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Tandem Oxidation of Allylic and Benzylic Alcohols to Esters Catalyzed by N-Heterocyclic Carbenes

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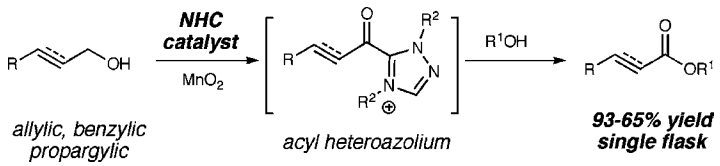
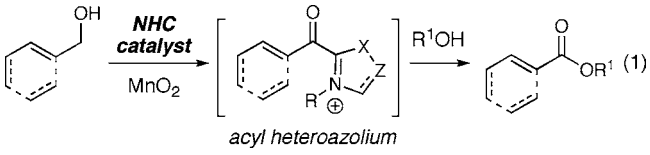
ABSTRACT



N-Heterocyclic carbenes catalyze the oxidation of allylic, propargylic, and benzylic alcohols to esters with manganese(IV) oxide in excellent yields. A variety of ester derivatives can be synthesized, including protected carboxylates. This one-pot tandem oxidation represents the first organocatalytic oxidation of alcohols to esters. Saturated esters can also be accessed from aldehydes using this method. Through the utilization of a chiral catalyst, the acyl–heteroazolium intermediate becomes a chiral acylating agent, which can desymmetrize *meso*-1,2-diols.

The development of mild and efficient oxidation methods remains an important goal in chemistry.[1] Tandem oxidation strategies hold particular interest[2] due to their potential to access higher oxidation states in one reaction flask and to generate and functionalize challenging substrates in situ. A seminal report by Corey detailed the two-step oxidation of allylic alcohols to esters in the presence of sodium cyanide and manganese(IV) oxide.[3] Gilman[4] and Taylor[5] further developed this process independently into one-pot tandem oxidation reactions to generate esters and amides. Although efficient, the major limitation of these oxidations is the large excess of cyanide used in the reaction. Iodine has also been reported to oxidize alcohols to esters,[6] although this method requires superstoichiometric amounts of a toxic oxidant. We have been interested in utilizing N-heterocyclic carbenes (NHCs) to promote the oxidation of aldehyde C−H bonds.[7] Herein, we report the tandem oxidation of allylic alcohols to esters with manganese(IV) oxide catalyzed by NHCs (eq 1). Importantly, the acyl heteroazolium intermediate presents



the opportunity to create a chiral environment around the activated carbonyl, lending this method to asymmetric applications.

Our proposed pathway for this tandem oxidation is outlined below (Scheme 1). Initial oxidation of the alcohol

(1) (a) Tojo, G.; Fernández, M. *Oxidation of Alcohols to Aldehydes and Ketones*; Springer: New York, 2006. (b) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499−3548. (c) Sheldon, R. A.; Arends, I.; Ten Brink, G. J.; Dijksman, A. *Acc. Chem. Res.* **2002**, *35*, 774−781. (d) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943−2989.

(2) For a review of tandem oxidation processes, see: Taylor, R. J. K.; Reid, M.; Foot, J.; Raw, S. A. *Acc. Chem. Res.* **2005**, *38*, 851−869.

(3) (a) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616−5617. (b) Corey, E. J.; Katzenellenbogen, J. A.; Gilman, N. W.; Roman, S. A.; Erickson, B. W. *J. Am. Chem. Soc.* **1968**, *90*, 5618−5620. (c) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096. (d) Davidsen, S. K.; Chumoyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558−5567. (e) Fisher, M. J.; Chow, K.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2900−2907.

(4) Gilman, N. W. *J. Chem. Soc.* **1971**, 733−734.

(5) Foot, J. S.; Kanno, H.; Giblin, G. M. P.; Taylor, R. J. K. *Synthesis* **2003**, 1055−1064 and references cited therein.

(6) Mori, N.; Togo, H. *Tetrahedron* **2005**, *61*, 5915−5925.

(7) (a) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 4558−4559. (b) Castells, J.; Llitjos, H.; Morenomanas, M. *Tetrahedron Lett.* **1977**, 205−206. (c) Inoue, H.; Higashiura, K. *J. Chem. Soc., Chem. Commun.* **1980**, 549−550. (d) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254−1258.

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Scheme 1. Proposed Mechanistic Pathway for Tandem Oxidation

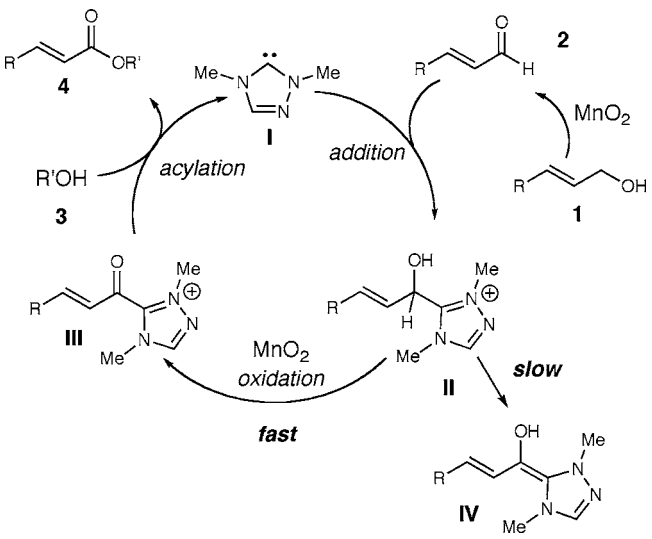
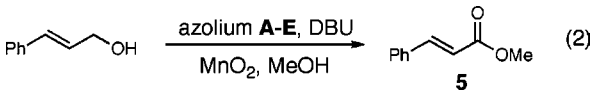
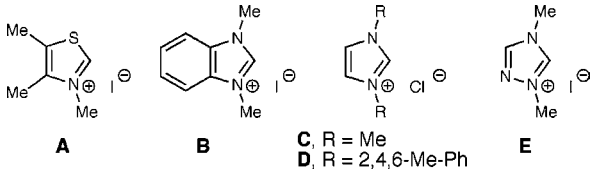


Table 1. Survey of Heteroazolium Salts[a]



entry	azolium	mol %	time, h	yield, %
1	20 mol % DBU only		24	0
2	**A**	20	24	0
3	**B**	20	24	0
4	**C**	20	24	0
5	**D**	20	24	40
6	**E**	10	12	93
7	**E**	2	48	83



[a]All reactions were performed with 1:1 NHC/DBU, 15 equiv of MnO_2, 0.2 M in MeOH at 23 °C.

(**1**) by manganese(IV) oxide provides in situ generation of aldehyde **2**. The deprotonation of the heteroazolium salt generates the N-heterocyclic carbene (**I**), which then adds to the carbonyl to yield tetrahedral intermediate **II**. This secondary alcohol is rapidly oxidized to acyl heteroazolium **III** by manganese(IV) oxide.[8] It should be noted that no generation of homoenolate equivalents[9] (**IV**) is observed. The implication from these observations is that the secondary alcohol generated in situ (**II**) presumably undergoes oxidation faster than deprotonation of the carbinol carbon to afford **IV**. Acylation[10] of the nucleophilic alcohol (**3**) by activated ester **III** completes the oxidation to an unsaturated ester (**4**) and regenerates the NHC catalyst in the presence of base.

Our investigation began by surveying heteroazolium salts as potential catalysts. Cinnamyl alcohol was used as the initial substrate with methanol as the nucleophile and solvent (Table 1, eq 2). The two alcohols were stirred in the presence of DBU, manganese(IV) oxide, and catalytic quantities of the NHC precursor. This oxidation sequence is particularly sensitive to azolium structure. In our hands, thiazolium, benzimidazolium and imidazolium salts **A**−**D** gave no product or incomplete conversion (entries 2−5).[11] However, with simple triazolium salt **E**,[12] we were delighted to isolate methyl cinnamate (**5**) in a 93% yield (entry 6) with no dimer product. Reducing the catalyst loading (2 mol %) resulted in good yields but longer reaction times (entry 7).

With heteroazolium salt **E** identified as an effective precatalyst, we surveyed potential substrates using 1-butanol as the nucleophile (Table 2). A variety of activated alcohols are smoothly oxidized to the respective unsaturated esters in excellent yields.[13] The use of α-substituted allylic alcohols gave comparable yields (entry 2) but required longer reaction times and increased catalyst loading. Propargyl substrates afford the ynoate ester without complications resulting from undesired conjugate addition reactions (entry 5). These conditions also accommodate heteroaromatic systems (entry 6) as well as alkyl (entry 7) and ester (entry 8) functional groups. It is interesting to note that the ethyl ester of **12** does not undergo NHC-catalyzed transesterification in the protic media of the reaction.[14] Substituted benzylic alcohols were the most reticent to undergo oxidation (entries 9 and 10), and electron-rich alcohols such as 4-methoxybenzyl alcohol showed no reactivity in this system, yielding only *p*-anisaldehyde. The slow rate of the second oxidation step with benzylic systems (i.e., **II**−**III**, Scheme 1) may be due to the destabilizing interaction between the aromatic ring and the heteroazolium core that would be generated if the acyl heteroazolium species were formed. However, the success with naphthyl systems (entries 3 and 4) should suffer similar

(8) In the absence of manganese(IV) oxide, the combination of aldehydes with triazolium salt **E** and DBU yielded only benzoin products. See: (a) Breslow, R.; Schmuck, C. *Tetrahedron Lett.* **1996**, *37*, 8241−8242. (b) White, M. J.; Leeper, F. J. *J. Org. Chem.* **2001**, *66*, 5124−5131.

(9) (a) Chan, A.; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 905−908. (b) Sohn, S. S.; Rosen, E. L.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 14370−14371. (c) Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *Org. Lett.* **2006**, *8*, 507−509. (d) Sohn, S. S.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3873−3876. (e) He, M.; Bode, J. W. *Org. Lett.* **2005**, *7*, 3131−3134. (f) Nair, V.; Poonoth, M.; Vellalath, S.; Suresh, E.; Thirumalai, R. *J. Org. Chem.* **2006**, *71*, 8964−8965.

(10) Acyl heteroazolium species have been proposed as acylating agents in several NHC-catalyzed processes. See: (a) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770−2771. (b) Reynolds, N. T.; de Alaniz, J. R.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 9518−9519. (c) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126−8127.

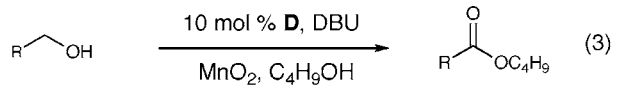
(11) In a related, but strongly discouraging result, Taylor reported that 2 full equiv of a thiazolium salt in the presence of 20 equiv of manganese(IV) oxide only afforded 4% yield (calculated by ^{1}H NMR) of methylcinnamate from cinnamyl alcohol (see ref 5).

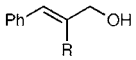
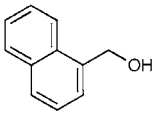
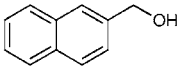
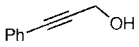
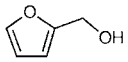
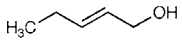
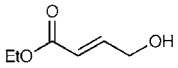
(12) Mirzaei, Y. R.; Twamley, B.; Shreeve, J. M. *J. Org. Chem.* **2002**, *67*, 9340−9345.

(13) The use of *cis*-allylic alcohols in this reaction leads to slower reaction times and partial isomerization of the double bond (1:5 *E*/*Z* mixture). *n*-Butyl *cis*-cinnamate can be isolated in moderate yield (62%).

(14) (a) Connor, E. F.; Nyce, G. W.; Myers, M.; Mock, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914−915. (b) Grasa, G. A.; Guveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812−2819. (c) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453−2456.

Table 2. Examination of Activated Alcohol Scope[a]



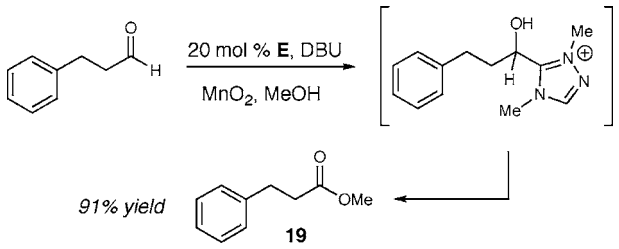
entry	alcohol	product	yield, %
1		**6a**, R=H	93
2		**6b**, R=Me	91[b]
3		**7**	90
4		**8**	91
5		**9**	85
6		**10**	73
7		**11**	87
8		**12**	65
9	BnOH	**13**	88[c]
10	2-Br-BnOH	**14**	70[b]

[a] See Table 1 for reaction conditions. [b]25 mol % of NHC/DBU. [c]50 mol % of NHC/DBU.

unfavorable interactions and provide high yields of the desired esters. Experiments to investigate this divergence in reactivity are currently ongoing.

In addition to allylic and benzylic substrates, hydrocinnamaldehyde was oxidized to the corresponding methyl ester **19** using catalytic amounts of the NHC precursor and DBU (Scheme 2). The alcohol resulting from addition of the NHC

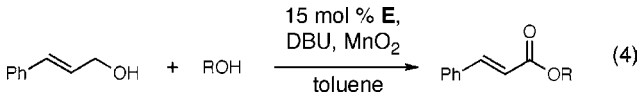
Scheme 2. Oxidation of Hydrocinnamaldehyde



is sufficiently activated to undergo oxidation to the acyl triazolium intermediate. The excellent yield of this reaction demonstrates the feasibility of this process as a method to access not only unsaturated but also saturated esters.

A modification of the reaction conditions allows the use of the nucleophilic alcohol as a reagent rather than as a solvent. With 5 equiv of the nucleophilic alcohol in toluene, a full equivalent of DBU is added to aid proton transfer during acylation because using catalytic amounts of DBU results in reduced yields. A variety of alcohols can be employed to trap the acyl triazolium intermediate (Table 3, eq 4). The hindered nature of the acylating agent is evidenced by the fact that primary alcohols were the most reactive as nucleophiles, with the use of methanol resulting in the highest yield (entry 1). Secondary alcohols such as 2-propanol (entry 2) are effective nucleophiles in the reaction, and *tert*-butanol (entry 3) affords no product.[15] This approach allows for the efficient synthesis of carboxylate derivatives such as 2,2,2-trichloroethyl (Troc),[16] 2-methoxyethyl (ME),[17] and 2-(trimethylsilyl)ethyl (TMSE)[18] cinnamyl esters (entries 4−6).

Table 3. Variation of Nucleophilic Alcohol[a]



entry	nucleophile	product	yield, %
1	methanol	**5**	95
2	2-propanol	**15**	89
3	*tert*-butanol	–	0
4	2,2,2-trichloroethanol	**16**	82
5	2-methoxyethanol	**17**	82
6	2-(trimethylsilyl)ethanol	**18**	74

[a] Reactions run at a 1 mmol scale using 15 mol % of NHC, 1.15 equiv of DBU, 5 equiv of ROH, 15 equiv of MnO_2, 0.2 M in toluene at 23 °C.

A promising feature of this tandem oxidation reaction is the in situ generation of a chiral activated ester, presumably in the form of the acyl heteroazolium intermediate **III**. An application for this chiral acylating agent is the desymmetrization of *meso*-diols. Initial results for the selective acylation of *cis*-1,2-cyclohexane diol (Table 4, eq 5) yielded modest levels of enantioselectivity that decreased with time, presumably due to base-catalyzed acyl transfer[19] of the product (Table 4, entries 1 and 2). The use of a milder base such as a proton sponge (entries 3 and 4) supresses acyl transfer and allows for the isolation of **21** in >60% yield with ~60% ee.

A survey of solvents for this desymmetrization indicates that methylene chloride provides the best combination of

(15) See Supporting Information for details.

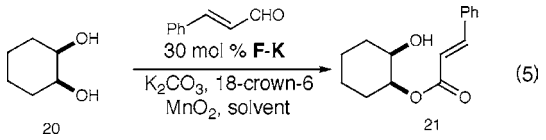
(16) (a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganat, S.; Vorbrugg, H. *J. Am. Chem. Soc.* **1966**, *88*, 852−853. (b) Pearson, A. J.; Lee, K. S. *J. Org. Chem.* **1994**, *59*, 2304−2313.

(17) Gewehr, M.; Kunz, H. *Synthesis* **1997**, 1499−1511.

(18) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711−2716.

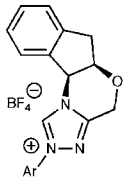
(19) Resubjecting optically enriched acylated material to reaction conditions led to complete racemization after 90 min. For examples of acyl transfer of monoacylated 1,2-cyclohexane diols, see: Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430−431. Laumen, K.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1990**, 49−51.

Table 4. Desymmetrization of *cis*-1,2-Cyclohexane Diol[a]

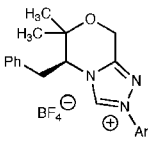


(5)

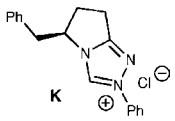
entry	catalyst	conditions	yield, %	ee, %
1[b]	**F**	toluene, 23 °C	53	20
2[b]	**G**	toluene, 23 °C	47	41
3	**F**	proton sponge, toluene, 23 °C	66	52
4	**G**	proton sponge, toluene, 23 °C	62	60
5	**G**	proton sponge, 4-CF_3-Ph, 23 °C	39	63
6	**G**	proton sponge, THF, 23 °C	53	54
7	**G**	proton sponge, CH_2Cl_2, 23 °C	78	59
8	**H**	proton sponge, CH_2Cl_2, 23 °C	76	23
9	**J**	proton sponge, CH_2Cl_2, 23 °C	57	20
10	**K**	proton sponge, CH_2Cl_2, 23 °C	76	37
11	**G**	proton sponge, CH_2Cl_2, 0 °C	67	65
12	**G**	proton sponge, CH_2Cl_2, −30 °C	58	80
13	**G**	proton sponge, CH_2Cl_2, −40 °C	38	73



F, Ar = Ph
G, Ar = Mes



H, Ar = Ph
J, Ar = Mes



K

[a]Reactions performed with 30 mol % of K_2CO_3, 15 mol % of 18-crown-6, 1 equiv of proton sponge, and 0.25 M solvent. [b]Reaction performed with 1.5 equiv of K_2CO_3, 20 mol % of 18-crown-6, and 0.25 M solvent. Proton sponge = *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine.

yield and selectivity (entry 7). A variety of chiral triazolium salts were screened in this reaction. Triazolium **G**[20] in the presence of both potassium carbonate and a proton sponge provides the highest selectivity and reactivity with **20** and cinnamaldehyde (entry 7). When this reaction is conducted at −30 °C, chiral triazolium **G** catalyzes the oxidation of cinnamaldehyde and subsequently selectively acylates *cis*-1,2-cyclohexane diol in 58% yield and 80% ee (entry 12).[21] This strategy of accessing activated acylating agents from aldehydes and an oxidant only in the presence of an N-heterocyclic carbene has potential applications with nucleophiles that undergo fast background reactions with acid chlorides or anhydrides.

In conclusion, a tandem oxidation of allylic and benzylic alcohols to esters has been developed using N-heterocyclic carbenes as catalysts. This operationally simple one-pot process avoids the use of cyanide and delivers esters in good to excellent yield using a simple triazolium salt as the precatalyst. Saturated esters can also be prepared by the oxidation of saturated aldehydes in the same manner. An asymmetric desymmetrization can be achieved using a chiral heteroazolium salt. Studies utilizing N-heterocyclic carbenes as catalysts in oxidation reactions are ongoing.

Acknowledgment. Financial support was generously provided by Northwestern University, the PRF (Type-G), Abbott Laboratories, Amgen, 3M, and Boerhinger-Ingelheim (New Investigator Awards). A.C. is the recipient of a Dow Chemical Company Fellowship. We thank FMCLithium, Sigma-Aldrich, and BASF for providing reagents used in this research. The funding for the NU Analytical Services Laboratory has been furnished in part by the NSF (CHE-9871268).

Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL062940F

(20) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418−8420.

(21) (a) Wills, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1096−1109.