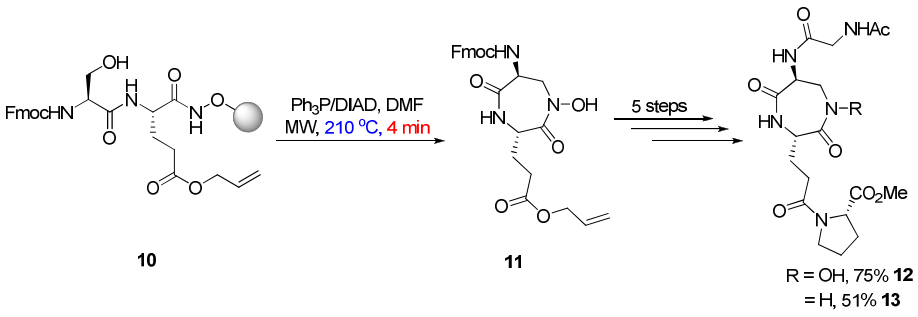
(Scheme 2). Therefore, THF can be super-heated at 180 °C, rather than at its normal boiling point (66 °C), in the presence of microwaves. Finally, the target derivatives **3** and **4** were prepared by subsequent reductive deacetylation utilising $LiAlH_4$ in THF, delivering the corresponding enantiomers with excellent *ee* and high overall yields. In contrast, conventional Mitsunobu inversions resulted in extremely poor conversions (13–17%) after prolonged stirring (24 h) at ambient temperature. As a consequence, Mitsunobu inversions under drastic microwave irradiation in super-heated THF at 180 °C under pressure are highly beneficial to showcase one of the most powerful stereochemical transformations that are usually conducted at lower temperatures in order to achieve the desired stereoselectivities (rt versus 180 °C).



Scheme 3.



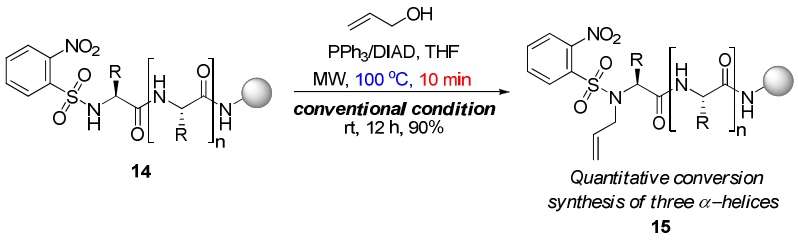
Scheme 4.



Scheme 5.

2.2 Solution- and solid-phase Mitsunobu couplings: Regarding the peptides containing (macro)cyclic ring systems, the conformationally restricted architectures have been widely exploited to investigate the novel 'lead' candidates. Peptidomimetics can dramatically improve biological profiles, for instance binding with an active site or the stability of modified peptide to endopeptidase.[30a] In an exhaustive review, the microwave-assisted synthesis of peptides, proteins and peptidomimetics has recently been outlined.[30b] In this context, the research group of Taddei[30c] has elegantly addressed intramolecular Mitsunobu cyclisation in microwave thermal heating, delivering macrocyclic peptides via solution- or solid-phase strategy. To achieve this synthetic goal, the conformationally constrained peptide **5** was irradiated under mono-mode microwave flash heating in the presence of Ph_3P/DIAD in DMF at 210 ^oC for 10 min in a sealed tube, affording the expected cyclic peptide **6** a yield of 75%, along with competing alkyl hydrazine dicarboxylate **7** (4%) in a trace amount **(Scheme 3).** By contrast, under classical oil-bath heating in toluene at 110 ^oC (12 h), the desired peptide **6** was also obtained in a yield of 63%, in conjunction with a substantial amount of the undesired **7** (26%). However, the use of sterically hindered dicarboxylate (DTAD = Di-*tert*-butyl azodicarboxylate) in a microwave was found to be ineffective in terms of circumventing the formation of **7**. To demonstrate the utility of microwave-assisted Mitsunobu cyclisation on solid-phase couplings, PS-DVB (polystyrene-divinylbenzene)-2-chlorotrytyl resin was employed. The desired Mitsunobu cyclisation of Fmoc-dipeptide **8** proceeded within 4 min under the optimal condition. After the removal of resin and the deprotection of Fmoc, the acetylated cyclic peptide **9** was isolated in a 66% yield **(Scheme 4)**. Interestingly, the merits of this solid-phase Mitsunobu strategy have shown to prepare peptidomimetics **12** and **13** in 75% and 51% yields (respectively) over the five steps **(Scheme 5)**. Undoubtedly, these examples clearly show that Mitsunobu coupling via microwave-assisted

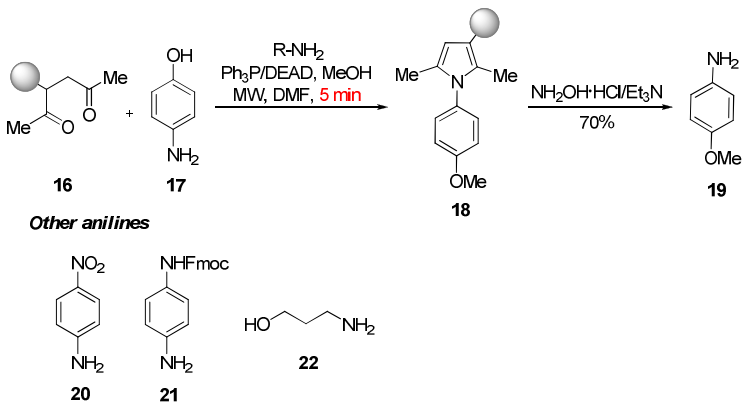
super-heating is highly advantageous in terms of time, yields and the purity of the products as compared to sluggish conductive or convective heating.



Scheme 6.

Similarly, the role of Mitsunobu coupling in decorating peptidomimetics, which is the modification of the Mitsunobu reaction involving *N*-alkylation (C-N coupling), is generally referred to as Mitsunobu–Fukuyama coupling.[31a] In this methodology, the *N*-alkylation of secondary sulphonamide with the redox reagents can be efficiently succeeded in the presence of nitrobenzenesulphonamide pronucleophiles. Following the *N*-alkylation, the sulphonamide moiety can be strategically cleaved by the treatment of thiols.

Arora and coworkers[31b] devised the practical solid-phase Fukuyama modification to synthesise hydrogen bond surrogate (HBS) helices. The resin-bound peptide **14** was heated with allyl alcohol and Ph_3P/DIAD in THF at 100 ^oC in a microwave synthesiser for 10 min, affording the regioselective *N*-allylation quantitatively **(Scheme 6).** Notably, the stirring at room temperature (12 h) also permitted the required allylation in impressive yields, which clearly denotes that reaction time can be effectively reduced in the presence of microwave dielectric heating with equal efficiency (10 min versus 12 h). Under focused microwave heating, the robust Fukuyama–Mitsunobu strategy was proven to be a valuable alternative to ambient conditions in preparing three α-helices domains, which constitute the largest class of protein secondary structures and play a crucial role in mediating protein–protein interactions.



Scheme 7.

In a similar approach, Botta and coworkers[32] achieved Mitsunobu coupling by employing TentaGel S-NH_2 (TG) polymer-bound diketone and anilines via microwave flash heating. The resin-bound acetylacetone **16** and 4-aminophenol **17** were irradiated with Ph_3P/DEAD duet in DMF for 5 min in a sealed-vessel mono-mode reactor, delivering the corresponding methyl ether **18**. In the next step, the 2,5-dimethylpyrrole masking/protecting group was readily cleaved utilising NH_2OH•HCl/Et_3N, with complete restoration of aniline **19** in a yield of 70% **(Scheme 7)**. The aniline variants **20–22** were also employed in this transformation, and the protocol was proven to be a judicious choice for the synthesis of guanidine domains (e.g. Agmatine). The comparison with the conventional Mitsunobu condition was not studied in this paper. Thus, it is apparent that microwave thermal heating has been continually proven to be a highly beneficial tool for the solid- and solution-phase synthesis of invaluable peptidomimetics.

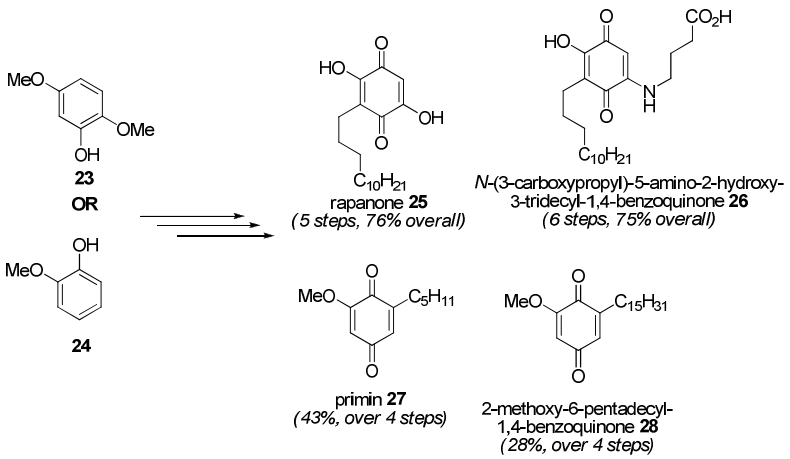
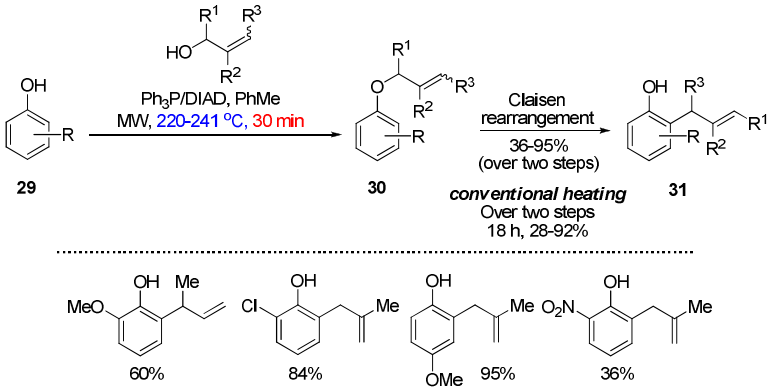


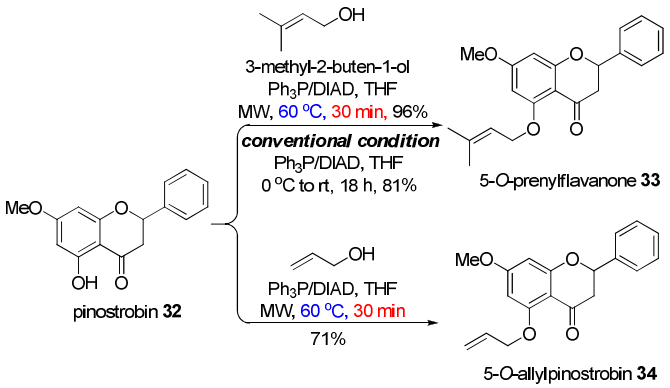
Figure 1.



Scheme 8.

2.3 Combined Mitsunobu–Claisen rearrangement: Quinone natural products have received a great deal of attention for their potent biological activities. For example, adriamycin (doxorubicin) is the front-line anticancer agent.[33a] Primin **27** isolated from the primos *Primula obconica* and *Miconia* species is a potent skin sensitiser and induces contact dermatitis. Further, they are also being used in a wide range of biological processes. Moody and coworkers[33b] developed a step-economical route for the modular synthesis of benzoquinone domains via Claisen rearrangement. Further, a noteworthy development via one-pot microwave-assisted Mitsunobu coupling and Claisen rearrangement was envisaged.[33c] This combined strategy enabled the rapid access of benzoquinone natural products, for instance rapanone **25**, *N*-(3-

carboxypropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone **26**, primin **27**, 2-methoxy-6-pentadecyl-1,4-benzoquinone **28**, etc. **(Figure 1)**. The optimised condition involved the microwave heating of the representative phenols **29**, allyl alcohols and Ph_3P/DIAD utilising toluene as a solvent in a sealed-tube mono-mode microwave synthesiser at 220–241 ^oC for 30 min **(Scheme 8)**. The 2-allylphenols **31** were isolated up to 95% yields, devoid of any noticeable degradation of the redox duet, as well as the products via one-pot Mitsunobu coupling and Claisen rearrangement. It is particularly noteworthy that the reaction time in the microwave was dramatically reduced in comparison to conductive heating, as well as furnishing good to excellent yields over two steps (30 min versus 18 h). It is evident that Mitsunobu coupling can be efficiently carried out at 241 ^oC utilising super-heated toluene in a microwave with excellent overall yields without any noticeable isomerisation of the alkenes. Consequently, microwave heating is useful to expedite the atom economy by diminishing the reaction time and number of steps in this transformation.



Scheme 9.

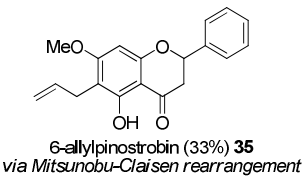
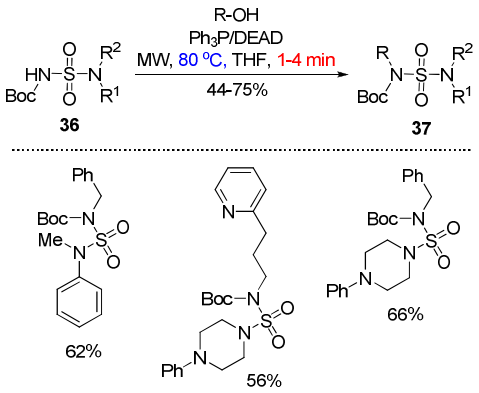


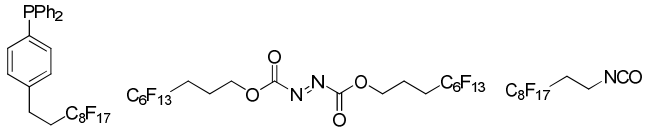
Figure 2.

A closely related approach has been outlined by Higashiyama and coworkers.[34] This involved the *O*-allylation and prenylation of the flavonoid pinostrobin via microwave flash heating. Interest in the synthetic variation of pinostrobin is steadily increasing because of its wide array of bioactivities, such as cytotoxicity, microbial resistance, inflammation resistance, gastroprotection, antioxidant properties, aromatase inhibition, antinociceptive properties, protease inhibition, DNA topoisomerase I inhibition, quinone ruductase induction, etc. Using microwave-assisted prenylation and allylation through the Mitsunobu redox protocol, 5-hydroxy-7-methoxyflavanone (pinostrobin) **32** was heated with 3-methyl-2-butene-1-ol (prenyl alcohol) and allyl alcohol with Ph_3P/DIAD using THF in a sealed vessel in a microwave at 60 ^oC for 30 min, delivering 5-*O*-prenylflavanone **33** and 5-*O*-allylpinostrobin **34** in 96% and 71% yields, respectively **(Scheme 9)**. By contrast, prolonged stirring at room temperature (18 h) furnished **33** at a yield of 81% in otherwise identical conditions. The rapid Mitsunobu coupling in microwaves is greatly facilitated in respect to time and yields in comparison to sluggish ambient stirring. Moreover, the microwave-assisted Mitsunobu–Claisen methodology was also beneficial in preparing 6-allylpinostrobin **35**, albeit at lower yields (33%) **(Figure 2)**. Essentially, Mitsunobu coupling and subsequent Claisen rearrangement can be efficiently accessible in a one-pot format in microwave via an atom- and step-economical reaction sequence.



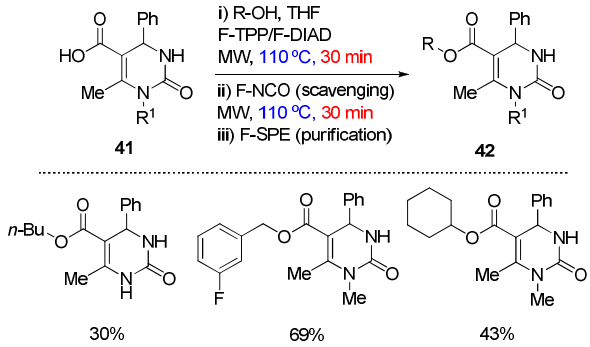
Scheme 10.

2.4 Synthesis of sulphamides: The discovery of sulphonamides as antibacterial agents in the early 1930s was the inception of the fascinating era of chemotherapeutic agents. Since the commercial availability of Prontosil (the first antibacterial), sulpha drugs have been widely utilised for the treatment of microbial diseases.[35a] Sulphamides are also prominent antibacterials; unsymmetrical sulphamides have been found to be highly potent HIV-1 protease inhibitors in comparison to their symmetrical counterparts.[35b] The strategies for the decoration of symmetrical sulphamides are more straightforward than they are for unsymmetrical sulphamides, which are extremely challenging and often low yielding. In search of an easy route for the synthesis of unsymmetrical sulphamides, Ghassemi and coworkers[35c] have taken advantage of microwave thermal heating for Mitsunobu alkylations. Under optimised microwave conditions, Boc-sulphamides **36** and alcohols were heated with Ph_3P/DEAD redox couple in THF, utilising a sealed-tube mono-mode reactor at 80 ^oC for 1–4 min. The corresponding substrates underwent much-improved *N*-alkylation to deliver unsymmetrical sulphamides **37** in moderate to good yields (44–75%) without generating any potential impurities, such as bis-alkylations **(Scheme 10)**. No comparison with classical thermal heating or stirring was made. These sulphamide derivatives were utilised for the authors' drug discovery programme.

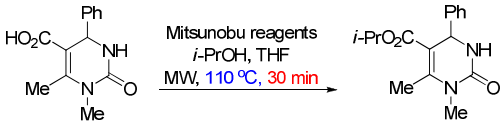


F-TPP **38** F-DIAD **39** F-NCO **40**

Figure 3.



Scheme 11.



Mitsunobu reagents	Yields (%)
TPP/DIAD	75
F-TPP/DIAD	71
TPP/F-DIAD	49

Scheme 12.

2.5 Fluorous Mitsunobu reactions: Multi-component reactions (MCRs) are of increasing interest in medicinal and synthetic organic chemistry.[36a–c] The multi-functionalised DHPM (1,4-dihydropyrimidine) domains synthesised via MCR have widespread therapeutic applications. The fluorous synthesis of DHPM was first introduced by Wipf and Curran in 1997; this is also referred to as a Fuginelli reaction or a fluorous Biginelli reaction.[36d] In a very elegant piece of work, Kappe and coworkers[36e] have achieved fluorous Mitsunobu coupling on DHPM motifs by employing the polymer-bound fluorous Mitsunobu reagents diphenyl-[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine (F-TPP) **38** and bis(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*-perfluorononyl)azodicarboxylate (F-DIAD) **39 (Figure 3)**. F-TPP and F-DIAD were irradiated with DHPM-acid **41** at 110 °C for 30 min, delivering the corresponding esters **42** in moderate to good yields. Fluorous solid-phase extraction was employed to remove F-reagents and F-by-products. Subsequently, fluorous isocyanate, 2-(perfluorooctyl)ethyl isocyanate (F-NCO) **40** was

employed as an electrophilic scavenger to eliminate excess non-volatile alcohol. Notably, this scavenging step was also performed in a microwave under a similar set of temperatures and for a similar length of time **(Scheme 11)**. Surprisingly, this fluorous protocol failed for more complex alcohol (e.g. 1-butynol) or long-chain alcohol (e.g. hexanol). Furthermore, the reactivity of F-Mitsunobu reagents was examined with the corresponding non-fluorous Mitsunobu reagents **(Scheme 12)**. The DHPM-acid **41** was irradiated with non-fluorous redox coupling at 110 ^{o}C for 30 min, affording **43** in a yield of 75%. Employing F-TPP/DIAD produced a similar yield (71%), whereas utilising TPP/F-DIAD produced a drastic reduction in yield (49%) in otherwise similar conditions. The above comparison clearly demonstrates that the fluorous reagent F-DIAD is considerably less reactive in esterification than classical DIAD is. Essentially, the non-fluorous redox reagents were found to be superior to the expensive fluorous reagents in Mitsunobu coupling assisted by microwave for the esterification of DHPM-acids, highlighting the drawbacks of the fluorous reagents in this transformation.

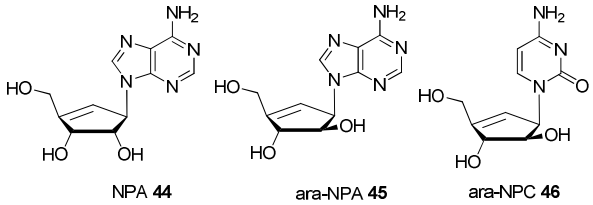
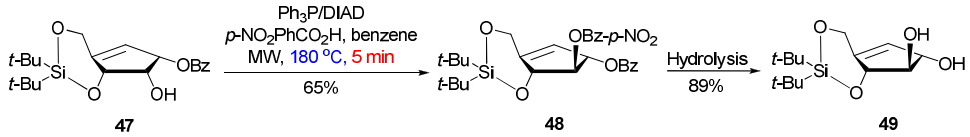
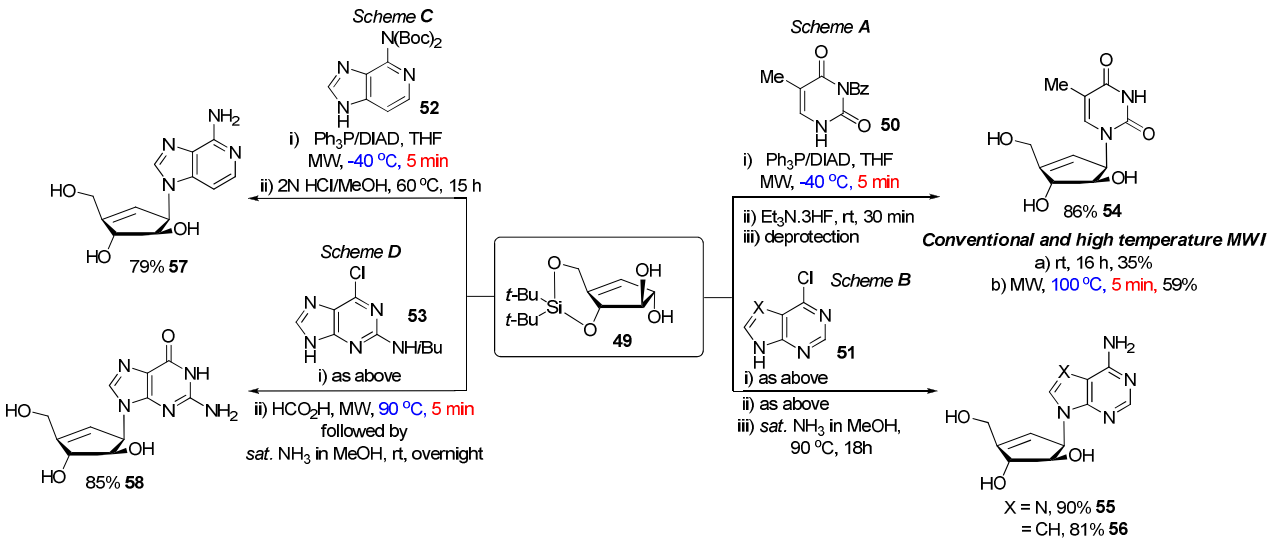


Figure 4.



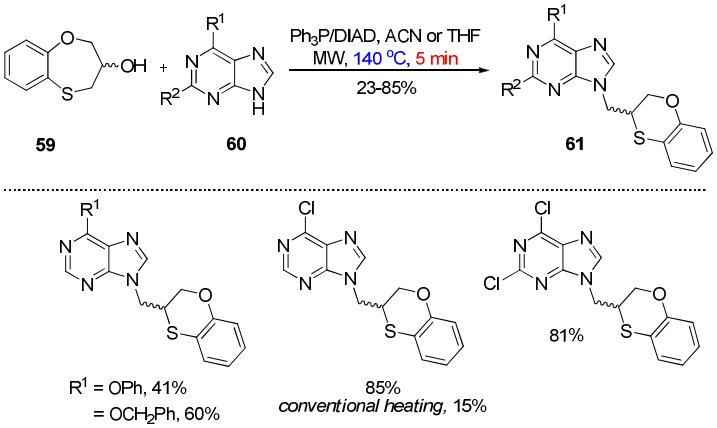
Scheme 13.



Scheme 14.

2.6 Mitsunobu couplings in purines and pyrimidines: The neplanocin family isolated from *Ampullariella regularis*, including neplanocin (NPA), has promising antitumor and antiviral properties **(Figure 4).** The adenine derivative, ara-NPA, has shown less cytotoxicity but has been identified as a prominent antiviral; the cytosine analogue, ara-NPC, has significant antitumor properties.[37a] Mitsunobu coupling is often exploited in nucleoside and nucleotide chemistries but scant references are available regarding microwave super-heating in this context.[37b] A modular approach to Mitsunobu inversion was successfully achieved by Chu and coworkers.[37c] A 1,2-diol intermediate **49** was prepared for 5 min via microwave assistance. The compound **47** was irradiated with *p*-nitrobenzoic acid utilising Ph_3P/DIAD in benzene at 180 °C for 5 min, to afford *O*-benzoyl-protected intermediate **48** in a 65% yield with complete S_N2 inversion. The debenzoylation was accomplished with lithium hydroxide, delivering 1,2-diol **49** in a 89% yield **(Scheme 13)**. Subsequently, the intermediate **49** was subjected to the Mitsunobu redox protocol with nucleobases **50–53** under subzero microwave conditions (-40 °C) using the CEM Discover CoolMate system for a much shorter reaction time (5 min), providing the appropriate neplanocin analogues. After basic work-up and deprotection or amination, this delivered the ara-neplanocin

derivatives **54** (ara-NPT), **55** (ara-NPA), **56** (ara-7DNPA) and **58** (ara-NPG) in good to excellent overall yields **(Scheme 14A–D)**. The subzero microwave condition was used for the first time to prepare ara-3DNPA **57** with a much-improved yield in a single step. Likewise, the synthesis of **46** (ara-NPC) was carried out via Mitsunobu alkylation as a key step, with a reasonably higher (71%) overall yield. The key to success was found to be the CoolMate system, due to the fact that the same reaction was studied at ambient temperature (16 h) as well as at 100 ^{o}C (MW, 5 min), producing decent yields (35% and 59%, respectively) **(Scheme 14A)**. These illustrations demonstrate that Mitsunobu coupling could be furnished successfully through microwave heating at -40 ^{o}C with the help of built-in rapid simultaneous cooling.



Scheme 15.

The 2,3-dihydrobenzo[*b*][1,4]oxathiine and 2,3-dihydrobenzo[*b*][1,4]dioxine structural units are considered to be multi-potent pharmacophores.[38a] The role of purine as a small-molecule inhibitor and as a modulator of the key biological targets has been reviewed extensively.[38b] By employing the fragment-based strategy, Campos and coworkers[38c] probed the Mitsunobu coupling between alcohol, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxathiepin-3-ol **59** and C^2 and C^6 substituted purines **60** in a microwave. In this study, **59** and the versatile purines **60** were heated in a sealed-tube mono-mode microwave synthesiser at 140 ^{o}C for 5 min with Ph_3P/DIAD

in THF or MeCN, affording the drug-like compounds **61** at 23–85% yields **(Scheme 15).** The rationale for the ring contraction in the products was illustrated via S^3 neighbouring-group participation. Surprisingly, in normal oil-bath heating, an undesired side reaction between THF and purine was considerably noticeable, and the expected product was formed in an extremely poor yield of 15%. Thus, the microwave treatment facilitated the reactions in a few minutes as opposed to hours under conductive heating, which also delivered far lower yields (15% versus 85%).

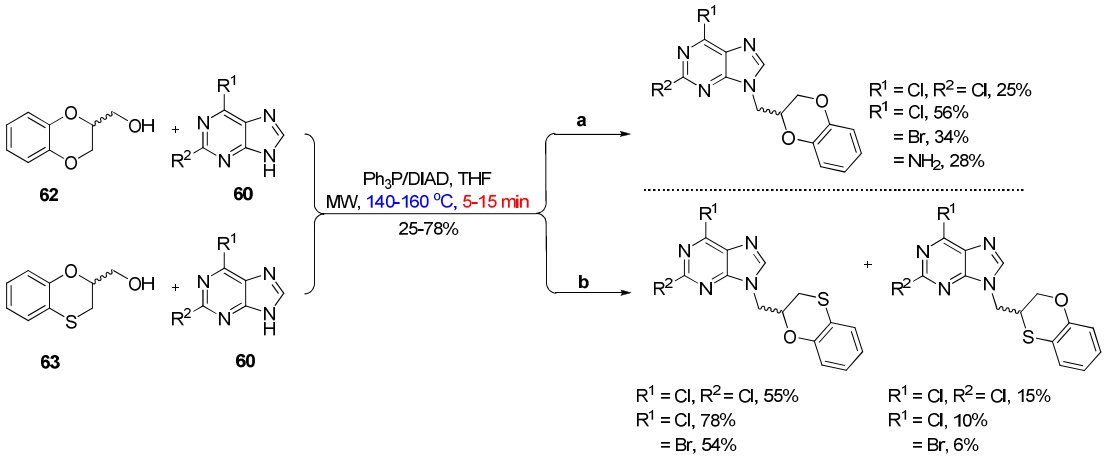
Table 1. Mitsunobu couplings of (*RS*)**-59**, (*R*)**-59** and (*S*)**-59** with various purines.

Alcohol	Nucleophiles	C^3-alkylation	C^9-alkylation
(*RS*)-**59**	6-(*N,N*-Dimethyl)adenine	32% (*RS*)	5% (*RS*)
(*S*)-**59**	6-(*N,N*-Dimethyl)adenine	38%	5%
ee = 95.3%		*ee* = 96.9% (*R*)	*ee* = 94.2% (*R*)
(*R*)-**59**	6-(*N,N*-Dimethyl)adenine	34%	5%
ee = 74.7%		*ee* = 76% (*S*)	*ee* = 73.7% (*S*)
(*RS*)-**59**	2-Chloro-*N*-methyladenine	ND	45% (*RS*)
(*S*)-**59**	2-Chloro-*N*-methyladenine	ND	42%
ee = 95.3%			*ee* = 99.9% (*R*)
(*R*)-**59**	2-Chloro-*N*-methyladenine	ND	49%
ee = 74.7%			*ee* = 73.7% (*S*)
(*RS*)-**59**	*N*-Methyladenine	45% (*RS*)	45% (*RS*)
(*S*)-**59**	*N*-Methyladenine	47%	42%
ee = 95.3%		*ee* = 96.1% (*R*)	*ee* = 99% (*R*)
(*R*)-**59**	*N*-Methyladenine	48%	42%
ee = 74.7%		*ee* = 78.1 (*S*)	*ee* = 59.1% (*S*)

ND = Not detected.

The same group successfully accomplished microwave-assisted Mitsunobu inversions of (*RS*), (*R*)- and (*S*)-alcohols **59** with purine derivatives, such as 6-(*N,N*-dimethyl)adenine, 2-chloro-*N*-methyladenine and *N*-methyladenine.[38d] The corresponding results for the Mitsunobu reactions in microwave dielectric heating are depicted in **Table 1.** Under optimal microwave flash heating, the Mitsunobu inversion can be furnished in moderate to excellent yields (37–90%) with a remarkable *ee* (up to 99.9%). The formation of the regio-isomeric products (C^3

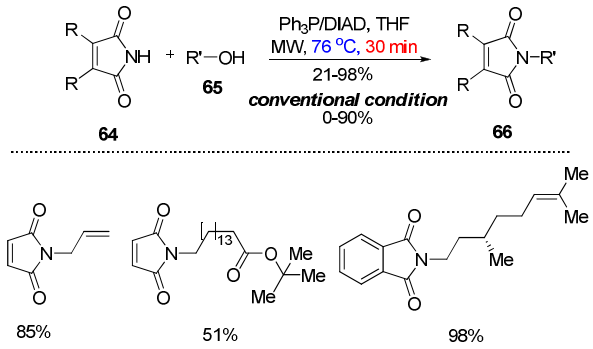
versus C^9 alkylations) can be rationalised by the mesomeric electron-releasing effect of NMe_2 group, which is identical at the N^1 and N^3 positions of the purine nucleus. Therefore, the electronic influence of the NMe_2 group on N^1 and N^3 is identical, while the lake of *N*-alkylation at the N^1 and N^7 could be explained as due to the steric hindrance caused by the NMe_2 group. A highly stereoselective Mitsunobu inversion can be accomplished at a high temperature (140 °C for 5 min) under microwave flash heating in excellent yields without any noticeable degree of racemisation of the products.



Scheme 16.

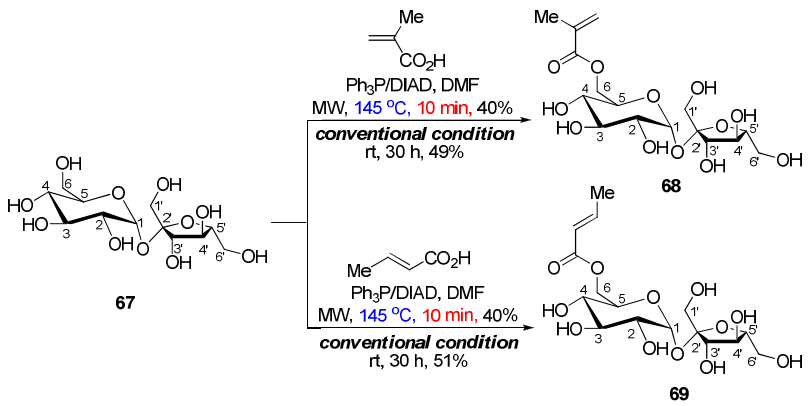
In a similar context, the Mitsunobu alkylation between the racemic alcohols *(RS)*-(2,3-dihydro-1,4-benzodioxin-2-yl)methanol **62** or *(RS)*-2,3-dihydro-2*H*-1,4-benzoxanthiin-2-methanol **63** with purines **60** was investigated by the same group. The purine variants **60** were heated with **62**, employing Ph_3P/DIAD in THF at 140–160 °C for 5–15 min irradiation time in a sealed-vessel mono-mode reactor, which led to regioselective Mitsunobu coupling in modest yields of 25–56% **(Scheme 16)**.[39a] Notably, under the optimal microwave parameters, the Mitsunobu coupling between *thia*-analogue **63** and purines **60** was also successfully accomplished in moderate to good yields as a racemic mixture, despite the isomerisation of the product being observed through sulphur neighbouring-group participation[39b] without interrupting

the N^9 regioselectivity. No straightforward comparison with the classical Mitsunobu conditions was made. Thus, highly efficient chemo-, regio- and stereo-selective Mitsunobu couplings assisted by microwave flash heating can be successfully applied in purine chemistry with good to excellent yields.



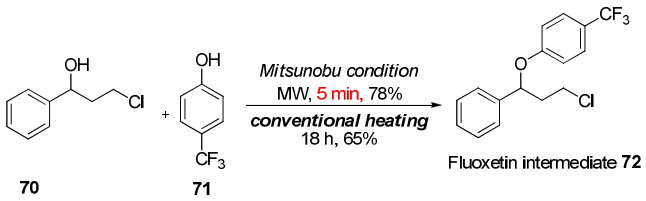
Scheme 17.

2.7 Alkylation of maleimides and phthalimides: Mayer and coworkers[40] studied the direct *N*-alkylation of Michael-acceptor terminal maleimides and phthalimides under Mitsunobu conditions by utilising alcohols and alkyl group donors. The maleimides or phthalimides **64** were irradiated with alcohol variants **65** in the presence of Ph_3P/DIAD (2 equiv.) under microwave thermal heating at 76 ^oC for 30 min, furnishing facile *N*-alkylations **66** in moderate to excellent yields **(Scheme 17).** The challenging alcohols, for instance allyl alcohol, benzyl alcohol, 3-buten-1-ol, alcohol with long-chain alkanoic esters, etc. can be effectively used in this Mitsunobu protocol. Conventional ambient stirring was found to be extremely sluggish (24 h), as it proved difficult to react most of the alcohols with the redox reagents. No specific or non-thermal microwave effects were observed for this transformation. Undoubtedly, high-throughput *N*-alkylation was achieved within a short period of time with excellent yields.



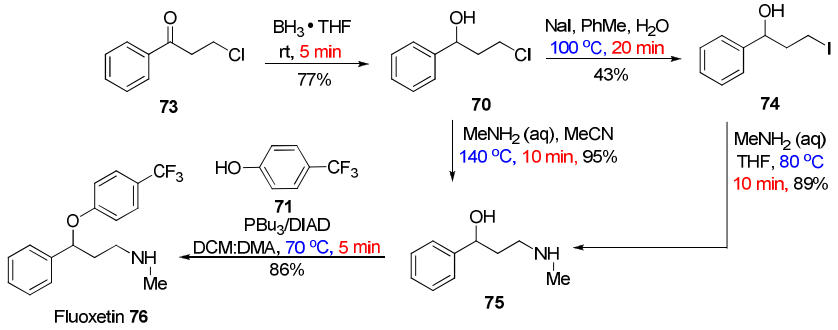
Scheme 18.

2.8 Chemoselective Mitsunobu coupling of sucrose: In a nice illustration, Mitsunobu esterification of the complex polyols of carbohydrate feedstock (e.g. sucrose) in a highly chemoselective fashion was elaborated by Barros and coworkers.[41] The sucrose **67** was irradiated in the presence of Ph_3P/DIAD duet with the nucleophilic partner methacrylic acid or crotonic acid in a highly microwave-absorbing dipolar aprotic solvent DMF at 145 °C for 10 min. The chemoselective esterifications were successfully achieved with 40% yields of sugars **68** and **69** in the case of both nucleophiles **(Scheme 18)**. In contrast, comparative or slightly higher yields were found with room-temperature stirring for an exceedingly longer reaction time (30 h), furnishing a mixture of 6-*O*-monoester and 6,6'-*O*-diesters of the sucrose. Remarkably, the microwave-assisted heating benefitted the Mitsunobu esterification of the unprotected sucrose, bearing eight equivalent hydroxyl groups with very similar reactivities in respect to time (30 h versus 10 min) and chemoselectivity (mono- versus mono- and di-esters).



Scheme 19.

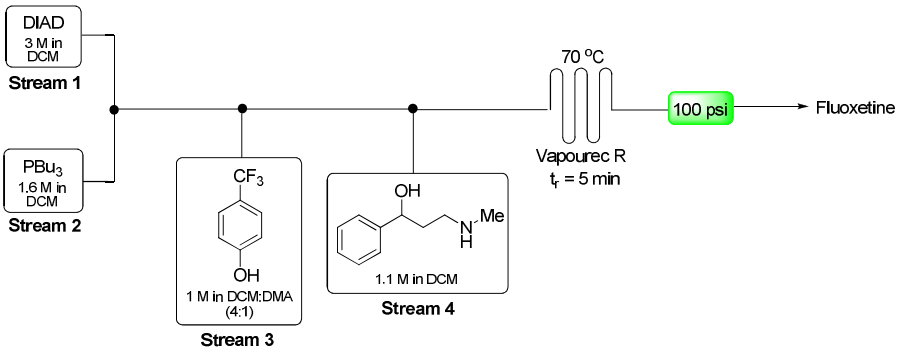
2.7 *Synthesis of Fluoxetin in microwave and flow:* Microwave-assisted Mitsunobu coupling has also proven to be successful in the synthesis of the antidepressant Fluoxetine intermediate **72**. Mitsunobu coupling between 3-chloro-1-phenylpropan-1-ol **70** and 4-(trifluoromethyl)phenol **71** under microwave thermal heating delivered a 78% yield within 5 min irradiation time, while conventional oil-bath heating afforded a yield of 65% after prolonged stirring at room temperature (18 h). **(Scheme 19).**[42] No comparisons with other experimental observations or detailed studies on Mitsunobu coupling were made. The flow chemistry approach for the synthesis of (±) Fluoxetine is depicted as follows.



Scheme 20.

The synthesis of Fluoxetine (Prozac) via multiple flow-processing steps has been elegantly addressed by Sanderson and coworkers.[43] The overall reaction pathway for the synthesis of the final drug is depicted in **Scheme 20**, and all the steps are elaborated in the commercially available Vapourtec R series flow system.

In view of the focus of this review, herein we scrutinise the flow-assisted Mitsunobu coupling rather than providing an exhaustive discussion on the flow chemistry of the individual steps leading to the synthesis of the final drug.



Scheme 21.

The flow diagram to implement Mitsunobu coupling is portrayed in **Scheme 21.** Four different reagent reservoirs containing DIAD (3 M in DCM), PBu_3 (1.6 M in DCM), *p*-hydroxybenzotrifluoride (1 M in DCM/*N,N*-dimethylacetamide: 4/1) and 3-(methylamino)-1-phenylpropan-1-ol (1.1 M in DCM) were introduced individually, after rigorous optimisation in the flow reactor. The DIAD and PBu_3 were pumped through to generate phosphonium betaine intermediate in situ; next, *p*-hydroxybenzotrifluoride and 3-(methylamino)-1-phenylpropan-1-ol were introduced by two separate streams. All four streams of solutions were mixed using a T-connector and were finally heated by using a PFA tubing reactor at 70 ^{o}C for 5 min (residence time, t_r = 5 min). After routine work-up and purification, this delivered (±) Fluoxetine at a yield of 86% (4.8 mmol/h), while the room-temperature flow condition was not successful and furnished with far fewer conversions. Remarkably, the direct amination of **70** to **75** was easily performed in flow due to BPR, as otherwise it is extremely difficult to achieve in flasks, thereby reducing the number of steps in the complete drug sequence. Thus, a multi-step flow approach for the synthesis of (±) Fluoxetine can be developed in an efficient, scalable and step-economical synthetic route that can replace the conventional flask method for the total synthesis of the drug.

3. Conclusion and future perspectives

Apparently, microwave thermal heating or continuous flow has become a very routine exercise in every chemical arena. The sensitivity of this reaction would suggest that Mitsunobu couplings in super-heating would have very little success. The current review provides a roadmap of the potential applications of microwaves in fragile Mitsunobu reactions, which are typically reported under mild heating or at ambient temperature. Microwave heating seems to be particularly competitive with the redox Mitsunobu reagents, not only bringing sluggish reactions down to minutes but also minimising the undesired side products, as well as preventing the reagents from decomposition at very high temperatures.

This review also highlights the merits of super-heating produced by batch microwave reactors or continuous flow in respect to time, yield, undesired side reactions and purity (both chiral and product) in comparison to conductive or convective heating. From the literature surveyed, it is clear that the temperature window to perform Mitsunobu chemistry in microwaves or flow is -40 ^{o}C to 241 ^{o}C with excellent stereo- or chemo-selectivities. The fast-growing field of continuous flow/microreactors will also have tremendous impacts on miniaturising the Mitsunobu chemistry. We hope that the content covered in this review will be useful to the synthetic chemistry community who are interested in accomplishing one of the most widely utilised Mitsunobu reactions in a very easy and highly scalable way (>4,500 citations in *SciFinder* since its discovery until June 2014).[22] The key learning points of this review are as follows:

- Fragile Mitsunobu reagents are compatible under super-heating (e.g. 241 ^{o}C).
- Subzero microwave irradiation (-40 ^{o}C) also enables Mitsunobu coupling to be conducted effectively.
- The temperature window of Mitsunobu chemistry in continuous flow or microwaves was

found to be -40 ^{o}C to 241 ^{o}C for 1–30 min irradiation time.

- Stereochemical Mitsunobu transformations can also be achieved in the presence of harsh microwave heating without affecting the desired stereoselectivities.

Acknowledgements

Financial support of the DST (India), Government of Gujarat (India) and Saurashtra University, Rajkot (India) are gratefully acknowledged. The authors are also thankful to Harrison Daly for proofreading of this manuscript.

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