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N-Heterocyclic carbene-catalyzed oxidations

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ABSTRACT

N-Heterocyclic carbenes catalyze the oxidation of allylic and benzylic alcohols as well as saturated aldehydes to esters with manganese(IV) oxide in excellent yields. A variety of esters can be synthesized, including protected carboxylates. The oxidation proceeds under mild conditions, with low loadings of a simple triazolium salt pre-catalyst in the presence of base. Substrates containing potentially epimerizable centers are oxidized while preserving stereochemical integrity. The acyl triazolium intermediate generated under catalytic conditions can be employed as a chiral acylating agent in the desymmetrization of *meso*-diols.

1. Introduction

New methods employing mild conditions for efficient oxidations remain an important goal in organic chemistry.[1–4] Processes that facilitate the generation and functionalization of challenging substrates in situ are increasing in importance and use in synthesis. Tandem oxidation strategies that accomplish multiple oxidations or other transformations have garnered significant interest due to their efficiency and ability to streamline synthetic routes.[5] Of particular focus is the oxidation of alcohols or aldehydes to esters, which has inspired many investigations due to the synthetic utility of the ester products and the ready availability of the starting materials. However, a general solution to this transformation remains elusive.

In 1968, Corey reported the oxidation of alcohols to esters by a two-step process in the presence of sodium cyanide and manganese(IV) oxide (MnO_2).[6–8] Based on numerous pre-1960 studies of the reactivity of acyl cyanides,[9] this method has found application in several synthetic endeavors[10–12] despite its reliance on excess sodium cyanide (in some cases >20 equiv) as a promoter for the oxidation. Other transformations of this type require harsh oxidants such as chromium[13] or iodine,[14] which have both been shown to oxidize alcohols to esters. However, these methods require super-stoichiometric amounts of toxic and difficult to handle reagents.

The single-flask oxidation of aldehydes to esters has also attracted considerable interest.[15–19] Recently, pyridinium hydrobromide perbromide,[20] peroxides,[21,22] and Oxone[23] have all been reported to function as oxidants in these transformations. These approaches can suffer from toxic or expensive reagents as well as non-selective oxidation of the alcohol that serves as the nucleophile. The standard two-step approach involves oxidation of the aldehyde to the carboxylic acid followed by alkylation of the acid. These transformations, such as the Pinnick oxidation, can be complicated by over-oxidation of electron-rich aromatic rings or undesired interactions with heteroatoms.[24] Furthermore, the subsequent alkylation of the carboxylate formed in the second step can suffer from chemoselectivity complications particularly in the case of a saturated, enolizable substrate. Saturated aldehydes pose additional problems as reactants due to the potential for aldol side reactions. Given this litany of potential complications, a mild oxidation providing access to esters without the use of a toxic reagent and with the potential for application to saturated substrates is a compelling goal with potential broad utility.

2. Background

In biological systems, the thiamine-pyrophosphate cofactor has long been known to catalyze oxidative transformations such as the oxidative decarboxylation of pyruvic acid to form ‘active acetate’ acylating agents in the presence of oxidants such as NAD+ (nicotinamide adenine dinucleotide), molecular oxygen, and flavins.[25] Initial investigations in this area were focused on discovering alternative oxidants, which could be paired with the enzyme to accelerate the transformation.[26,27]

With the elucidation of the active component of thiamine-pyrophosphate as a nucleophilic carbene/zwitterion,[28] other work was focused on designing an enzyme/cofactor mimic, which would catalyze useful acylation reactions. Using a non-enzymatic thiazolium-based *N*-heterocyclic carbene (NHC), very brief studies concerning the oxidative transformation converting aromatic aldehydes to esters were reported.[29–32] More recently, Miyashita[33]

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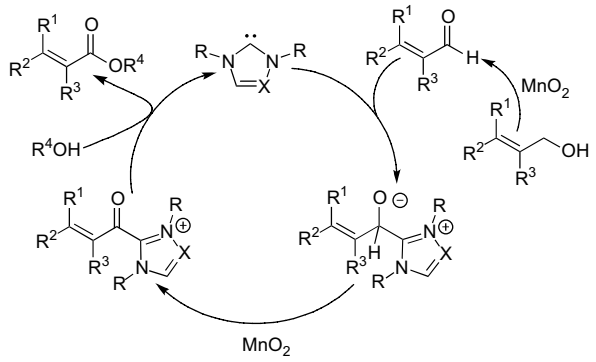
has demonstrated that other NHCs derived from triazolium and benzimidazolium salts are capable of catalyzing the oxidation of aryl aldehydes. These processes generally employed organic oxidants such as substituted nitrobenzenes, azobenzene derivatives, and flavin. These reports represent the initial discovery of this reactivity, but the full potential of this carbene-catalyzed oxidative reaction pathway remains unrealized. In light of this observation, we sought to expand the scope of NHC-catalyzed oxidation reactions by utilizing a more efficient oxidant and exploring our extensive catalyst library. At the onset of these investigations, we hoped to develop a mild, efficient, Lewis base-catalyzed oxidation protocol for facile access to esters from readily available substrates.

3. Results and discussion

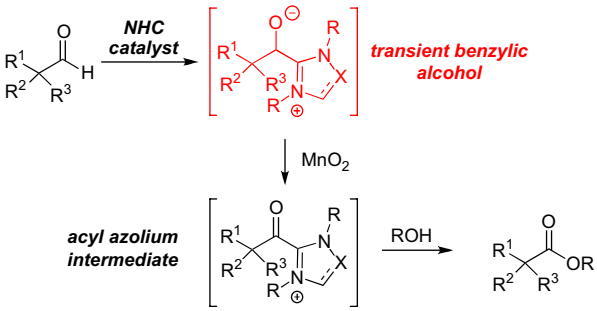
Our proposed pathway for this carbene-catalyzed reaction is initiated by a standard oxidation of the allylic alcohol (Scheme 1) by MnO_2. The resulting aldehyde combines with the NHC catalyst in order to form a tetrahedral intermediate, which is itself an allylic alcohol.



Scheme 1. Pathway of oxidation of allylic alcohols.

This intermediate is oxidized by MnO_2 to yield an acyl azolium intermediate, which we have employed as an activated acylating agent in many recent new reactions.[34–40] The nucleophilic alcohol is acylated, generating the ester product and regenerating the NHC catalyst in the presence of a base. The initial addition of the NHC to the aldehyde is similar to Umpolung processes catalyzed by these Lewis base catalysts,[41,42] but importantly, the oxidation must be fast enough to preclude the formation of any acyl anion or homoenolate equivalents.

A distinctive advantage of this potential pathway is that the oxidation of saturated aldehydes to esters is possible due to the generation of an activated alcohol by the addition of the NHC generated in situ. In this particular case, the aromatic nature of the azolium core of the catalyst serves to activate the secondary alcohol generated by addition to the aldehyde (Scheme 2). This activated

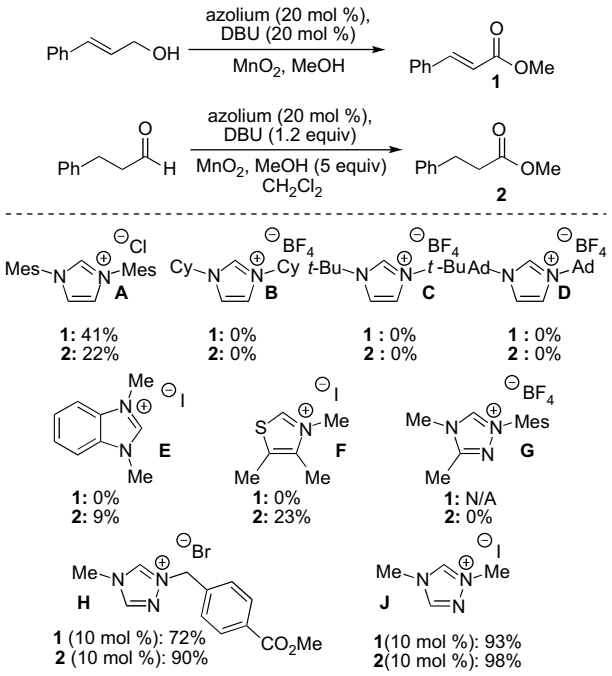


Scheme 2. Oxidation of unactivated aldehydes.

alcohol is capable of undergoing oxidation[43] by a selective oxidant such as MnO_2.

3.1. Reaction development

The initial aim was to establish the catalyst core structure that most efficiently catalyzed the proposed oxidation pathway. A variety of simple imidazolium, benzimidazolium, thiazolium, and triazolium salts were screened as pre-catalysts in this transformation (Scheme 3). Commercially available imidazolium salts **B**, **C**, and **D** showed no conversion to ester in either reaction manifold, although using IMes (**A**) did result in a low amount of conversion to the desired ester product. Simple triazolium salts **H** and **J** gave excellent results with reduced catalyst loading. The simpler and more readily accessible of the effective catalysts (**J**) were employed going forward in the explorations of this reaction.



Scheme 3. Catalyst screen for NHC-catalyzed oxidation.

Additionally, different sources of MnO_2 were surveyed. It was found that commercial activated MnO_2 (purchased from Sigma–Aldrich) was capable of effecting this transformation in a timely manner (18 h for **1**, 3 h for **2**). When freshly prepared MnO_2 was employed[44–46] there was a mild rate enhancement observed (12 h for **1**, 2–3 h for **2**). Unless otherwise noted, the work reported herein was carried out with commercial MnO_2.

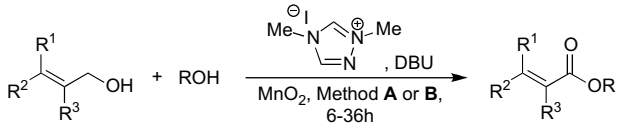
3.2. Reaction scope

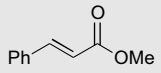
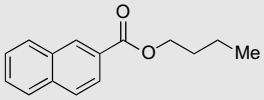
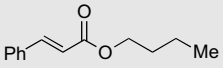
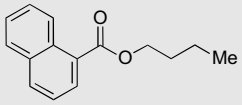
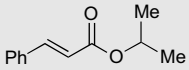
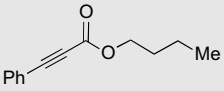
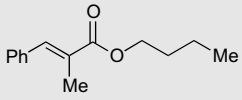
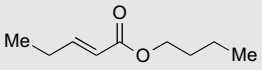
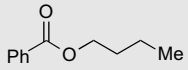
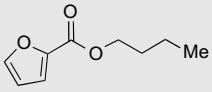
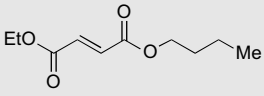
With the simple triazolium salt **J** established as the optimal catalyst precursor, we began our investigation of this oxidation pathway by subjecting allylic and benzylic alcohols to manganese(IV) oxide.[47]

3.2.1. Oxidation of allylic and benzylic alcohols to esters

Potential substrates were surveyed with a variety of different nucleophilic alcohols. Two different methods can be employed for this catalytic oxidation. The nucleophilic alcohol can be used as the solvent (method A) providing an excess of the nucleophile to undergo addition to the acylating intermediate. Alternatively, the oxidation could be run in toluene (method B) with a more modest

Table 1
Oxidation of allylic and benzylic alcohols to esters[a]



Entry	Product	Method	Yield (%)	Entry	Product	Method	Yield (%)
1		A	93	10		A	91
2		B	95				
3		A	93	11		A	90
4		B	91				
5		A	81	12		A	85
6		B	89				
7		A	91[b]	13		A	87
8		A	88[c]				
9		A	73	14		A	85

Method A: 10 mol % triazolium salt, 10 mol % DBU, 15 equiv MnO_2, 0.2 M in ROH at 23 °C. Method B: 10 mol % triazolium, 1.1 equiv DBU, 3–5 equiv ROH, 15 equiv MnO_2, 0.2 M in toluene at 23 °C (see Section 5 for full details).

[a] Isolated yields.

[b] Triazolium/DBU (25 mol %).

[c] Triazolium/DBU (50 mol %).

3–5 equiv of the nucleophilic alcohol. These two methods give similar results in most cases, with little difference in other aspects of the process (i.e., reaction time, purification procedure, etc.), and can be used interchangeably. Methanol generates the most efficient reaction (complete in 6 h, Table 1, entries 1, 2), but 1-butanol and other primary alcohols provide the ester product in similar reaction times and yield (Table 1, entries 3, 4). Secondary alcohols can also be employed, although reaction times are prolonged (up to 36 h) due to the difficult addition of the hindered nucleophile to the congested acylating agent (Table 1, entries 5, 6).

The allylic alcohol substrate can be varied to create a range of acylating agents. Substitution at the α-position (Table 1, entries 7, 8) requires increased catalyst loading to effectively generate the unsaturated esters. Benzylic alcohol substrates result in the most difficult oxidation, requiring increased catalyst loading (up to 50 mol %). However, with an inexpensive catalyst, the utility is not compromised as the yield is still synthetically useful. Electron-rich alcohols, such as 4-methoxybenzyl alcohol, yield only aldehyde as the product with increased catalyst loading and prolonged reaction times. The electron-rich furfuryl alcohol (entry 9) undergoes oxidation to the ester under the standard conditions, but the ester is isolated in an uncharacteristically mediocre yield. The naphthyl substrates (entries 10, 11) are the most successful of the benzylic alcohol substrates, providing the esters in excellent yields. Propargyl alcohols are easily oxidized in this system (entry 12). Alkyl substitution (entry 13) as well as electron withdrawing groups (entry 14) is tolerated. It is interesting to note that no evidence of transesterification of the ethyl ester is observed under these protic conditions.

3.2.2. Oxidation of saturated aldehydes to esters

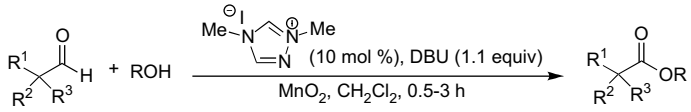
The success of the tandem oxidation of allylic alcohols led us to investigate further applications of the combination of NHCs and manganese(IV) oxide. Namely, we became interested in the oxidation of saturated, unactivated substrates through the generation of an activated substrate in situ via addition of the nucleophilic triazolium catalyst.[48]

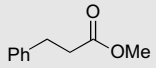
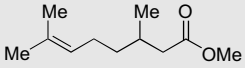
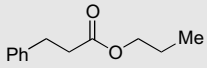
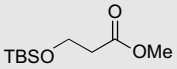
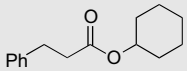
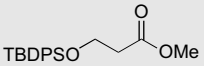
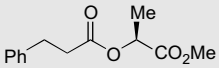
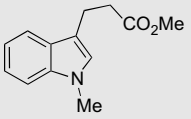
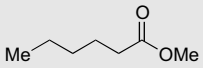
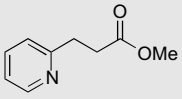
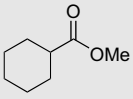
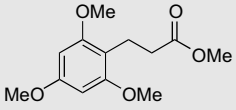
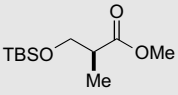
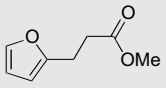
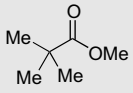
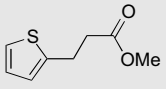
A wide variety of alcohols and aldehydes can be employed in this oxidation. Methanol is once again the most efficient nucleophile (Table 2, entry 1), generally resulting in better yields than other primary alcohols (entry 2) or secondary alcohols (entries 3, 4). It is important to note, however, that increased substitution of the nucleophilic alcohol does not preclude access to synthetically useful yields of the ester products.

Subjecting an alcohol with a potentially sensitive stereogenic center such as (*S*)-(−)-methyl lactate (97% ee) to the reaction conditions results in acylation without significant epimerization; the ester is afforded in 93% ee. The lack of epimerization under these mild oxidation conditions demonstrates the potential for application of this method to more complex and sensitive substrates prevalent in target-oriented synthesis.

A variety of saturated aldehydes can be employed in this oxidation. In contrast to the benzylic oxidation, substitution at the α-position (entries 6, 7) of the less rotationally restricted saturated aldehydes is tolerated without any change in the efficiency of the process. Steric considerations are still important, as increased substitution (entry 8) does result in a decreased yield. This is attributed to the difficulty of the addition of the triazolium catalyst to the congested aldehyde. Unsurprisingly, substitution at the β-position (entry 9) has no effect on the yield of the oxidation.

Table 2
Oxidation of saturated aldehydes to esters

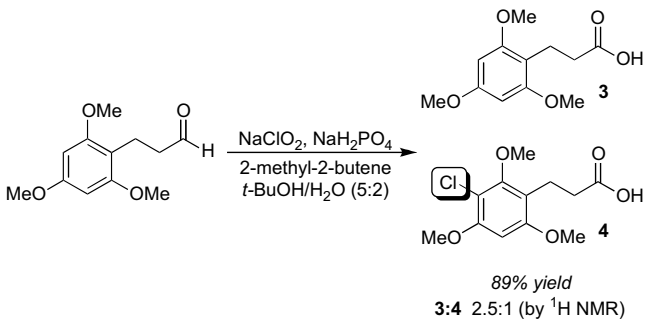


Entry	Product	Yield[a]	Entry	Product	Yield[a]
1		98	9		93
2		82	10		94
3		88	11		95
4		74[b]	12		90
5		91	13		88
6		96	14		99
7		91[c]	15		92
8		56	16		96

[a] Isolated yield, 5 equiv ROH, 5 equiv MnO_2 (see Section 5 for full details).
[b] Use of methyl (*S*)-(−)-lactate (97% ee) furnished the ester in 93% ee.
[c] Triazolium (25 mol %) was employed to give the methyl ester in 92% ee from enantiopure aldehyde.

Previous reports in the area of carbene catalysis have shown O–Si bonds to be cleavable in the presence of an NHC catalyst and an aldehyde.[49,50] Under our oxidation reaction conditions, no deprotection of silyl ethers was observed with –TBS (entries 7, 10) and –TBDPS (entry 11) ethers. It seems that the rate of oxidation is faster than any possible rate of desilylation for these substrates using these conditions. Additionally, the potentially epimerizable Roche ester derivative ((*S*)-3-hydroxy-2-methylpropionic acid methyl ester, entry 7) could be obtained without significant loss of stereochemical information. The ester was accessed in 92% ee from enantiopure aldehyde. In this reaction the amount of the triazolium catalyst is increased to 25 mol % in order to decrease the reaction time to 0.5–0.75 h. If the reaction is allowed to continue beyond that point, the integrity of the stereogenic center is eroded to <90% ee.

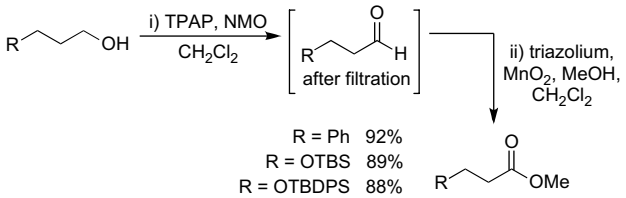
The oxidation is also compatible with a variety of heterocycles and electron-rich aromatic rings. Nitrogen-containing indole and pyridine substrates (entries 12, 13) are smoothly oxidized in excellent yields. Electron-rich aromatic rings can pose problems in traditional oxidations of aldehydes, due to the potential for reactions with electrophilic chlorine.[51,52] In fact, upon treatment of 3-(2,4,6-trimethylphenyl)propanal with Pinnick oxidation conditions[24] (Scheme 4), chlorination of the aromatic ring was a prevalent side reaction. In contrast, by employing the NHC-catalyzed process the same aldehyde is oxidized to the methyl ester as the sole product in nearly quantitative yield (Table 2, entry 14). Other electron-rich heterocycles such as furans (entry 15) and thiophenes (entry 16) are also successfully oxidized in very good yields.



Scheme 4. Chlorination of electron-rich aromatic rings.

Although it is possible to access saturated aldehydes through a variety of methods (ozonolysis of olefins, periodate cleavage of diols, reduction of Meldrum's acid derivatives,[53] etc.) the most common procedure is oxidation of the corresponding alcohol. Thus we sought to apply our oxidation protocol to a sequence that would allow easy access to an ester from any alcohol.

Manganese(IV) oxide, the most effective oxidant for the NHC-catalyzed process, is an inefficient oxidizing agent for unactivated alcohols, thus a one-pot procedure was impractical. However, simple TPAP oxidation[54] of the alcohol, followed by filtration and immediate treatment with the triazolium/MnO_2 system (Scheme 5) gives facile access to the ester with only a single chromatographic purification carried out at the conclusion of the procedure. The yield for this transformation is comparable to that reported for the oxidation of the aldehyde.



Scheme 5. Oxidation of alcohols to esters.

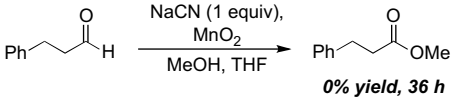
3.2.3. Comparative analysis

Our method represents the most general and efficient NHC-catalyzed oxidation reaction reported to date. Several reports exist of thiazolium or benzimidazolium reagents catalyzing the oxidation of aromatic aldehydes to esters.[29–33,35] A representative example is the recent disclosure by Connon and co-workers of an approach utilizing a thiazolium catalyst and azobenzene as an oxidant.[55] While this method gives good yields for the oxidation of substituted benzaldehydes (46–97% yield, 8 substrates), application to unactivated substrates results in poor yields of the ester. Employing the thiazolium/azobenzene system, hexanal is oxidized to methyl hexanoate in 16% yield after 48 h. Under our triazolium/MnO_2 conditions outlined in the previous section, hexanal (Table 2, entry 5) is oxidized to the methyl ester in 91% yield in under 3 h.

Our NHC-catalyzed reaction compares favorably to other methods for the oxidation of activated substrates to esters as well. The use of a catalytic amount of the non-toxic triazolium NHC precursor represents an attractive alternative to the Corey–Gilman oxidation,[6–8] that, while efficient and high yielding, employs a full equivalent of sodium cyanide as a nucleophilic promoter of the oxidation. Taylor has reported the tandem oxidation of alcohols to methyl esters using sodium cyanide,[56,57] but the use of nucleophilic alcohols other than methanol results in prolonged reaction times (up to 7 days) and significantly depressed yields. Further, the cyanide-promoted process shows no activity in the oxidation of saturated aldehydes (Scheme 6).

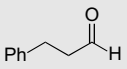
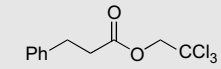
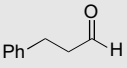
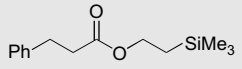
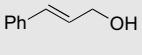
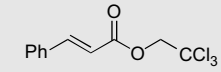
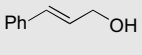
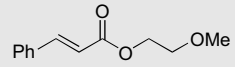
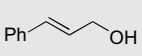
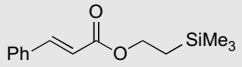
3.2.4. Applications

As a simple oxidation procedure providing access to ester derivatives, this method presents the opportunity to synthesize protected carboxylate derivatives.[58] The carboxylic acid, which is the common precursor in the standard synthesis of these esters, often presents potential problems with isolation and/or handling, while this method does not proceed through the acid intermediate.



Scheme 6. Cyanide-promoted oxidation.

Table 3
Synthesis of protected carboxylate derivatives

Entry	Substrate	Product	Yield
1			85[a]
2			87[a]
3			82[b]
4			82[b]
5			74[b]

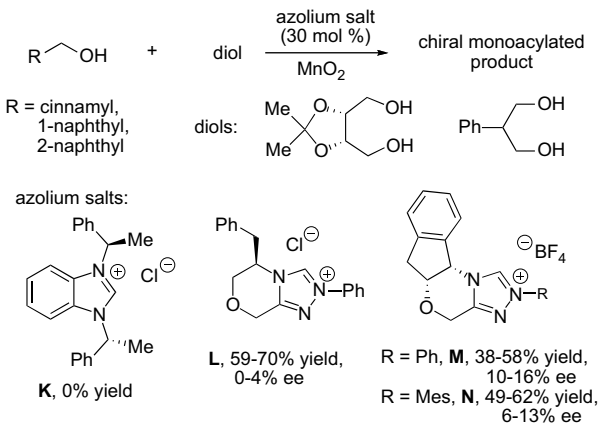
[a] Isolated yield, see Table 2 for conditions.
[b] Isolated yield, see Table 1, method B for conditions.

Access to the protected carboxylates can be accomplished either from the saturated aldehyde (Table 3, entries 1, 2) or the allylic alcohol (entries 3–5). The trichloroethyl (Troc),[59,60] (trimethylsilyl)-ethyl (TMSE),[61] and methoxyethyl (ME)[62] derivatives are synthesized in very good yields following the general procedures for the corresponding starting substrates.

The acyl triazolium intermediate presents a further opportunity for application of this method toward asymmetric reactions. The use of a chiral triazolium pre-catalyst creates a chiral acylating agent. With that inspiration, we applied the reaction to the desymmetrization of *meso*-diols.[63]

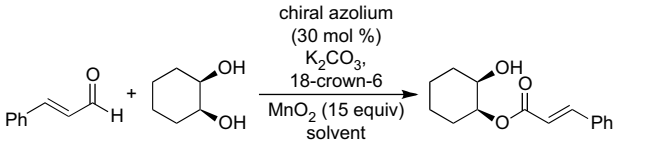
A variety of chiral acylating agents generated by the combination of various allylic or benzylic alcohols and benzimidazolium or triazolium catalysts have proved incapable of selectively acylating primary diols (Scheme 7). The low levels of enantiomeric excess observed upon the isolation of the desired monoacylation product indicate the presence of a nontrivial background rate.

A more hindered nucleophile was sought that would engender a more selective reaction with the acyl azolium intermediate. The secondary hydroxyl groups of *cis*-1,2-cyclohexanediol were particularly promising. In fact, triazolium salts **M** and **N** yielded the monoacylated product in 20 and 41% ee, respectively (Table 4, entries 3, 4). The non-nucleophilic K_2CO_3/18-crown-6 base system was employed in an effort to suppress the degradation of ee through acyl transfer. Unfortunately, a stoichiometric amount of this base was required, and upon treatment of the enantioenriched product with K_2CO_3/18-crown-6 racemic material was observed in

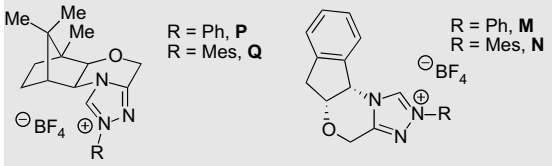


Scheme 7. Desymmetrization of primary diols.

Table 4
Desymmetrization of *cis*-1,2-cyclohexanediol



Entry	Conditions[a]	Yield	% ee
1[b]	**P**, toluene, 23 °C	43	5
2[b]	**Q**, toluene, 23 °C	40	9
3[b]	**M**, toluene, 23 °C	53	20
4[b]	**N**, toluene, 23 °C	47	41
5	**N**, Proton Sponge, toluene, 23 °C	62	60
6	**N**, Proton Sponge, CH_2Cl_2, 23 °C	78	59
7	**N**, Proton Sponge, CH_2Cl_2, 0 °C	67	65
8	**N**, Proton Sponge, CH_2Cl_2, −30 °C	*58*	*80*
9	**N**, Proton Sponge, CH_2Cl_2, −40 °C	38	73



[a] K_2CO_3 30 mol %, 15 mol % 18-crown-6, 1 equiv Proton Sponge, 0.25 M in solvent.
[b] K_2CO_3 1.5 equiv, 20 mol % 18-crown-6, 0.25 M in solvent. Proton Sponge=*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine.

less than 2 h. This result identified base-catalyzed acyl transfer as a significant obstacle to the successful application of this method.

The acyl transfer was successfully suppressed by the reduction of K_2CO_3/18-crown-6 to substoichiometric quantities and adding a full equivalent of Proton Sponge™ (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine) as a weaker non-nucleophilic base (Table 4, entry 5). A screen identified methylene chloride as the most ideal solvent for the reaction (entry 6). Reducing the temperature of the reaction (entries 7–9) suppressed the background rate and any remaining acyl transfer reactions to give the monoacylated diol in ~60% yield and 80% ee (entry 8). This successful desymmetrization demonstrates the potential of this method as an alternative to reactions of nucleophiles with acid chlorides and anhydrides.

4. Conclusions

The oxidation described herein utilizes a simple and readily available catalyst and proceeds under mild conditions with easily accessible starting materials. The potentially problematic isolation, handling, and functionalization of carboxylic acids or, in some cases, aldehydes have been obviated by the ability of this reaction to access higher oxidation states in a single-flask operation. Sensitive substrates, i.e., those prone to epimerization or electrophilic chlorination, are smoothly oxidized by this protocol. This carbene-catalyzed oxidation manifold compares favorably to other published strategies for similar transformations and presents unique opportunities due to the potential to generate a catalytic chiral acylating agent in situ. The NHC-catalyzed oxidation of alcohols and aldehydes with manganese(IV) oxide is a potentially powerful tool that will undoubtedly find use in organic synthesis.

5. Experimental

5.1. General

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium permanganate, or phosphomolybdic acid followed by heating. Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian Inova 500 (500 MHz) or Mercury 400 (400 MHz) spectrometer and are reported in parts per million using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as ap=apparent, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad; coupling constant(s) in hertz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Inova 500 (125 MHz) or Mercury 400 (100 MHz) spectrometer and are reported in parts per million using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer and Micromass Quadro II Spectrometer.

5.2. General procedure for oxidation of allylic alcohols to esters (Table 1)

5.2.1. Method A

A flame-dried round bottom flask was charged with triazolium salt **J** (22 mg, 0.10 mmol). The flask was sealed with a septum and put under positive pressure of nitrogen. The allylic alcohol (1 mmol) and the nucleophilic alcohol (5 mL) were added. The septum was removed and to the flask was added MnO_2 (1.304 g, 15 mmol). The flask was then sealed with septum and DBU (0.015 mL, 0.10 mmol) was added via syringe. The reaction stirred at ambient temperature until allylic alcohol and aldehyde were consumed (monitored by GC). The mixture was filtered through a thin pad of Celite. The Celite was washed with ethyl acetate (15 mL). The filtrate was then concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel.

5.2.2. Method B

A flame-dried round bottom flask was charged with triazolium salt **J** (34 mg, 0.15 mmol). The flask was sealed with a septum and put under positive pressure of nitrogen. Toluene (5 mL), the allylic alcohol (1 mmol), and the nucleophilic alcohol (5 mmol) were added. The septum was removed and to the flask was added MnO_2 (1.304 g, 15 mmol). The flask was then sealed with septum and DBU (0.165 mL, 1.1 mmol) was added via syringe. The reaction stirred at ambient temperature until allylic alcohol and aldehyde were consumed (monitored by GC). Upon consumption of allylic alcohol and aldehyde, methanol (10 mL) was added to the reaction. The mixture was then quickly filtered through a thin pad of Celite (prolonged stirring with methanol resulted in transesterification to the methyl ester). The Celite was washed with ethyl acetate (15 mL). The filtrate was then concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel.

5.3. General procedure for oxidation of saturated aldehydes to esters (Table 2)

A flame-dried round bottom flask was charged with triazolium salt **J** (11 mg, 0.05 mmol). The flask was sealed with a septum and put under positive pressure of nitrogen. Dichloromethane (2.5 mL) and DBU (82 μL, 0.55 mmol) were added followed by the aldehyde (0.5 mmol). The septum was removed and to the flask was added MnO_2 (217 mg, 2.5 mmol). The flask was then sealed with septum and methanol (0.100 mL, 2.5 mmol) was added via syringe. The reaction stirred at ambient temperature until aldehyde was consumed (monitored by GC or TLC). The mixture was filtered through a thin pad of silica, which was washed with ethyl acetate (15 mL).

The filtrate was then concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel.

5.4. Pinnick oxidation of 3-(2,4,6-trimethoxyphenyl)propanal (Scheme 4)

A flame-dried round bottom flask was charged with aldehyde (56 mg, 0.25 mmol) and sealed with a septum and put under positive pressure of nitrogen. A 5:2 mixture of *tert*-butanol and water (1.0 mL) was added and the mixture was cooled to 0 °C. 2-Methyl-2-butene (66 μL, 0.625 mmol), $NaH_2PO_4 \cdot H_2O$ (86 mg, 0.625 mmol), and sodium chlorite (80%) (70 mg, 0.625 mmol) were added sequentially and stirring was continued at 0 °C for 1.5 h. The reaction was warmed to ambient temperature and allowed to stir for an additional 1.5 h, then quenched with saturated ammonium chloride, diluted with dichloromethane and extracted with dichloromethane (3×10 mL) and ethyl acetate (1×10 mL). The organic layers were combined, dried with Na_2SO_4, and concentrated to give an inseparable mixture (56 mg) of 3-(2,4,6-trimethoxyphenyl)-propionic acid (**3**) and 3-(3-chloro-2,4,6-trimethoxyphenyl)-propionic acid (**4**). The ^{1}H NMR spectrum of the residue showed **3** and **4** in a 2.5:1 mixture favoring **3** based on integration of the protons attached to the aromatic rings; **3**: δ 6.12 (s, 2H); **4**: δ 6.05 (s, 1H). LRMS (APCI): Mass calculated for **3**, $C_{12}H_{16}O_5$ $[M+H]^+$ 241.1. Found 241.0. Mass calculated for **4**, $C_{12}H_{15}O_5Cl$ $[M+H]^+$ 275.1. Found 274.8.

5.5. Tandem TPAP/MnO_2 oxidation of unactivated alcohols to esters (Scheme 5)

Tetrapropylammonium perruthenate (TPAP) (14 mg, 0.04 mmol, 5 mol %) was added to a stirred mixture of the unactivated alcohol (0.8 mmol), 4-methylmorpholine-*N*-oxide (144 mg, 1.24 mmol, 1.5 equiv), and activated 4 Å molecular sieves (400 mg) in CH_2Cl_2 (2.0 mL). The mixture was stirred at room temperature for 30 min until the alcohol was consumed as judged by TLC. The reaction mixture was filtered through a pad of Celite and concentrated. The residue was then subjected to the conditions outlined in Section 5.3, resulting in the isolation of the methyl ester product after purification by flash chromatography on silica gel.

5.6. Cyanide-catalyzed oxidation of saturated esters (Scheme 6)

A flame-dried round bottom flask was sealed with a septum and put under positive pressure of nitrogen. Tetrahydrofuran (5 mL) was added followed by hydrocinnamaldehyde (66 μL, 0.5 mmol) and sodium cyanide (24 mg, 0.5 mmol). The septum was removed and to the flask was added MnO_2 (650 mg, 7.5 mmol). The flask was then sealed with septum and methanol (0.100 mL, 2.5 mmol) was added via syringe. The reaction was stirred at ambient temperature and monitored by GC or TLC. No methyl ester product was observed (by GC, TLC, or ^{1}H NMR) and the aldehyde starting material remained after 12 h of reaction time.

5.7. General procedure for desymmetrization of 1,2-diols (Table 4)

A flame-dried 10 mL round bottom flask equipped with stir bar was charged with the chiral triazolium salt **N** (50 mg, 0.119 mmol), K_2CO_3 (16.4 mg, 0.119 mmol), and 18-crown-6 (15.7 mg, 0.06 mmol). The flask was sealed with a septum and placed under a positive pressure of nitrogen. Into it was then added the *meso*-diol (115 mg, 0.99 mmol), Proton Sponge (85 mg, 0.397 mmol), and MnO_2 (517 mg, 5.95 mmol). Dichloromethane (1.6 mL, 0.25 M) was added resulting in a black suspension. Lastly, cinnamaldehyde (50 μL, 0.397 mmol) was added via syringe. The reaction was allowed to stir at −30 °C under a positive pressure of nitrogen until the aldehyde was consumed as determined by TLC. Upon consumption of the aldehyde, the mixture was filtered through a thin pad of Celite and washed with ethyl acetate (25 mL). The filtrate was then concentrated in vacuo and the resulting residue was purified by flash chromatography on silica gel.

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