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Tandem Oxidation Processes Using Manganese Dioxide: Discovery, Applications, and Current Studies

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ABSTRACT

"One-pot" processes in which alcohol oxidations are combined with further elaboration of the carbonyl intermediate are reviewed. Sequential processes are briefly discussed, but most attention is centered on tandem processes; that is, oxidations carried out in the presence of a nucleophilic trapping agent, rather than those in which the trapping agent is added after the oxidation is complete. As part of this Account, a comprehensive review of the discovery of tandem oxidation processes (TOP) will be given together with applications in alkene-forming reactions, cyclopropanations, and imine, oxime, amine, and heterocycle formation.

1. Introduction

Preparative procedures in which two or more transformations are carried out as a "one-pot" process offer a number of advantages to the organic chemist: in particular, they result in a reduced number of operations, giving significant time-cost benefits, but they also can often allow "difficult" intermediate compounds (i.e., those that are volatile, toxic, or otherwise noxious) to be prepared and elaborated *in situ*, thus preventing problems associated with their isolation and handling. To this end, a range of "tandem oxidation processes" (TOP) utilizing MnO_2 in combination with a nucleophilic trapping agent have been developed by the York group and have found applications in the wider chemical community. In this Account, the discovery of the MnO_2 TOP methodology is reviewed, followed by its applications. The use of this technology by other groups is also summarized, as are related processes based on other oxidants.

2. Background and Discovery of Manganese Dioxide TOP Sequences

The MnO_2 TOP sequence was first developed during investigations to establish a synthetic route for the preparation of the manumycin family of antibiotics.[1−4] The key disconnection in this approach, as illustrated in Scheme 1, produced bromodienamide **2**, which was utilized in a Stille coupling procedure in the successful synthesis. Amide **2** was prepared from ester **3**, which in turn could be obtained by the Wittig olefination of *E*-3-bromopropenal **4** (caution: potential mutagen).

In initial studies, 3-bromopropen-1-ol **5** was oxidized to give aldehyde **4**, which was then treated with (carboethoxymethylene)triphenylphosphorane, but using a range of oxidants, the overall yields of dienoate **3** were typically 10−30% over the two steps. The highly lachrymatory nature of bromoenal **4** also caused problems, as did its propensity to isomerize/oligomerize,[5] upon isolation. To overcome these difficulties, a one-pot sequential Swern oxidation−Wittig trapping procedure, as popularized by Ireland,[6] was explored but with disappointing results, again emphasizing the labile nature of bromoenal **4**. Eventually, Dr. Xudong Wei modified the process by mixing together alcohol **5**, MnO_2, and the stabilized Wittig reagent in the same reaction vessel.[2,3] This approach was devised to trap aldehyde **4** as it was produced (as opposed to pregeneration in the sequential Ireland sequence); MnO_2 was chosen in view of its mild, heterogeneous nature to minimize the chance of it reacting with the stabilized Wittig reagent (see section 4 for a brief discussion of activated MnO_2). We were delighted to discover that this procedure afforded an excellent 78% yield of **3**, mainly as the desired *E*,*E*-isomer.[3] This method was dubbed a tandem oxidation process (to differentiate it from the consecutive Ireland procedure). This procedure for preparing **3** was subsequently employed by Negishi's group in a route to polyunsaturated macrolide antibiotics.[7]

The generality of this process was explored using both *E*- and *Z*-3-bromopropenol **5** and **6** (Scheme 3).[8] A range of stabilized Wittig reagents were shown to be compatible with the technology, although ketone-stabilized phosphoranes gave slightly lower yields than their ester counterparts. In addition, the faithful retention of the original

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Jonathan Foot graduated from the University of Edinburgh in 2001. He then joined Prof. Richard Taylor's research group at the University of York, where his Ph.D. involved TOP methodology, the Ramberg−Bäcklund reaction, and synthetic approaches to antiviral agents. He is currently a research fellow with Prof. Martin G. Banwell at the Australian National University, Canberra.

Steven Raw graduated from UMIST in 1999 and then joined Professor Richard Taylor's group at York, where his Ph.D. studies concentrated on synthetic approaches to the salicylate natural products. Postdoctoral work in the same group involved the development of new TOP sequences and a variety of methodologies for the construction of heterocyclic systems. He is now working as a Senior Chemist in Process Research and Development with AstraZeneca.

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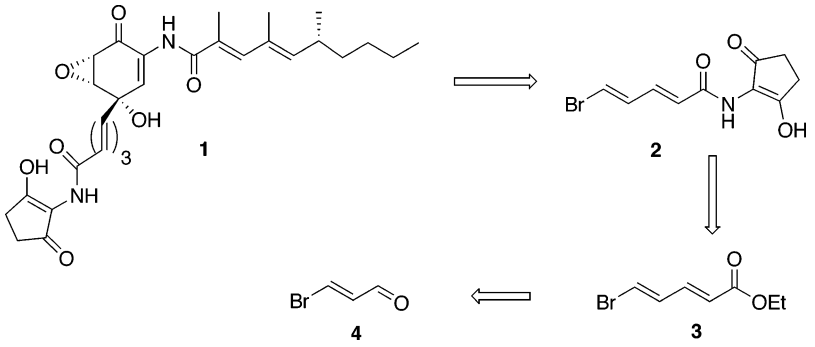
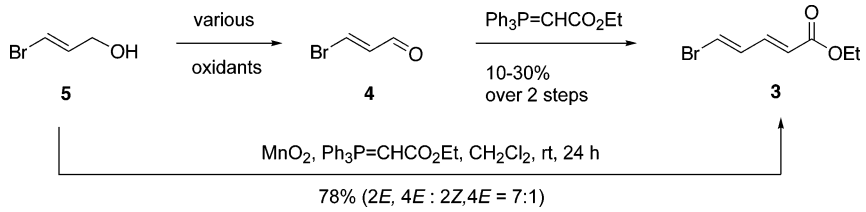
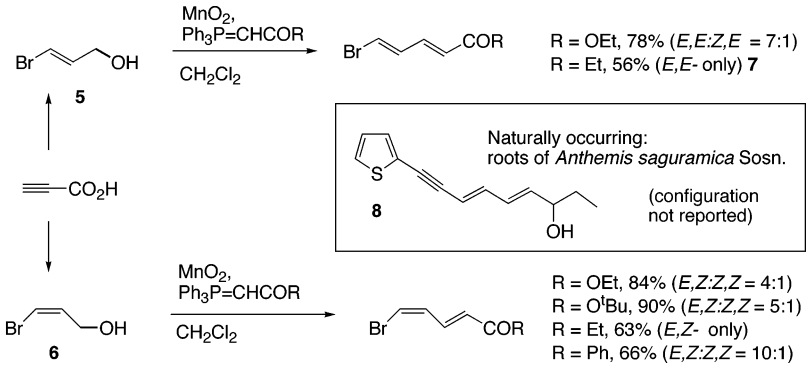
Scheme 1



Scheme 2



Scheme 3



stereochemistry (*E* or *Z*) in the above processes was noteworthy; i.e., the intermediate aldehydes were trapped before any isomerization took place. Adduct **7** was elaborated to prepare the simple natural product 9-(2-thienyl)-nona-4*E*,6*E*-dien-8-yn-3-ol **8**.[8]

This study prompted us to carry out further research into the development and applications of one-pot tandem oxidation procedures. Before discussing this research, however, related research in this area will be reviewed.

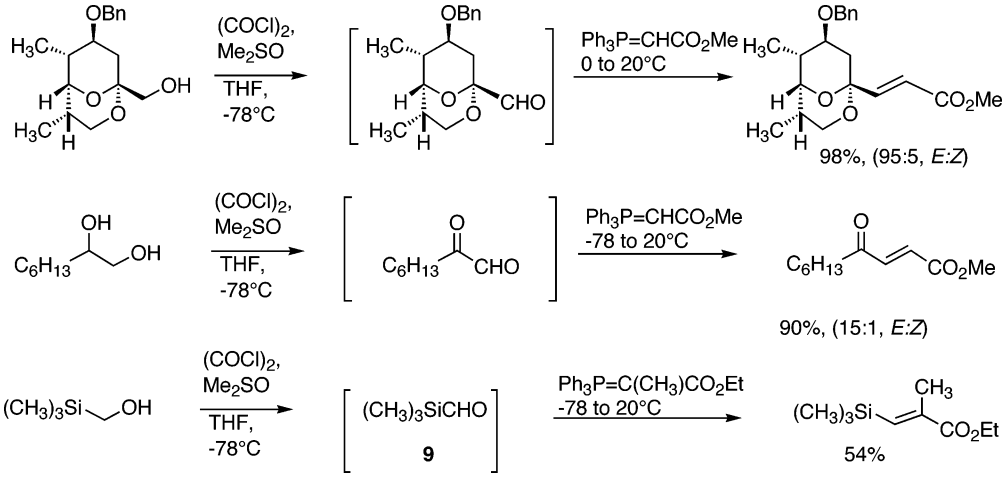
3. Related Tandem Oxidation Processes

The sequential one-pot Swern oxidation−Wittig trapping procedure developed by Ireland and Norbeck[6] is an important milestone in this area. As shown in Scheme 4, three unstable aldehydes were prepared and then treated *in situ* with stabilized phosphoranes as trapping reagents (an additional carbohydrate example using MeMgBr as the trapping agent was also reported).

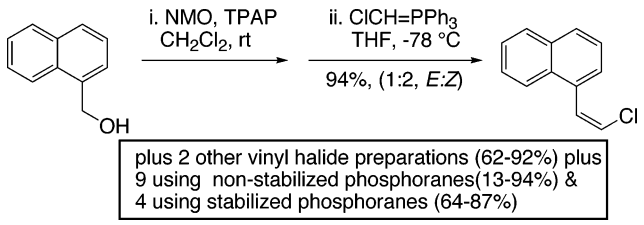
The Ireland procedure involves a sequential one-pot protocol; the trapping reagent is added after the oxidation is complete. More recently, the Ley group have described a sequential oxidation−Wittig procedure using tetra-*n*-propylammonium perruthenate (TPAP) with both stabilized and nonstabilized Wittig reagents.[9] In addition, a one-pot sequential route to vinyl halides was described (Scheme 5).[9] The Bressette group subsequently developed a sequential route that involves PCC/Celite.[10]

The first truly tandem (definitions and examples of sequential and tandem/domino/cascade procedures have been reviewed[11]) oxidation−trapping sequence was reported by Huang in 1987.[12] During the synthesis of carbon-14-labeled CI-933 **13**, which has amnesia-reversal activity, aldehyde **11** was required (Scheme 6). However, despite several procedures being tried, aldehyde **11** could not be obtained by oxidation of alcohol **10**. Fortunately, Huang found that by carrying out the oxidation using the Dess−Martin periodinane in the presence of Wittig reagent **14**, the desired unsaturated ester **12** could be prepared efficiently. The original procedure developed to prepare **12** from **10** involved a lengthy eight step route with several protection−deprotection steps and gave only a 20% overall yield.[12] Thus, the benefits of the tandem procedure in terms of reducing the number of operations (one versus eight) and yield (78 versus 20%) are clear, as are the advantages in terms of solvents, time, waste disposal, etc.

Scheme 4



Scheme 5



The scope of the tandem oxidation−Wittig procedure using the Dess−Martin periodinane was expanded by Barrett et al. They employed a range of activated and unactivated alcohols, with two examples being shown in Scheme 7.[13] The addition of benzoic acid is noteworthy; this was reported to "accelerate the reaction and to enhance the *E*:*Z* selectivity of the Wittig reaction" (presumably by catalyzing cis/trans isomerization).[13]

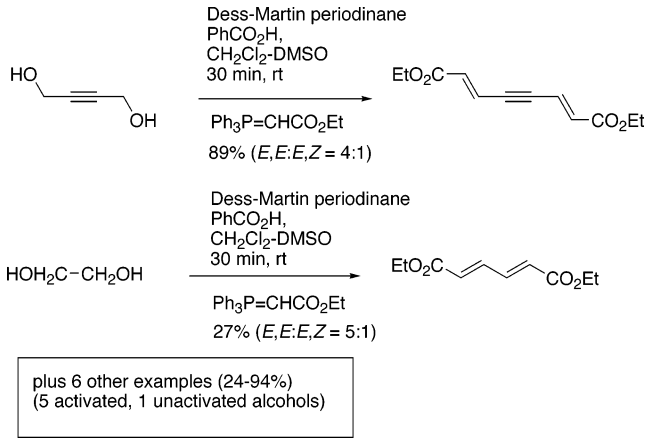
After the MnO_2 TOP protocol was published, Matsuda's group reported the use of barium permanganate for similar one-pot reactions with stabilized ylides to afford unsaturated esters and nitriles (Scheme 8).[14] The use of this tandem methodology on a cyclopropyl carbinol and on a carbocyclic nucleoside is noteworthy.

Crich and Mo subsequently used 2-iodoxybenzoic acid (IBX) as an *in situ* oxidant with a stabilized Wittig reagent for the preparation of several 2′-deoxynucleosides (one example is shown in Scheme 9a).[15] The stability of nucleoside bases to these conditions is noteworthy, as is the fact that the secondary alcohol does not need protecting. More recently, it was shown that this IBX procedure is applicable to a range of alcohols (Scheme 9b).[16]

Later, Kim et al. reported the development of an *in situ* oxidation−Wittig reaction, which utilized aerobic oxidation catalyzed by [(*eta*-*p*-cymene)$RuCl_2]_2$ **15** (Scheme 10). A range of alcohols were employed, although yields were highly substrate-dependent.[17]

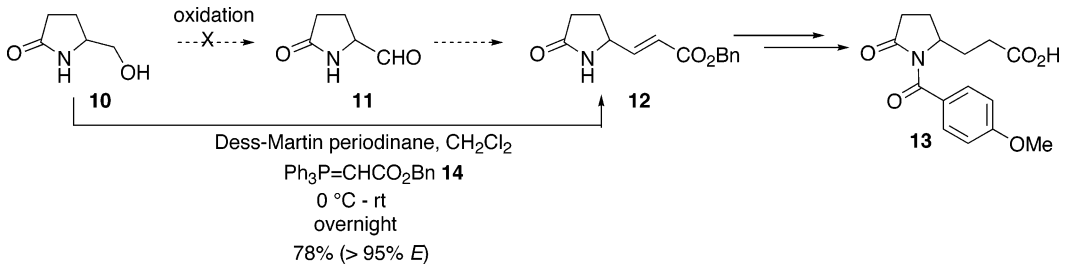
More recently, tandem oxidation-stabilized Wittig reactions have been carried out using pyridinium chlorochromate (Scheme 11).[18] Success was achieved with a range of activated and nonactivated alcohols.

Scheme 7

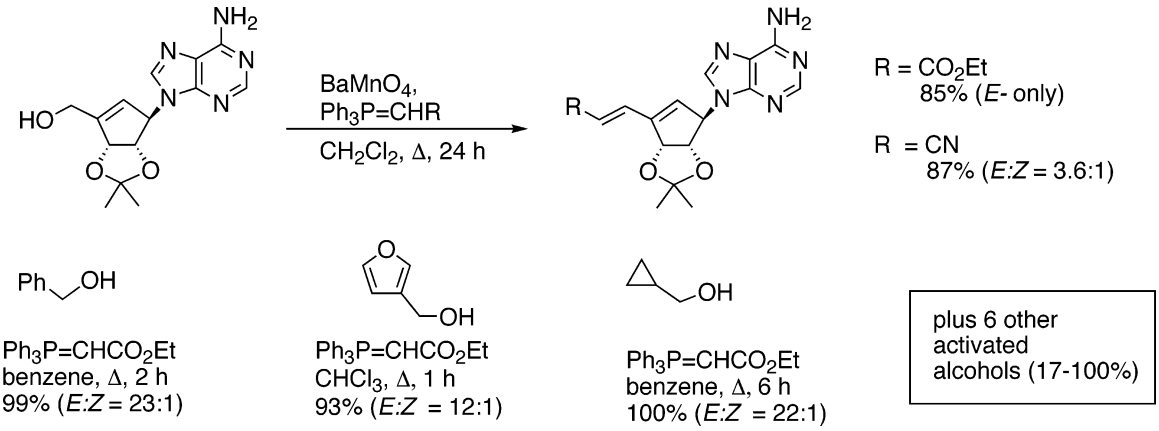


Despite the fact that a range of oxidizing agents have been employed in one-pot reaction oxidation sequences, we believe that MnO_2 has much to offer, largely because of the simplicity of use (see section 4) but also because its mild heterogeneous nature confers compatibility with a range of nucleophilic trapping agents (and even with reductants, as described in section 6b).

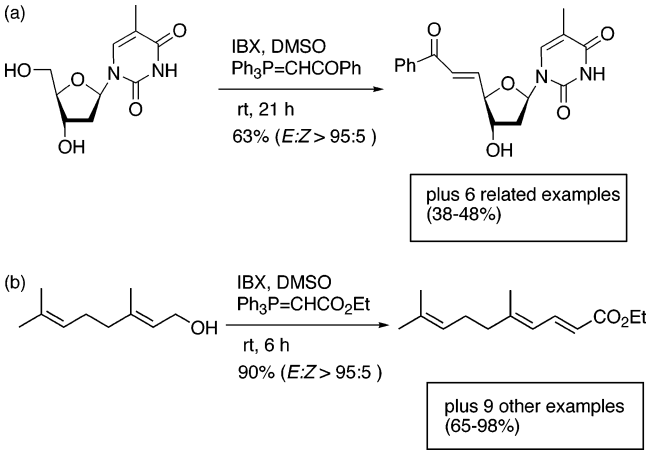
Scheme 6



Scheme 8



Scheme 9

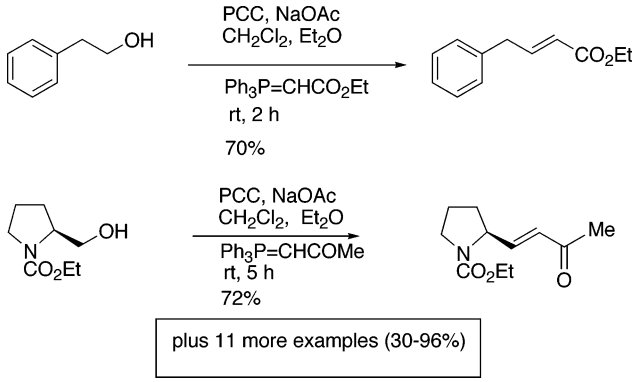


4. Activated Manganese Dioxide: A Brief Review

The first report of activated MnO_2 as an organic oxidant came in 1948, when it was found to give excellent yields of retinal **17** from vitamin A **16** (Scheme 12).[19] Detailed reviews on activated MnO_2 are available,[20,21] and what follows is a brief summary.

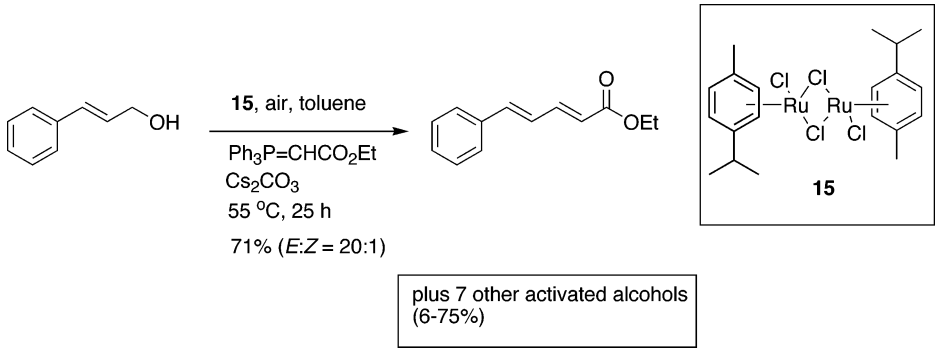
Activated MnO_2 can be prepared by a number of procedures,[20,21] most commonly by reduction of potassium permanganate, but it is also commercially available. Investigations into the exact nature of activated MnO_2 showed a complex structure, which was dependent upon the method of preparation. Stoichiometric analysis of the active species revealed the presence of lower oxidation state (Mn^{II} and Mn^{III}) oxides and hydroxides and a large number of associated water molecules, both bonded and nonbonded.

Scheme 11

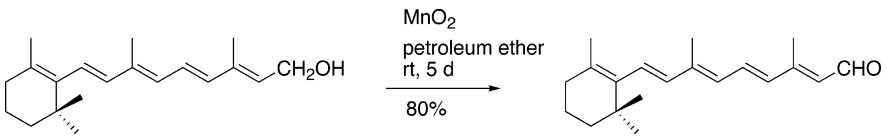


The low toxicity, low cost, and ease of handling of activated MnO_2, combined with its commercial availability and the absence of hazardous additives/byproducts, are attractive, and it is widely employed as a mild oxidant in organic chemistry. It is most commonly employed for the selective oxidation of activated alcohols (allylic, propargylic, benzylic, etc.) to form α,β-unsaturated aldehydes (without over-oxidation) and ketones. Oxidations are carried out under mild, neutral conditions in a range of hydrocarbon, chlorinated hydrocarbon, and ethereal solvents. The heterogeneous nature of the oxidant means

Scheme 10

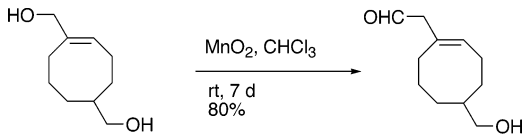


Scheme 12



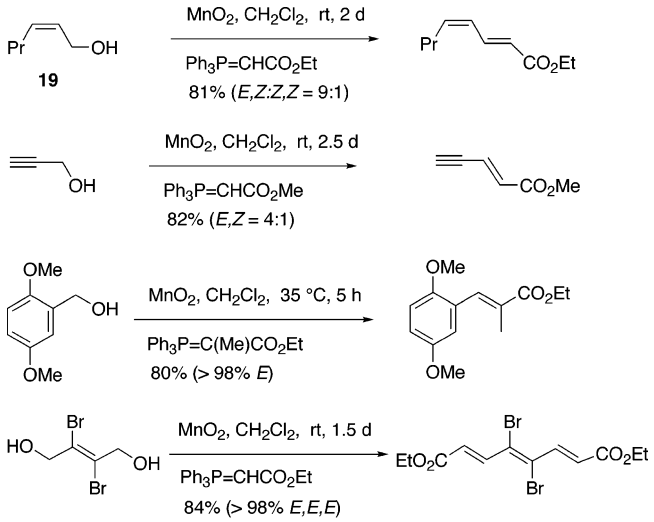
Vitamin A **16** Retinal **17**

Scheme 13



18

Scheme 14



19

plus 6 more examples of activated alcohols (51-81%)

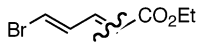
that the workup often consists of simple filtration followed by evaporation of the solvent. In addition, the recovered oxidant can be reactivated/recycled.[22] An excess of oxidant is usually employed (ca. 10 equiv is typical, but see Scheme 46 for catalytic use[23]).

Oxidation of polyunsaturated alcohols with MnO_2 usually results in the complete conservation of double-bond stereochemistry. The selectivity of MnO_2 as an oxidant is exemplified in the oxidation of 1,5-bis(hydroxymethyl)-cyclooctene **18** (Scheme 13).[24] For alcohol oxidation, both ionic and radical mechanisms have been described: for a more detailed discussion, see reviews on this topic.[20,21] Activated MnO_2 has also been used for the oxidation of phenols as well as other classes of organic substrates, including amines, hydazines, and heterocyclic compounds.[20,21]

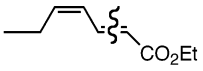
5. Manganese Dioxide TOP—Wittig and Related Reactions

a. Using Stabilized Ylides. Following our first report of TOP sequences in the synthesis of bromodienoate esters,[2,3,8] MnO_2 oxidation-stabilized Wittig trapping reactions have been extensively explored for the elaboration of alcohols to give conjugated alkenes, without the need to isolate the intermediate aldehydes. In terms of activated alcohols (Scheme 14),[25] allylic, propargylic, and benzylic examples were all performed successfully, and diols were

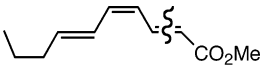
Scheme 15



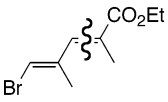
3, Negishi and colleagues[7]
68%



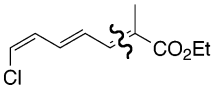
20, Petroski[26]
63% (*E,Z:E,E* > 98:2)



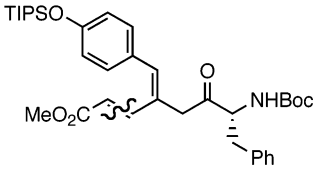
21, Khrimian[27]
62% (*E,Z,E:Z,Z,E* = 95:5)



22, Nicolaou and colleagues[28]
91%

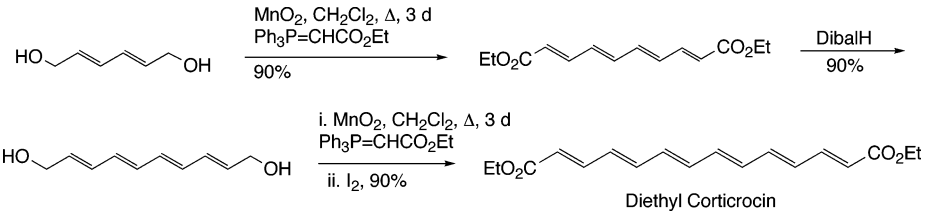


23, Mladenova and colleagues[29]
80% (*E,E,Z:Z,E,Z* = 87:13)
plus 14 related examples



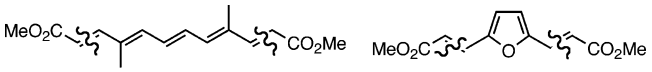
24, Aitken and colleagues[30]
75%

Scheme 16



Diethyl Corticrocin

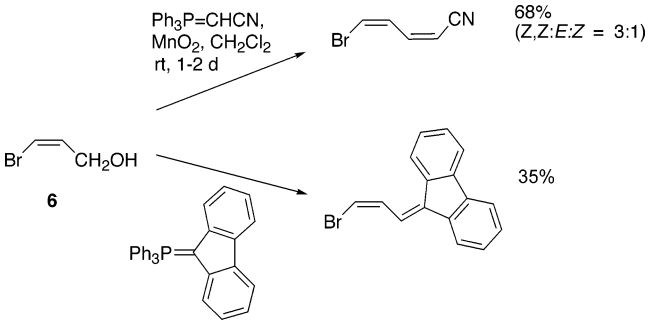
Scheme 17



25, Donate and colleagues[32] 75%

26, McDermott and Stockman[33] 87% (*E,E:E,Z* = 6.6:1)

Scheme 18



also employed as "two-directional" substrates. The successful homologation of *Z*-allylic alcohols (e.g., **19**) with complete retention of the pre-existing alkene geometry is noteworthy.

This methodology has been extensively adopted by other groups (Scheme 15).[7,26−30] Negishi's group used bromodiene **3** in a route to polyunsaturated macrolide antibiotics;[7] products **20** and **21** were employed to prepare insect pheromones;[26,27] bromodieneoate intermediate **22** was used in the total synthesis of the apoptosis-inducing natural product apoptolidin;[28] a range of ω-chloro-trienoic and tetraenoic esters including **23** were employed to prepare polyene natural product targets;[29] and adduct **24** was employed in synthetic approaches toward the marine natural product, cyclotheonamide.[30]

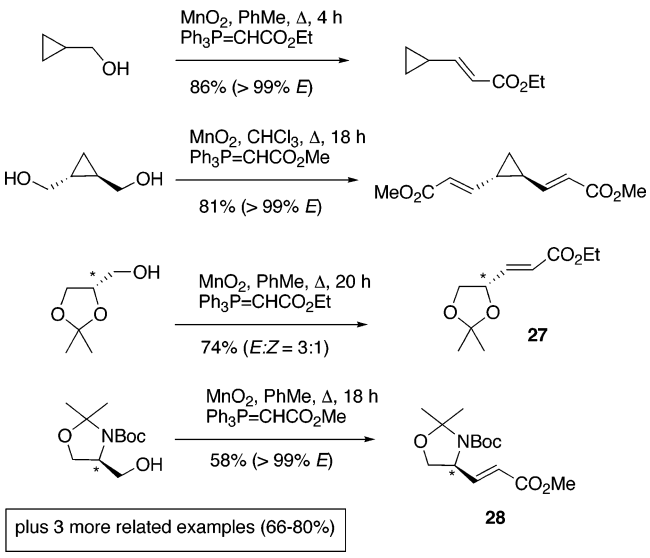
In terms of the TOP homologation with "two-directional" substrates, Blackburn and Taylor prepared diethyl corticrocin using TOP−Wittig procedures twice, as shown in Scheme 16.[31] More recently, Donate et al. used diester **25** as part of an expeditious synthesis of crocetin dimethyl ester and crocetindial,[32] and McDermott and Stockman used similar chemistry to prepare furan **26**, which was utilized in an elegant approach to trioxadispiroketals (Scheme 17).[33]

Although, most of the above TOP−Wittig reactions have employed ester- and ketone-stabilized Wittig reagents, other stabilized ylides have also been used to prepare unsaturated nitriles and fluorenes (Scheme 18)[8] and Weinreb amide adducts (Scheme 19).[34]

More recently, Huang and Sun demonstrated that this methodology can also be employed using the phosphonium salts of stabilized Wittig reagents with *in situ* deprotonation[35] (Scheme 20; for similar results using phosphonates and non-stabilized phosphonium salts, see section 5c).

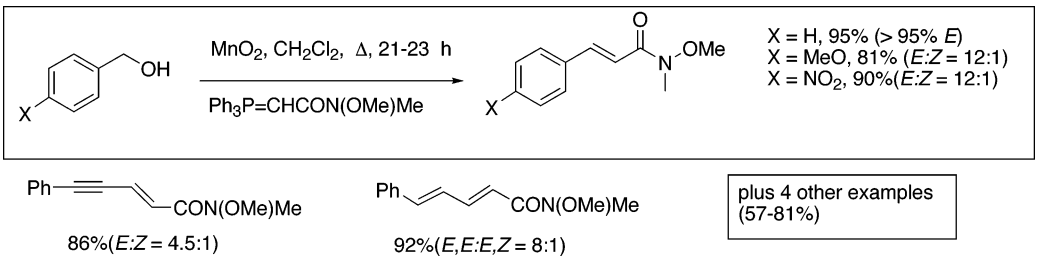
As well as activated alcohols, so-called "semi-activated" alcohols have also proven to be viable substrates for MnO_2 TOP−Wittig methodology (Scheme 21).[36] Cyclopropyl carbinols react well, as do primary alcohols bearing an α-heterocyclic group. The mildness of the MnO_2 TOP−Wittig sequence is emphasized by the fact that adducts **27** and **28** were obtained without any apparent racemization.

Scheme 21

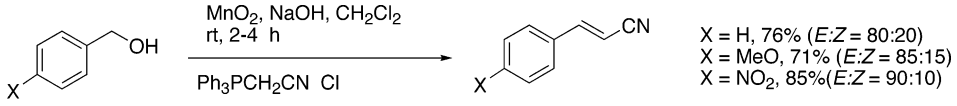


McKervey and Davies also studied the MnO_2 TOP−Wittig reactions of enantiopure amino alcohols and found no racemization (Scheme 22).[37] It was also shown that the "spent" MnO_2 could be recycled after it had been oven-

Scheme 19

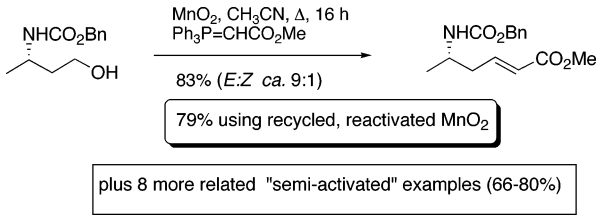


Scheme 20



plus 3 other examples using Ph_3PCH_2COMe Br and Ph_3PCH_2COPh Br (70-81%)

Scheme 22



dried (25 equiv of MnO_2 were used in the original reaction). Some of the unsaturated ester products were further elaborated to give alkaloids, including *S*-(−)-coniceine (Scheme 23).

The simple natural product podoscyphic acid (as its ethyl ester) was also prepared via a TOP sequence using a formally unactivated substrate (Scheme 24).[38]

Even more surprisingly, in the presence of stabilized phosphorane reagents, MnO_2 has been shown to be an efficient oxidant of unactivated alcohols to afford unsaturated esters in good yield (Scheme 25).[34,36] These results seem to contradict the well-known dictum that activated MnO_2 will oxidize only allylic/propargylic/benzylic alcohols, giving disappointing yields with primary aliphatic alcohols.[20,21,39] The activity of the MnO_2 seems to be enhanced by the presence of phosphorus reagents/byproducts because only 12% of decanal is isolated when decanol is treated with MnO_2 in toluene at reflux for 24 h (although another explanation is that the Wittig reagent removes small equilibrium quantities of aldehyde).[40]

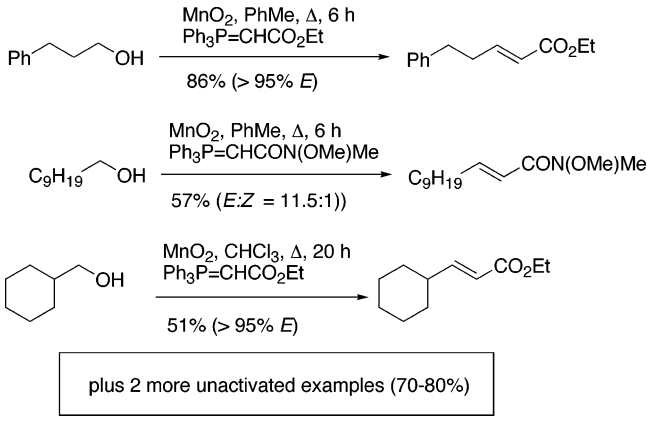
In the final example in Scheme 25, nine different types of commercial and "home-made"[20,21] MnO_2 were used in the TOP−Wittig elaboration of cyclohexylmethanol. A range of yields was obtained, but the commercial samples were consistently more efficient.[40] In view of this fortuitous discovery, Aldrich activated MnO_2 (catalog number 21764-6) was routinely used during studies by the York group.

It has recently been shown that α-hydroxy ketones also undergo efficient TOP−Wittig sequences (Scheme 26).[41] The synthetic utility of the intermediate α-keto aldehydes (e.g., **29**) had previously been limited by the "hyper-reactivity" of this group of compounds, particularly those with alkyl substituents.[6] However, when the MnO_2 TOP−Wittig protocol was employed, good to excellent yields of the resulting γ-keto-crotonates could be obtained. This methodology has recently been employed in a new route to substituted hydantoins.[42]

1,2-Diols have also been employed in TOP−Wittig processes, although in this case, the MnO_2 initially effects oxidative cleavage, with the resulting aldehydes then being trapped by the Wittig reagent (Scheme 27).[43] However, the process proved very substrate-dependent, and better yields were often obtained using silica-supported sodium periodate as the oxidant.[43,44]

b. Using Phosphonates (TOP−HWE Sequences). TOP sequences have also been carried out in conjunction with Horner−Wadsworth−Emmons (HWE) reactions using

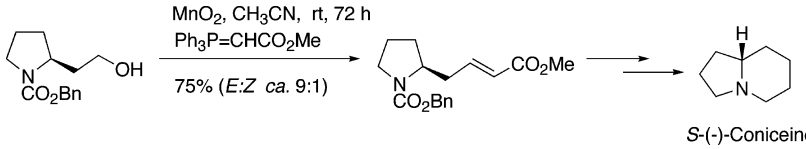
Scheme 25



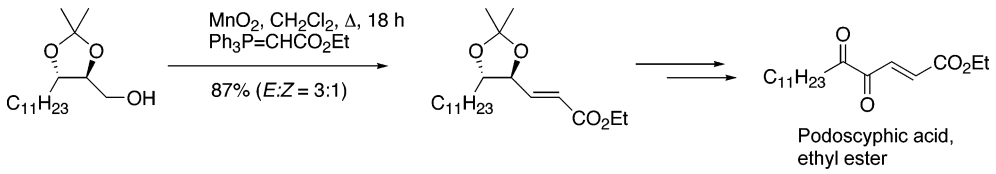
phosphonate reagents, with the anion being generated *in situ* by the bicyclic guanidine base, MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), or lithium hydroxide/molecular sieves (Scheme 28).[45] A range of activated alcohols has been employed with triethyl phosphonacetate and the corresponding amino-substituted analogue, giving a predominance of the *E*-α,β-unsaturated ester products. As shown in the last example, this methodology can also be employed with Ando's diphenyl phosphonate **30**,[46] giving mainly the *Z*-enoate.

c. Using Non- and Semistabilized Ylides. Somewhat surprisingly, a limited number of TOP sequences have been carried out using nonstabilized Wittig reagents generated *in situ* from the corresponding phosphonium salts by MTBD (Scheme 29).[45] These reactions were successful

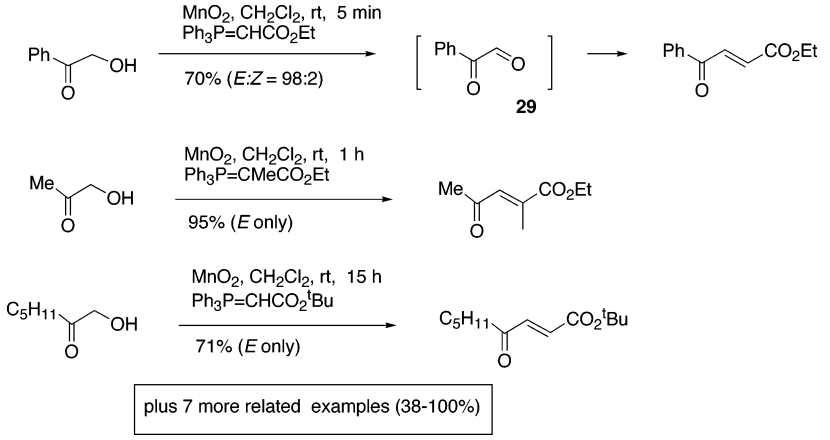
Scheme 23



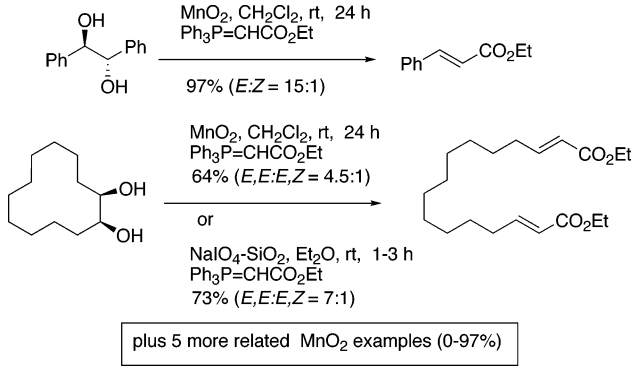
Scheme 24



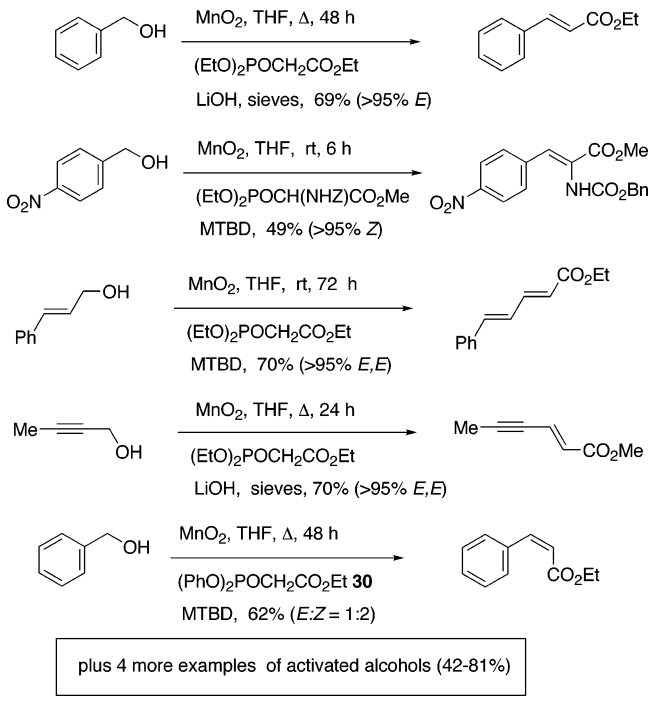
Scheme 26



Scheme 27

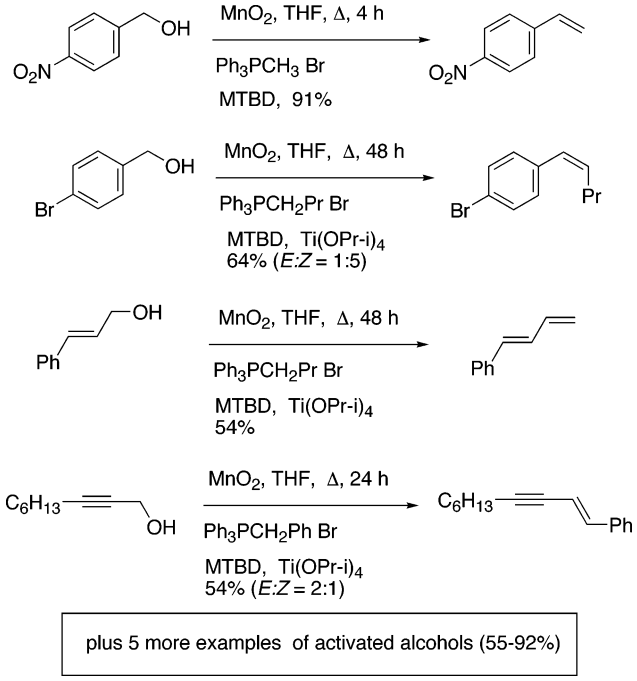


Scheme 28



with a small number of activated alcohols, although the reactions were slow and, in some cases, the addition of titanium tetraisopropoxide was required. It should be noted that this procedure was not successful with unactivated alcohols.

Scheme 29



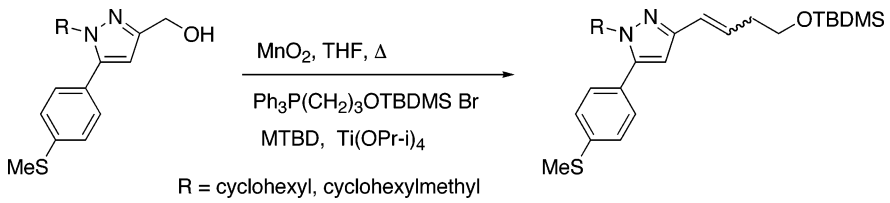
An application of this methodology to the preparation of novel COX-2 inhibitors was reported in 2004 (Scheme 30).[47]

Subsequent examples of this process have involved phosphonium salts substituted by electron-withdrawing groups, which presumably ensure a faster reaction time. For example, a concise route from activated alcohols and dioxolane phosphonium salt **31** to homologated *E*-α,*β*-unsaturated aldehydes through the intermediacy of unsaturated dioxolanes has been developed (Scheme 31).[48]

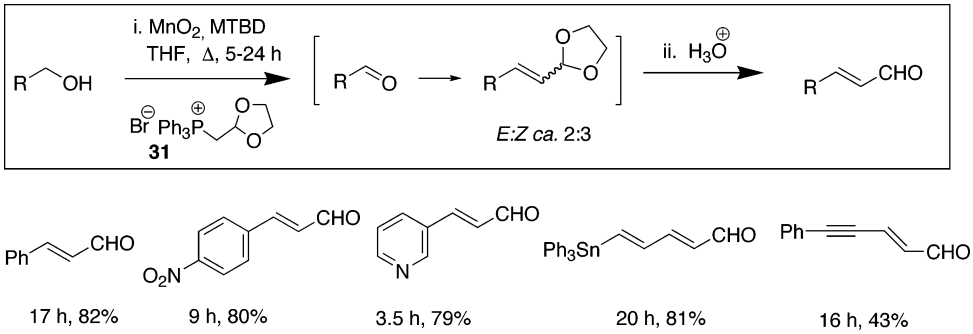
The synthesis of dibromoalkenes through an *in situ* oxidation, one carbon homologation approach has also been reported (Scheme 32).[49] Good to excellent yields of these synthetically versatile intermediates were obtained from a range of activated alcohols using dibromomethyl phosphonium salt **32**.

Alcohols can also be converted into alkynes via a TOP sequence using the Bestmann−Ohira[50] diazo-phosphonate reagent **33**.[51] With highly activated alcohols such as

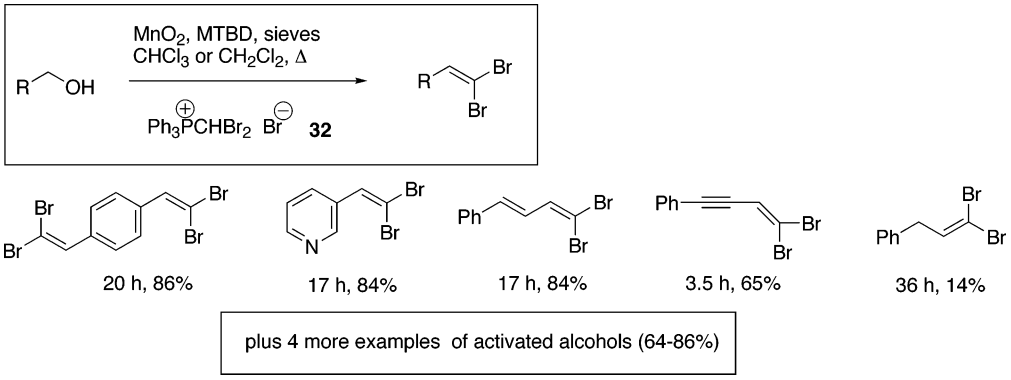
Scheme 30



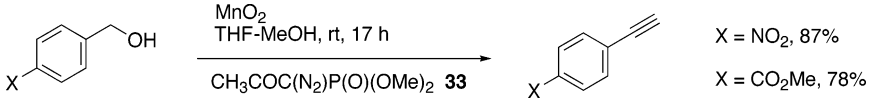
Scheme 31



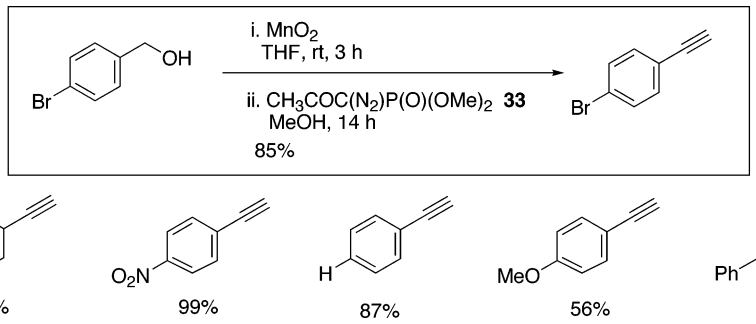
Scheme 32



Scheme 33



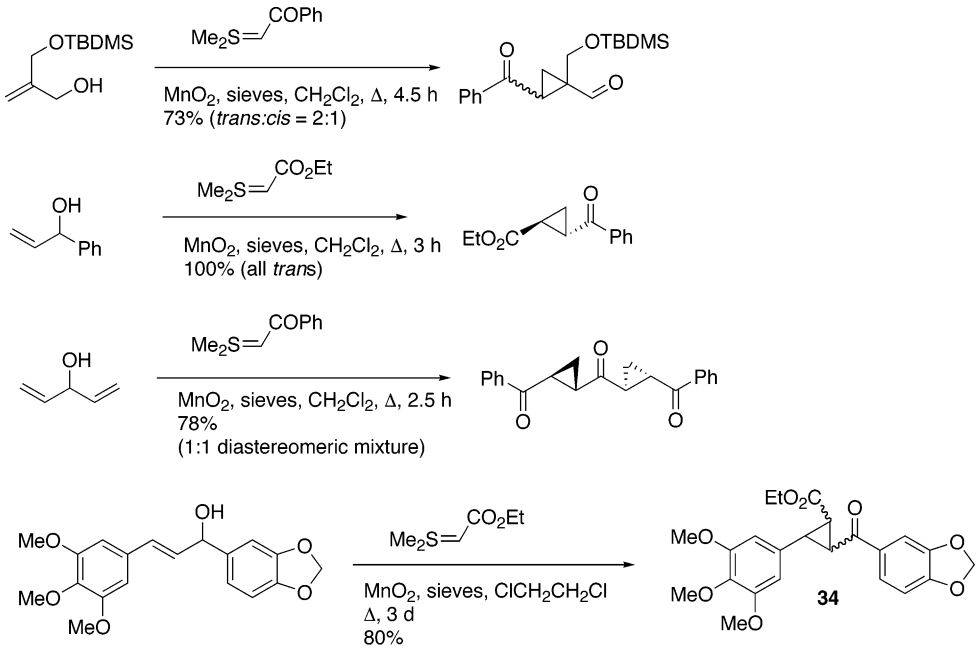
Scheme 34



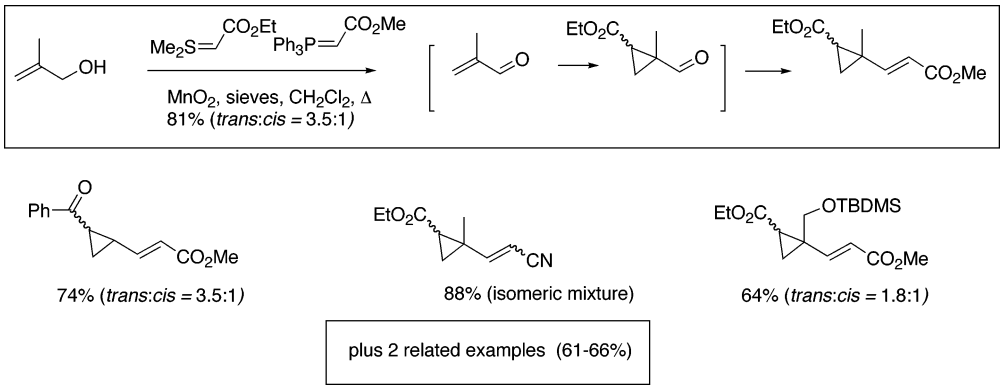
p-nitro-benzyl alcohol, direct conversion was achieved in good yield (Scheme 33). However, the presence of methanol was crucial for success, and methanol deactivates the manganese dioxide to the extent that it oxidizes most alcohols very slowly. For a more general protocol, therefore, a sequential one-pot procedure was developed in which the Bestmann−Ohira reagent **33** and methanol are added after the completion of the oxidation (Scheme 34).[51]

d. Using Sulfur Ylides. Recently, a TOP−cyclopropanation sequence has been reported in which α,*β*-unsatur-

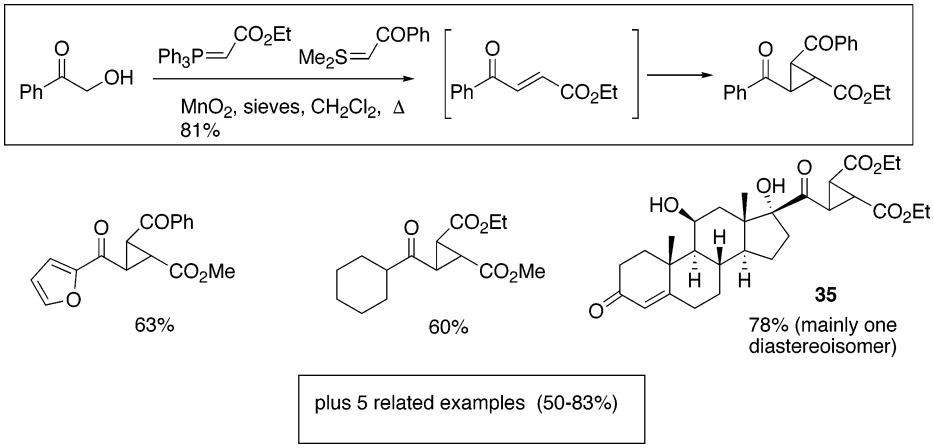
Scheme 35



Scheme 36

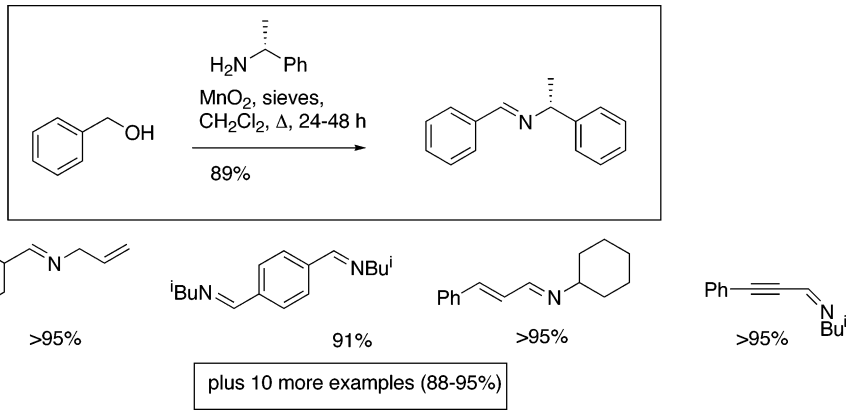


Scheme 37

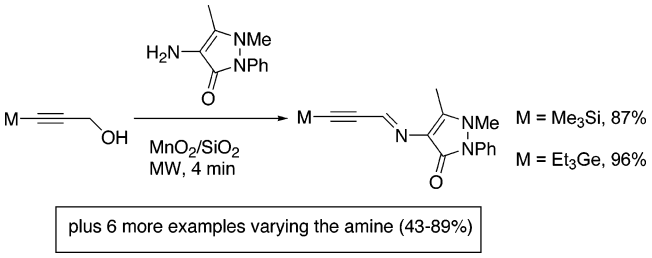


ated carbonyl compounds, formed by the oxidation of an allylic alcohol, are trapped *in situ* by 1,4 attack of a stabilized sulfur ylide, affording cyclopropanes (Scheme 35).[52] In general, the *in situ* cyclopropanation is only successful with terminally unsubstituted alkenes, but chalcones are an exception. This latter observation was

Scheme 38



Scheme 39



exploited in the TOP preparation of the highly substituted cyclopropane **34**, which has been converted into the naturally occurring lignan, (±)-podophyllone.[53]

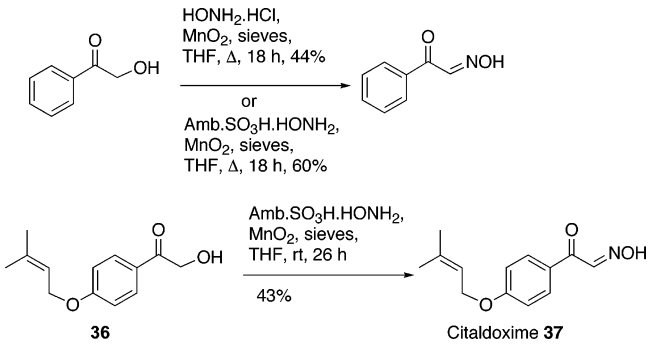
This TOP−cyclopropanation methodology has been extended and combined with the Wittig procedure to allow the conversion of allylic alcohols directly into di- and trisubstituted cyclopropanes via a three-step, one-pot process, which is presumed to involve oxidation−cyclopropanation−olefination (Scheme 36).[54]

When applied to α-hydroxy ketones, a complementary TOP sequence is observed where Wittig homologation must precede cyclopropanation (Scheme 37).[54] These cyclopropanation sequences usually proceed with poor stereocontrol, but the hydrocortisone adduct **35** is obtained as a predominant stereoisomer, although the stereochemistry still has to be confirmed.

6. TOP Sequences Using Nitrogen-Based Nucleophiles

a. Imine and Oxime Formation. TOP have also been developed in which amines and *O*-alkyl hydroxylamines

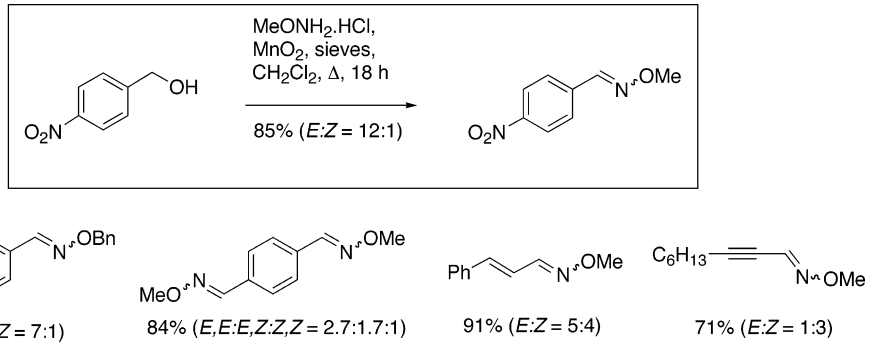
Scheme 41



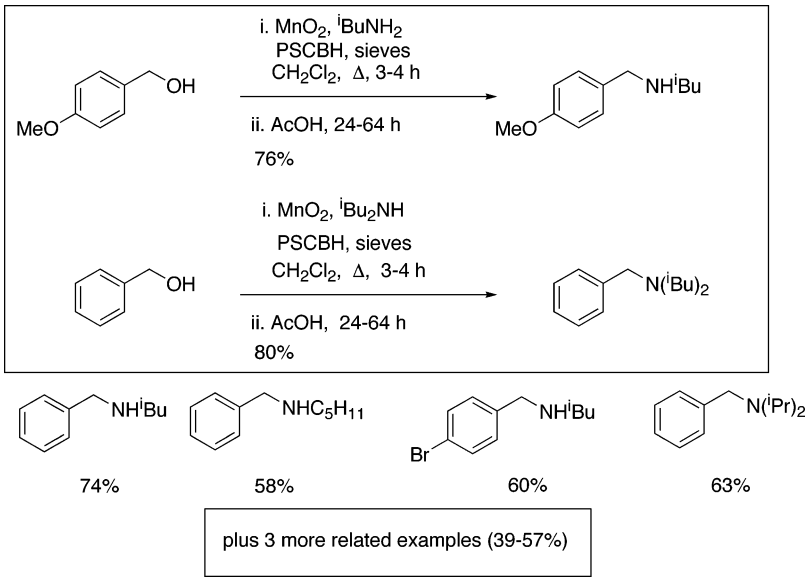
are used for the *in situ* trapping of intermediate aldehydes.[55,56] In the case of imine production (Scheme 38), the sequence is extremely efficient, usually giving near quantitative yields with activated alcohols.[55] Practically, this is a very straightforward process; after the completion of the reaction, the mixture is simply filtered through Celite and the solvent is removed in vacuo, giving the imines, which are usually pure by ^{1}H NMR spectroscopy.

This procedure was developed further by Medvedeva et al., who prepared a range of imines derived from 3-silyl-

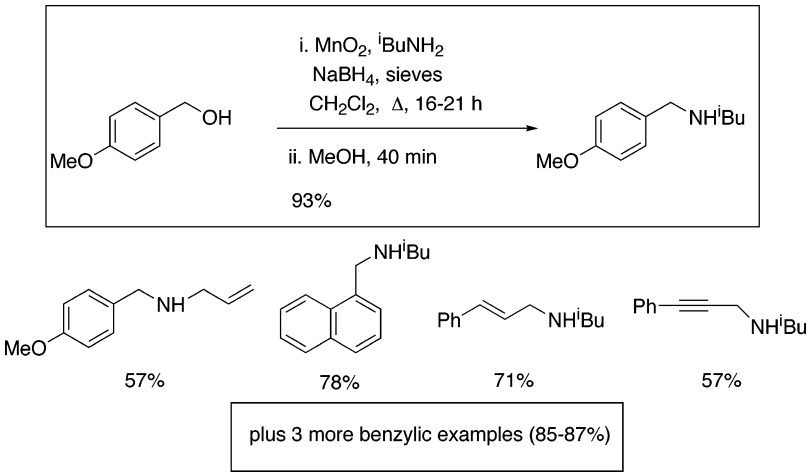
Scheme 40



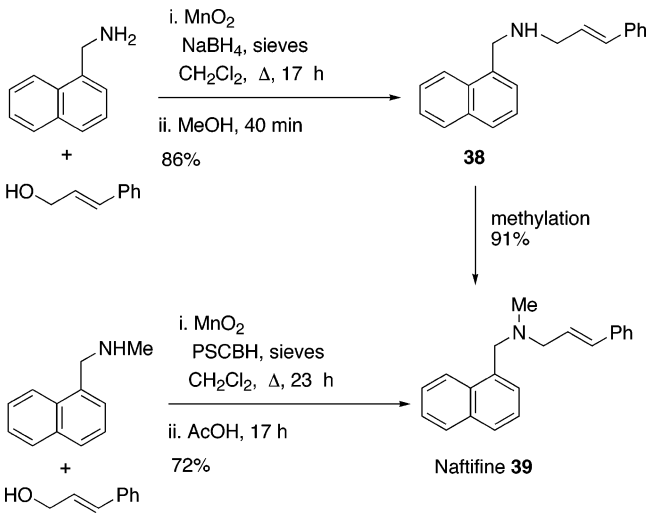
Scheme 42



Scheme 43



Scheme 44



and 3-germyl-prop-2-yn-1-ols using the MnO_2 methodology (Scheme 39).[57]

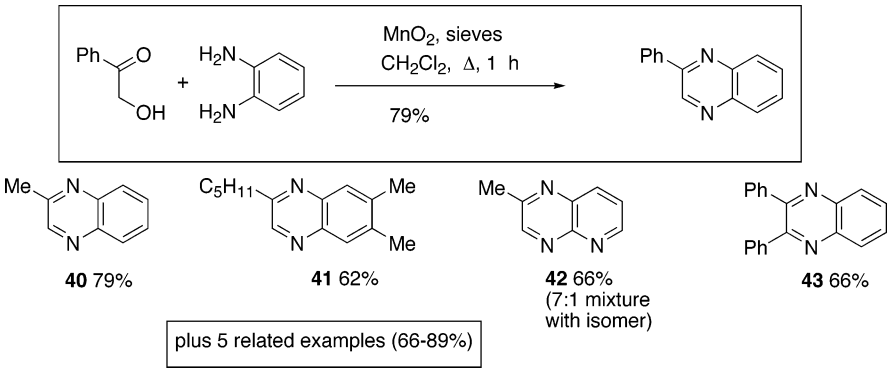
O-Alkyl oxime ethers have also been prepared via a TOP sequence (Scheme 40).[56] This methodology was successful with a range of activated alcohols when using *O*-methyl and *O*-benzyl hydroxylamines, but little product was obtained when hydroxylamine was used as *in situ* trapping agent.

However, when α-hydroxy ketones were employed as substrates, hydroxylamine could be employed, with the best yields being obtained when it was supported on Amberlyst 15 resin (Scheme 41).[56] As shown, this latter methodology was used to convert α-hydroxy ketone **36** into the natural product citaldoxime **37** by a one-pot TOP sequence.

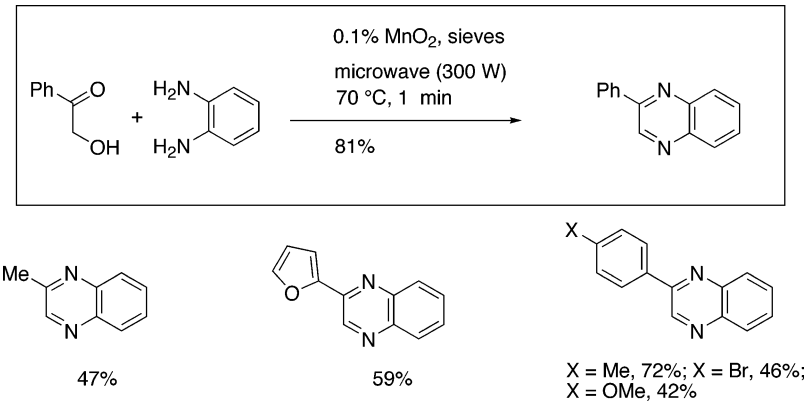
It should be noted that imine/oxime TOP reactions only proceed when using activated alcohols.

b. Reductive TOP Sequences Producing Amines. The MnO_2-amine trapping procedure can also be carried out in the presence of a heterogeneous reductant to effect an oxidation−imination−reduction sequence leading from activated alcohols directly to amines. Initial studies were carried out using polymer-supported cyanoborohydride (PSCBH) as the reductant (Scheme 42).[55] The use of poten-

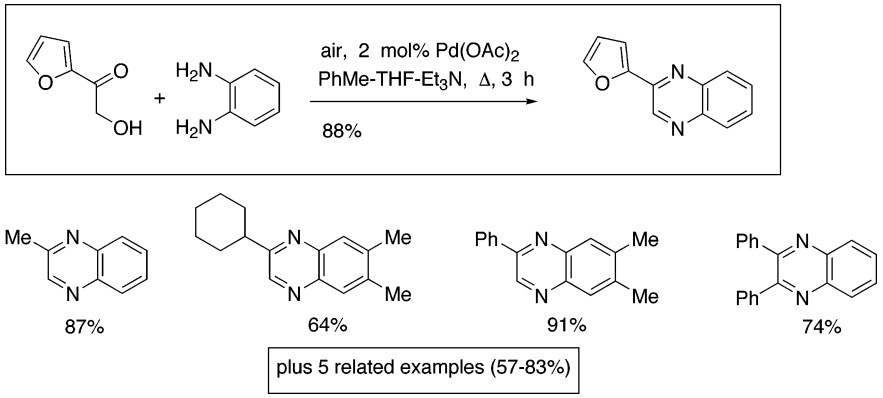
Scheme 45



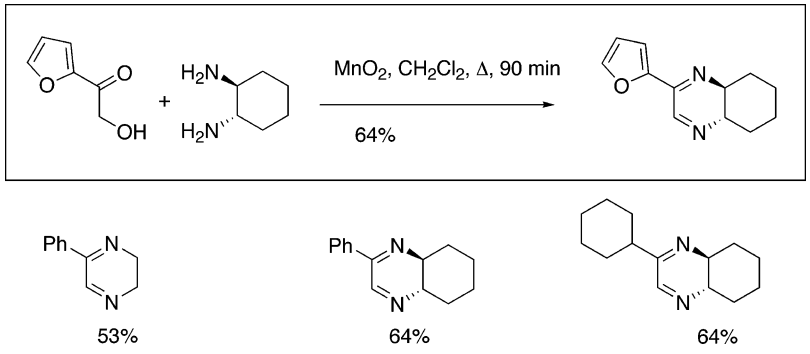
Scheme 46



Scheme 47



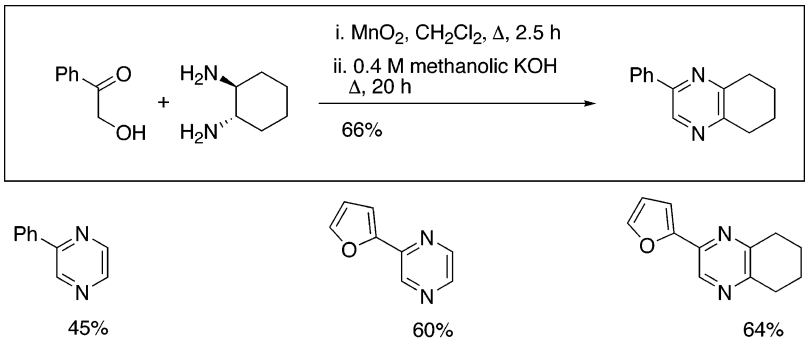
Scheme 48



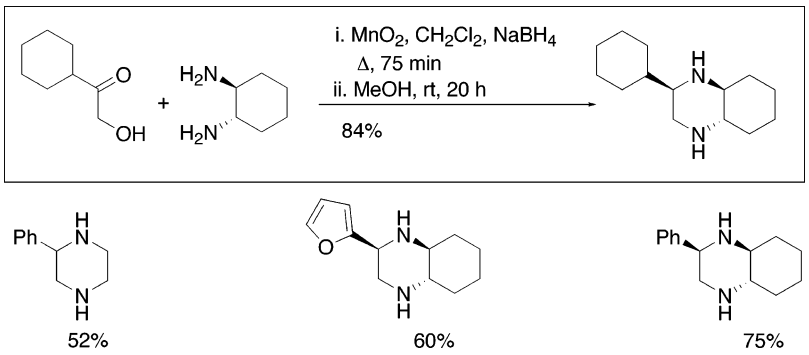
tially self-destructive reagents (oxidant and reductant) in the same transformation is noteworthy.

It was subsequently discovered that the heterogeneous reductant PSCBH could be replaced by sodium borohydride in dichloromethane, resulting in a much less expensive protocol (Scheme 43).[58]

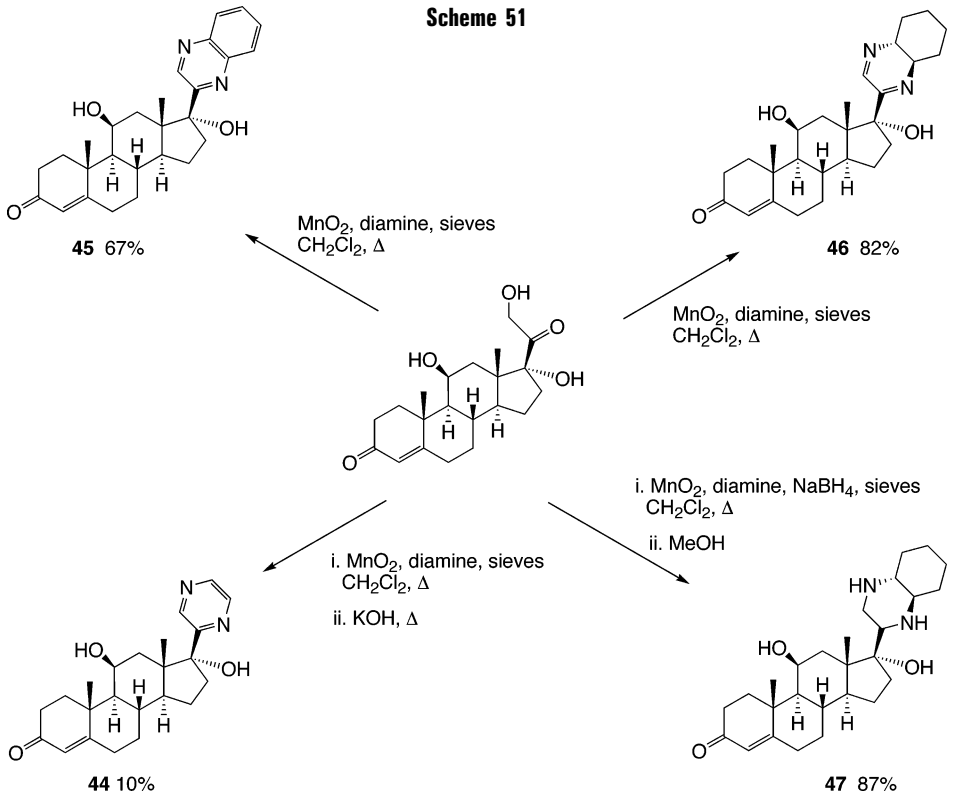
Scheme 49



Scheme 50

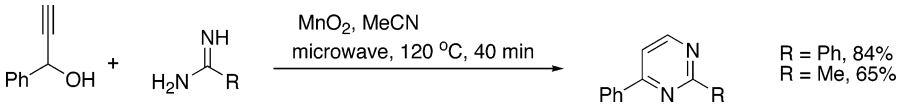


Scheme 51

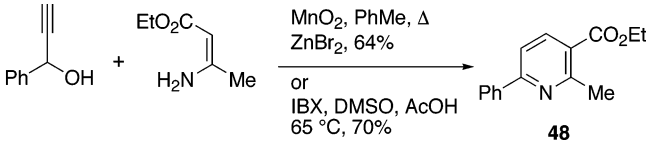


These methods are complementary in that the sodium borohydride procedure is best with primary amines, but with secondary amines, the PSCBH method is preferred. Both procedures were employed for concise preparations of the topical antifungal agent naftifine **39** (Scheme 44). Thus, the sodium borohydride method proceeded efficiently using cinnamyl alcohol and 1-(aminomethyl)-naphthalene, giving secondary amine **38**, which was then

Scheme 52



Scheme 53



methylated to produce naftifine **39**. Alternatively, naftifine could be produced directly from 1-(*N*-methylaminomethyl)naphthalene and cinnamyl alcohol in 72% yield using the PSCBH method (use of $NaBH_4$ in this sequence gave only 26% yield).[58]

c. Six-Membered Heterocycle Formation. As mentioned earlier, α-hydroxyketones can be useful substrates for MnO_2−TOP sequences. We have recently shown that using 1,2-diamines as trapping agents in such processes affords a diverse range of nitrogen-containing heterocycles. Thus, using MnO_2 oxidation and trapping *in situ* with aromatic 1,2-diamines produces quinoxalines in good to excellent yields (Scheme 45).[59] It is noteworthy that this procedure works well with "hyper-reactive" aliphatic α-keto aldehydes (giving products such as **40**−**42**) and also that benzoin is a suitable precursor, producing the disubstituted quinoxaline **43**.

More recently, Chung et al. have found that the MnO_2 requirement can be reduced to 1 mol % by carrying out the reaction in dichloromethane in a microwave reactor. Even more remarkably (Scheme 46), the MnO_2 could be further reduced to 0.1 mol % (1 mg/mmol substrate) by carrying out the process in the absence of solvent and the reactions were complete in one minute![23] Oxygen from air must be the stoichiometric oxidant (although the authors do not comment on this).

In our own laboratories, we have found that TOP−diamine trapping can also be accomplished efficiently using a palladium-catalyzed aerial oxidation procedure originally developed by Sigman et al.[60] Thus, a range of 2-substituted and 2,3-disubstituted quinoxalines was prepared in a one-pot process from equimolecular quantities of α-hydroxy ketone and diamine using only 2 mol % $Pd(OAc)_2$ and air (Scheme 47).[61]

Dihydropyrazines can be accessed using a TOP sequence with aliphatic diamines (Scheme 48), although the yields are only modest, presumably because of the low hydrolytic stability of the products and the ease with which the intermediates can undergo fragmentation.[59] Aromatization was not observed in the presence of MnO_2, but addition of methanolic KOH to the reaction mixtures, after dihydropyrazine formation was complete, gave fair to modest yields of pyrazines (Scheme 49).[59]

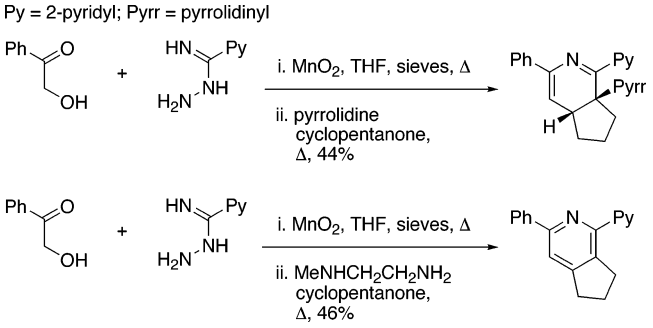
In contrast, when the above TOP heterocycle sequence was carried out in the presence of sodium borohydride, an efficient one-pot route from α-hydroxy ketones to piperazines was developed (Scheme 50).[59]

To illustrate the potential of the above heterocyclic TOP methodology, it was applied to the complex multifunctional substrate hydrocortisone, giving adducts **44**−**47** in fair to excellent yields (Scheme 51).[59]

Bagley et al. extended the MnO_2 TOP heterocycle methodology to achieve the one-pot preparation of pyrimidines from 2-phenylpropargylic alcohol (Scheme 52).[62]

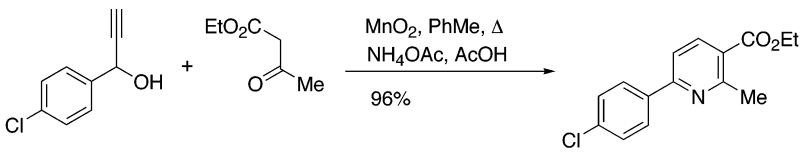
In a similar sequence, Bagley's group effected MnO_2 oxidation of 2-phenylpropargylic alcohol in the presence of ethyl α-aminocrotonate and a Lewis acid catalyst to produce pyridine **48**, although IBX gave a higher yield (Scheme 53).[62] A variant was developed in which the α-aminocrotonates were formed *in situ*, and here, MnO_2 proved to be the best oxidant (Scheme 54).[62]

Scheme 55

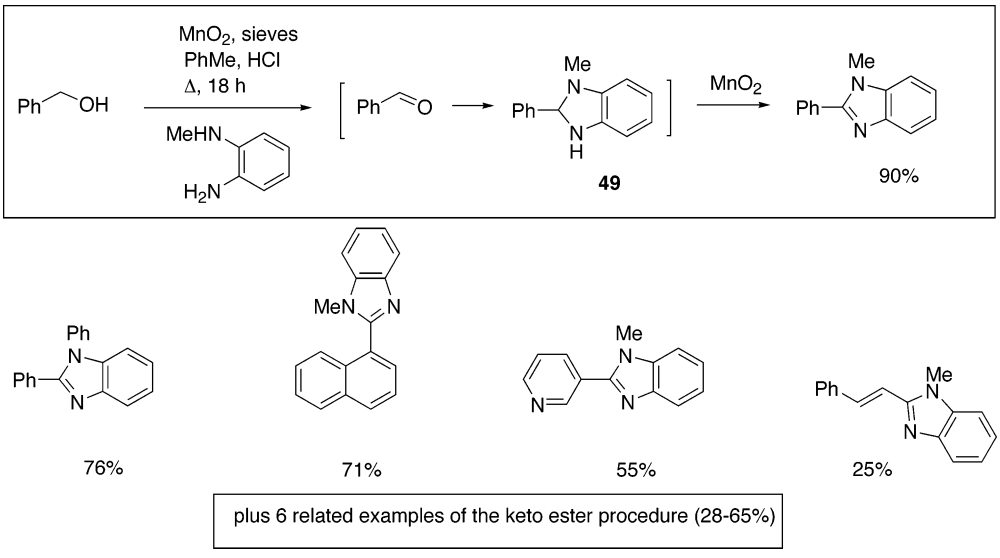


Polysubstituted pyridines are also available, albeit in moderate yield, by a cascade TOP sequence involving the intermediacy of 1,2,4-triazines and proceeding by way of an inverse electron demand Diels−Alder reaction with an

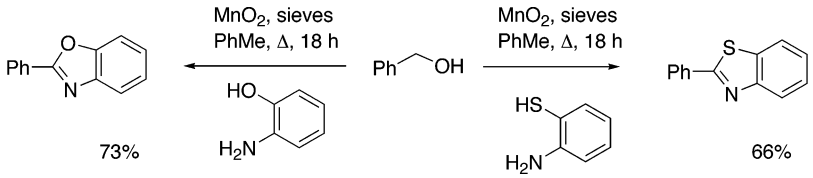
Scheme 54



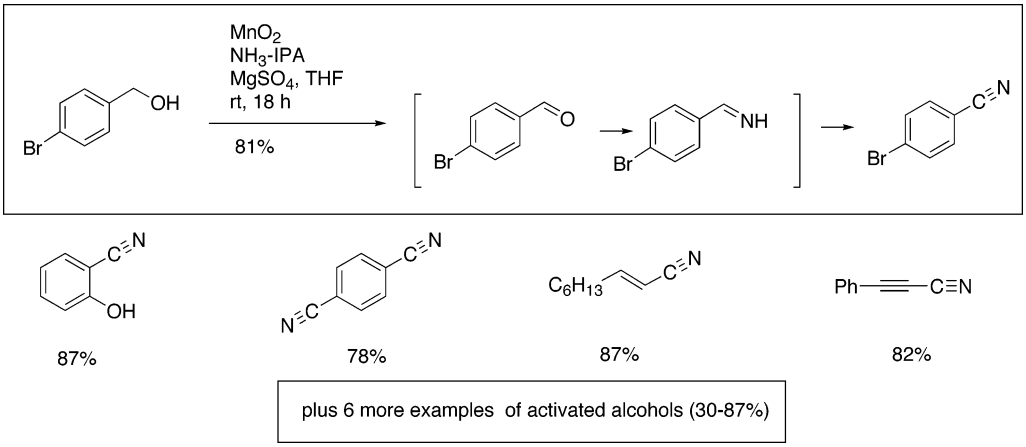
Scheme 56



Scheme 57



Scheme 58



enamine formed *in situ* from cyclopentanone and a secondary amine (Scheme 55).[63]

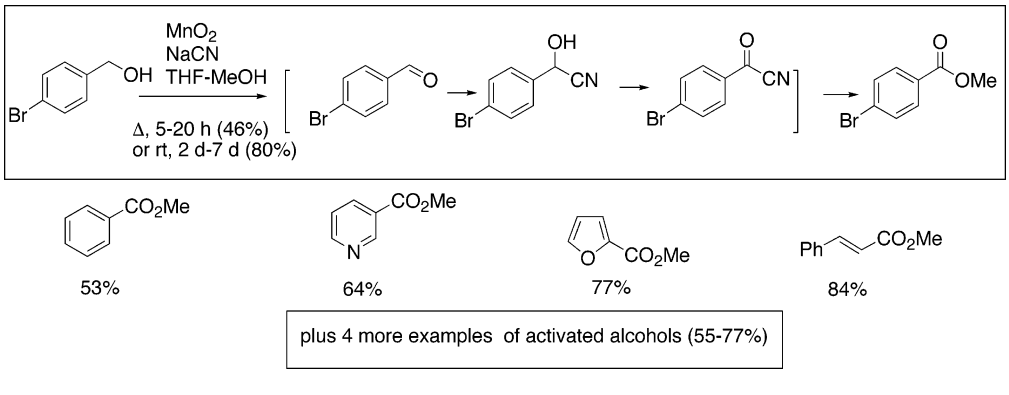
d. Five-Membered Heterocycle Formation. Manganese dioxide TOP sequences have also been used to prepare benzimidazoles and related heterocycles. Thus, treatment of activated alcohols with MnO_2 and *N*-methyl-1,2-phenylenediamine produces the corresponding 2-substituted benzimidazoles (Scheme 56).[64] This sequence involves oxidation to the aldehyde, double condensation, and then *in situ* aromatization of the intermediate dihydrobenzimidazole **49**. A number of examples were reported, with good to excellent yields being obtained for benzylic alcohols (allylic and propargylic alcohols were less efficient; unactivated alcohols did not give any of the desired product).

This procedure is also applicable to the one-pot preparation of 2-substituted benzoxazoles and benzothiazoles (Scheme 57).[64]

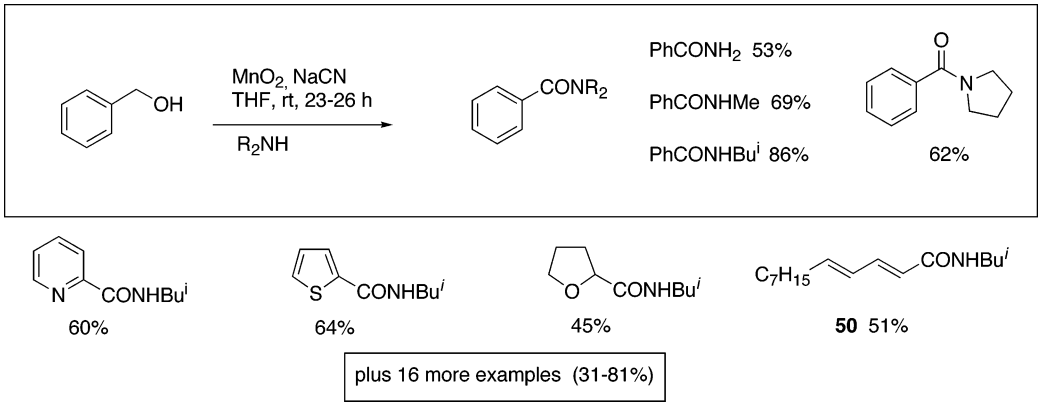
e. TOP for Functional Group Interconversions. The TOP route from activated alcohols to imines was subsequently extended to provide a procedure for the direct conversion of activated primary alcohols into nitriles using MnO_2 in THF containing ammonia in isopropanol (IPA) and magnesium sulfate (Scheme 58).[65] Again, good to excellent yields were obtained with a wide range of activated alcohols. This procedure was developed on the basis of the results published by Lai et al.[66]

Some time ago, Corey and Gilman developed routes for the conversion of aldehydes into methyl esters em-

Scheme 59



Scheme 60



ploying sodium cyanide as a catalyst.[67] This protocol has been incorporated into a TOP sequence, leading directly from alcohols to methyl esters (Scheme 59).[68]

Corey and Gilman also converted aldehydes into amides,[67] and the extension of this methodology to provide a one-pot procedure for the preparation of amides directly from activated alcohols was successful. A wide range of activated alcohols was employed, and a number of primary, secondary, and tertiary amides were prepared in a practically straightforward procedure (Scheme 60).[68] This TOP functional group procedure was even successful with tetrahydrofurfuryl alcohol and was also employed in a concise preparation of *N*-isobutyl-2*E*,4*E*-dodecadienamide **50**, isolated from *piper sarmentosum*.[68]

7. Current and Future Studies

We are currently optimizing a number of the TOP sequences outlined in this Account and investigating new tandem protocols, particularly those leading to heterocycles. In addition, further mechanistic studies are underway, particularly to shed more light on the apparent activation of MnO_2 by phosphorus reagents. We are also applying TOP methodology in natural product synthesis.

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