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Aerobic oxidation of secondary benzylic alcohols and direct oxidative amidation of aryl aldehydes promoted by sodium hydride

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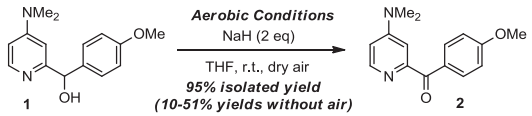
ABSTRACT

We reported herein new reactivities and possible mechanistic implications of a simplest oxidant (NaH/air) uncovered on a broad range of useful transformations, including aerobic alcohol oxidations, allylic alcohol isomerizations and oxidations, cyclopropyl alcohol fragmentations, and direct aryl aldehyde oxidative amidations. These readily implementable transition-metal-free processes feature exceptional material accessibility, operational simplicity, and environmental compatibility, and add new dimensions to its synthetic utilities that are fairly robust yet had not previously been fully realized and systematically explored.

1. Introduction

The oxidation of alcohols into their corresponding carbonyl compounds represents a fundamentally important functional group transformation and occupies a prominent position in modern synthetic organic chemistry. Advances in the development of new oxidation reagents and methodologies and their applications in both target- and diversity-oriented synthesis have been regularly surveyed, and constituted one of the most extensively and actively investigated areas of current organic synthesis.[1] In this context, an extensive range of classical oxidants, including those small organic molecule-based reagents (such as Dess–Martin periodinane, Swern oxidation, Moffatt oxidation, Corey–Kim oxidation, and SO_3/pyridine) and metal-based systems (such as Jones reagent, Collins reagent, pyridinium chloro-chromate, pyridinium dichromate, barium permanganate, manganese dioxide, ruthenium tetroxide, silver carbonate, and Oppenauer oxidation), have been known to be powerful tools for converting alcohols into their corresponding aldehydes or ketones, thus evolved as a most important class of tools in synthetic chemists' arsenal. A recent conceptually novel approach in this area, driven by the increasingly significant concerns of process environmental compatibility and sustainability, has been exploring aerobic oxidations with highly active transition-metal catalysts (such as Pd, Ru, Fe, Cu, Pt, Au, Ir, Rh, Co, Mn, Mo, etc.) and dioxygen gas as the terminal oxidant.[2,3] Despite these impressive advances, very few of the available methods are capable of offering truly economic and practical oxidation transformations across a broad spectrum of alcohol substrates. Many of these systems also suffer from high reagent cost, air-instability, employment of heavy metals or organic oxidants, stringent reaction conditions, operational complexity, functional group incompatibility, or production of wastes in their related processes. Thus, there is a continuing demand for new reagents that could help address the above-mentioned challenges. We herein report on an exceedingly simple secondary alcohols aerobic oxidation protocol and related direct aryl aldehydes oxidative amidation processes promoted by the widely available sodium hydride (NaH) reagent.

While pursuing another synthesis project, we lately had prepared a DMAP-derived benzylic alcohol **1** and desired to use its sodium alkoxide ion for an intended nucleophilic substitution event. However, upon treatment of **1** with NaH in freshly distilled THF at room temperature for 10 h, it was found that the reaction surprisingly gave ketone **2** cleanly in 95% isolated yield (Scheme 1). When



Scheme 1. Aerobic oxidation of DMAP-derived benzylic alcohol promoted by NaH.

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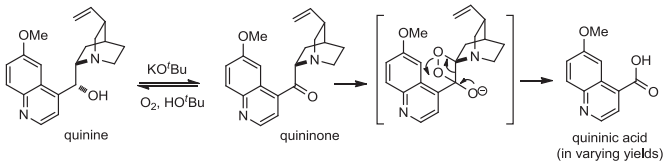
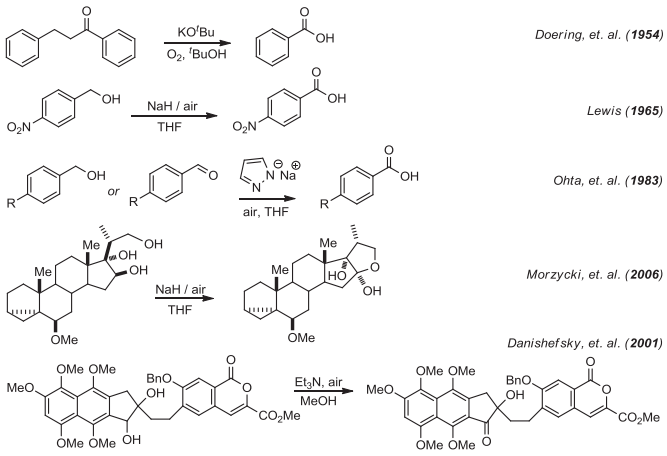
NaH was repeatedly washed with freshly distilled THF to remove possible air oxygen that might had been pre-absorbed on the commercial reagent (NaH from Aldrich), **2** was consistently obtained albeit with lower and varying yields (10–51%); but when dry air oxygen was purposefully introduced into the reaction system, the yield was essentially quantitative, demonstrating a remarkable level of oxidation efficiency.

Historically, an earliest significant documentation of alkaline aerobic oxidation of an aryl alcohol may be traced back to the autoxidation of quinine and quininone under the action of KO^tBu/O_2 reported by Doering and Woodward in their studies on the racemization and synthesis of quinine.[4] They proposed an Oppenauer-type oxidation pathway (initiated by self-generated quininone or externally added benzophenone) and addition of O_2 to the enolate ion from quininone to account for the observed establishment of quinine–quininone equilibrium and formation of quininic acid, respectively (Scheme 2).



Scheme 2. Alkaline autoxidation of quinine and quininone observed by Doering and Woodward.

Since these initial observations, a few other scattered examples of alkaline autoxidations had appeared during a considerably long course of time, and these were summarized in Scheme 3. Doering disclosed alkoxide-catalyzed autoxidative cleavage of ketones and esters in 1954;[5] Lewis reported on aerobic oxidation of *p*-nitrobenzylic alcohol into its carboxylic acid under NaH/air/THF conditions in 1965;[6a] Ohta and co-workers further showed in 1983 that aerobic oxidation of a range of benzylic alcohols or aryl aldehydes could be effectively promoted by sodium pyrazolide and transformed these substrates into their corresponding carboxylic acids;[6b] Morzycki and co-workers uncovered a striking example of aerobic oxidation of a purely aliphatic triol to form a lactol ring in a steroid synthesis in 2006;[6c] finally, conceptually relevant, the Danishefsky group recorded a remarkable 'chance observation' of conversion of an aryl diol to its hydroxyketone by simple exposure to Et_3N/air in 2001 that proved to be critical for the subsequent spirocyclization event in their total synthesis of heliquinomycinone.[6d]



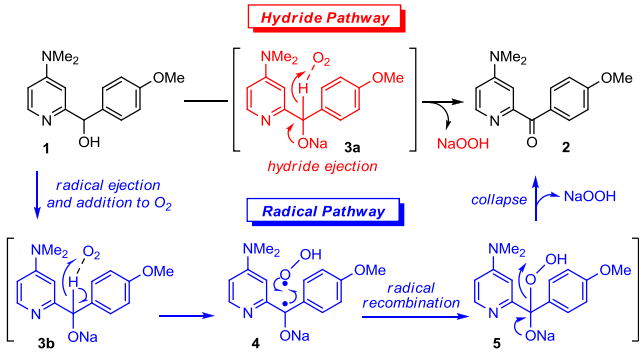
Scheme 3. Scattered literature on alkaline aerobic oxidations.

The feasibility of these alkaline alcohol autoxidations has also occasionally been manifested by the formation of varying amounts of ketone by-products during etherification of aryl alcohols with the conventional NaH/benzyl halide protocol when the manipulations were conducted without strict exclusion of air oxygen contaminant. Yet despite these recorded observations and empirical appreciations, this type of reactivities has usually been viewed as bypass culprits leading to side-reactions rather than methodology of constructive usefulness. The fact thus firmly remains that the scope and synthetic utilities of such a simple aerobic oxidation protocol as NaH/air have never before been fully realized and systematically explored, and consequently, this simple oxidant had not yet emerged as a viable methodology in synthetic chemists' toolbox. Intrigued by this observation of aerobic oxidation of **1** into **2** promoted by NaH/air, we embarked on an investigation on its reactivities in the general context of alcohol oxidation chemistry. The findings summarized here over a number of synthetically significant contexts surprisingly uncovered new dimensions of reactivities of this arguably simplest oxidant.

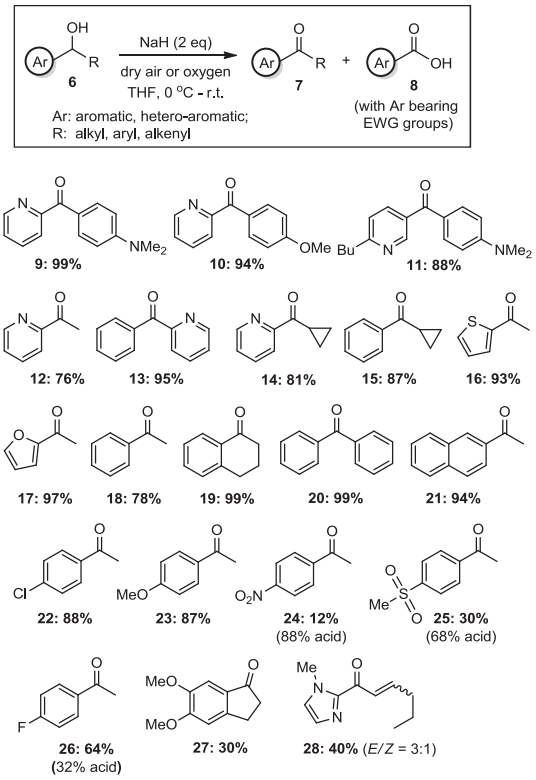
2. Results and discussion

2.1. NaH-promoted aerobic oxidation of secondary aryl alcohols

Mechanistically, it may be envisioned that the formation of sodium alkoxide ion **3** during the transformation of **1** into **2** under aerobic conditions would either stimulate the ejection of a hydride from the intermediate **3a** that subsequently could be captured by O_2 to form sodium hydrogen peroxide (NaOOH), or the ejection of a hydrogen radical from the species **3b** that could be formed from the homolytic cleavage of the benzylic C–H bond (Scheme 4). The resulted benzylic radical is structurally analogous to the well-established benzophenone ketyl. The hydrogen radical released would then add to O_2 to yield a hydrogen peroxide radical in **4** that recombines with the benzylic radical to yield the intermediate **5**. Collapse of this tetrahedron species should produce ketone product **2** with concomitant release of NaOOH. Indeed, NaOOH solid powder generated in this process could be easily recovered through a repeated centrifugation-THF washing procedure. Moreover, subsequent literature searching identified that, as a matter of fact, Berre had reported in 1961 a highly practical and large scale anhydrous NaOOH preparation procedure that actually takes advantage of alkaline oxidation of benzhydrol under oxygen atmosphere with NaO^tBu.[7] NaOOH could also be generally formed and recovered from aerobic oxidation of other substrates under similar conditions (vide infra, such as alcohol oxidation on **19** and **20** in Scheme 5, and direct aldehyde amidation of **70** in Scheme 11). Moreover, when a portion of this recovered NaOOH powder was dissolved in water and made acidic with HCl, H_2O_2 was readily generated and detected positively by the potassium iodide/starch test. It should be noted that NaOOH itself did not promote the above oxidation under otherwise identical conditions.[8] A number of other bases (Na, MeONa, ^{t}BuONa) and solvents (Et_2O, toluene, DMF, DMSO, 1,4-dioxane) were surveyed (with product yields ranging from 15 to 80%) and the NaH/THF combination was found to be



Scheme 4. Possible hydride and radical pathways in NaH-promoted aerobic oxidations.

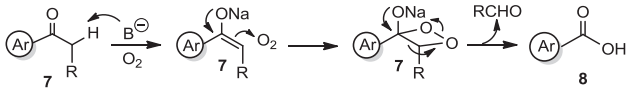


Scheme 5. NaH-promoted aerobic oxidation of secondary aryl alcohols.

most effective in terms of isolated yield, reaction time, and solvent recycling and compound purification easiness.

Among many secondary alcohols randomly surveyed under these aerobic oxidation conditions, aryl and hetero-aryl alcohols summarized as structure **6** (Scheme 5) were found to be substrates of choice, while alkyl alcohols and propargyl alcohols gave either no reaction or complicated decomposed mixtures.

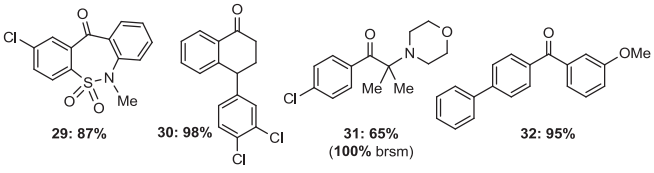
The oxidation occurred effectively at room temperature and went to completion usually within just a few hours (1–10 h). The isolated yields of ketone products **7** are generally high (with several of them being essentially quantitative), except in the cases of substrates bearing an electron-withdrawing substituent (**24**–**26**), in which a large amount of their corresponding carboxylic acid **8** was also obtained. Given the specific reaction conditions employed here and the observation that the formation of acid **8** is directly accompanied by the consumption of initially formed ketone **7**, this side-reaction is best explained by Doering's autoxidative cleavage mechanism[5] (Scheme 6), rather than a Dakin-type oxidation pathway.[9] As compared to transition metal complexes-promoted processes, these reactions are particularly operationally simple, product separation and organic waste recycling could be readily achieved, and there is no such issue as metal residue contaminants incurred during the process, thus offering a significant environmental and pharmaceutical advantage.



Scheme 6. Doering mechanism for autoxidative cleavage of ketone **7** bearing electron-withdrawing aryl substituent.

2.2. Applications of NaH-promoted aerobic oxidation in practical synthesis of some important fine chemical and pharmaceutical compounds

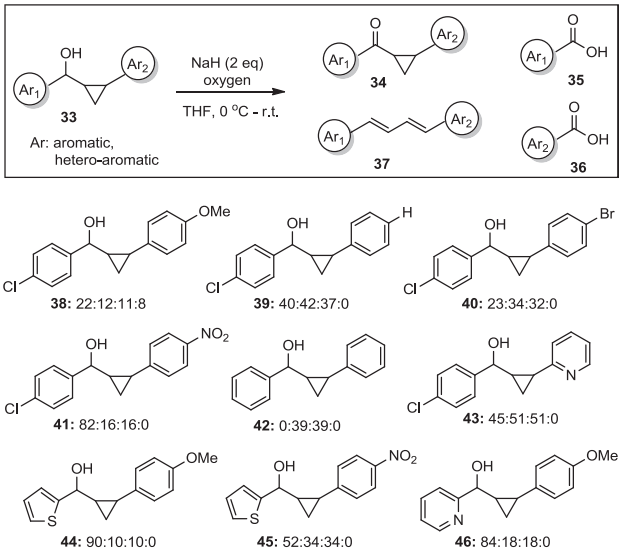
The value of this new oxidation methodology was further highlighted in the economic and environmentally benign synthesis of several important pharmaceutical and fine chemical compounds (Scheme 7). An intermediate (**29**) in the synthesis of *Tianeptine*®,[10a] a drug used for treating major depressive episodes; **30**, a key precursor to the structure of sertraline (*Zoloft*®), a selective serotonin reuptake inhibitor;[10b] can both be easily prepared in high yields at multi-gram scales. A photo-initiator (**31**) widely used in the coating material UV-curing processes,[10c] was produced in moderate yield (with the unreacted substrate quantitatively recovered) but with higher separation efficiency and compound purity as compared to the conventional $AlCl_3$-promoted Friedel–Craft acylation–halogenation–epoxide-opening technology. Particularly notable is the production of a proprietary new-generation environmentally friendly UV photo-initiator **32**, which has now been advanced to commercial bulk scales with an overall economic and environmental benefit well comparable to the low-yielding and massively waste-generating Friedel–Craft process.[10d]



Scheme 7. Economic preparations of some important pharmaceutical and fine chemical compounds through NaH-promoted aerobic oxidation technology.

2.3. Mechanism of radical-triggered cyclopropane ring fragmentation in NaH-promoted aerobic oxidations

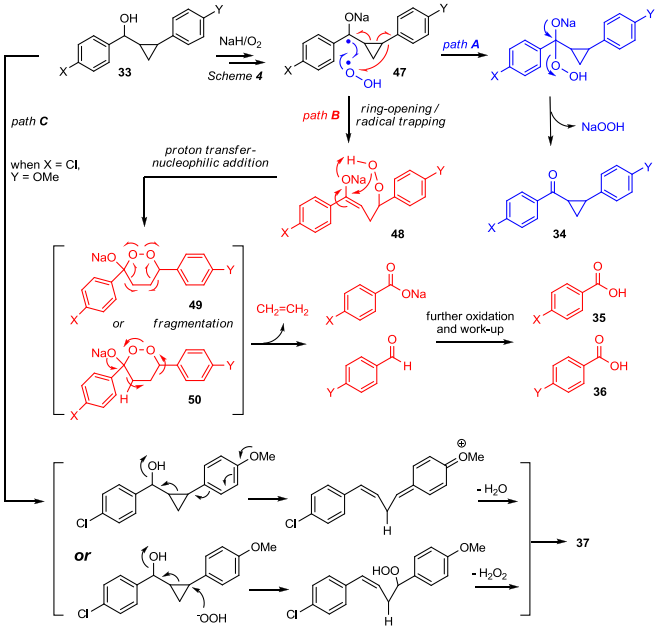
In attempts to mechanistically differentiate the radical-versus-hydride ejection pathway illustrated in Scheme 4 and further probe the structures of the intermediates involved in the aerobic oxidation pathway, some cyclopropane-containing radical clock substrates structured as **33** were prepared and subjected to the NaH/O_2/THF conditions (Scheme 8). Surprisingly, no formal ring-opening ketone product was obtained in each case examined, even with substrates bearing strong electron-withdrawing thus radical-stabilizing substituents (such as NO_2 in **41** and **45**). The reactions instead gave cyclopropyl ketone **34**, equal amount of carboxylic acids



Scheme 8. NaH-promoted aerobic oxidative cyclopropyl ring cleavages. The ratio of the four products in each case is listed in the sequence of **34**:**35**:**36**:**37**.

35 and **36**, and diene **37** with concomitant release of ethylene. These results clearly dispelled the possibility of participation of a hydride ejection pathway, under which ketone **34** would be exclusively formed.

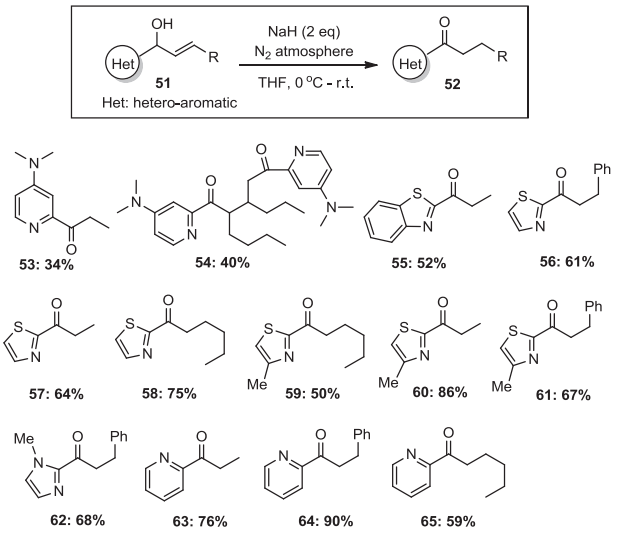
A radical-triggered fragmentation mechanistic scenario may thus be advanced (Scheme 9) to account for these fascinating oxidative cleavage processes. The cyclopropyl-carbinyl radical **47** initially formed under NaH/O_2 condition could either proceed through the pathway ***A*** (in blue) to yield ketone **34**, or, alternatively, undergo a ring-opening-radical recombination event as summarized in pathway ***B*** (in red) to give an enolate-hydroperoxide intermediate **48**. This species would then engage itself in a tandem intramolecular proton transfer–carbonyl nucleophilic addition–fragmentation process to produce the observed products **35** and **36**. The crucial fragmentation event may be initiated through either the homolytic cleavage of the weak O–O bond (in **49**) or collapse of the crowded tetrahedron peroxide intermediate (in **50**). The formation of diene **37** (when X=Cl, Y=OMe in structure **33**, i.e., substrate **38**), as summarized in the minor pathway ***C***, may be attributed to a tandem aryl cyclopropyl ring fragmentation–proton releasing event, or alternatively, a NaOOH-triggered cyclopropyl ring opening–HOOH elimination cascade.



Scheme 9. Mechanistic proposals.

2.4. NaH-promoted isomerization of allylic alcohols

Under these aerobic oxidation conditions, the formation of isomeric imidazole-derived α,β-unsaturated ketone **28** (*E*/*Z*=3:1, Scheme 5) from its (*E*)-allylic alcohol precursor caught our attention as this implied formally a reversible hydride or radical (hydrogen radical or hydrogen peroxide radical) conjugate reduction event following the initial allylic alcohol oxidation. The nitrogen atoms in the imidazole ring, as was the case of oxidation of DMAP-derived alcohol **1** under air-free conditions, seemed to be beneficial for reactivity, and phenyl-substituted allylic alcohols were found to yield no oxidation product but their corresponding alkoxide species. Encouraged by these observations, we set out to explore the reactivities of several other heterocyclic allylic alcohol systems represented by structure **51** (Scheme 10).

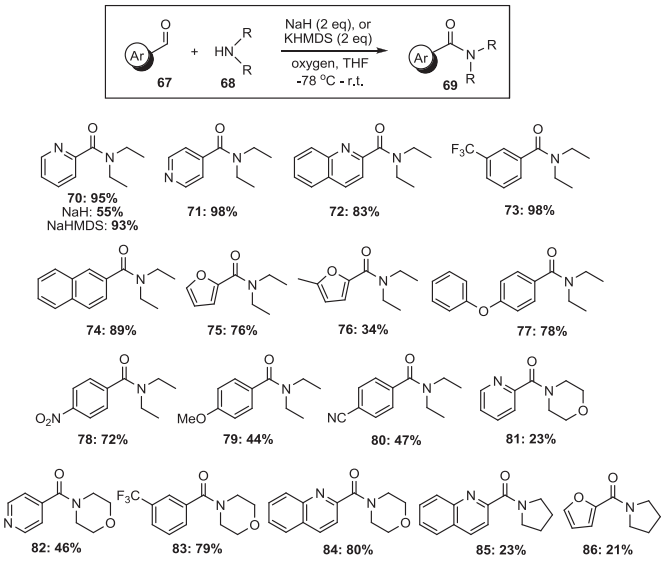


Scheme 10. NaH-promoted isomerization of allylic alcohols.

The reactions gave ketones smoothly and showed an interesting dependence on both the substrate concentration and the amount of oxygen introduced: higher concentrations led to the formation of more dimeric ketones (in **54** such a dimeric ketone became the major product), and excessive air or pure oxygen gas resulted in complicated mixture. The employment of commercially available NaH powder (i.e., not pre-treated through THF-washing O_2-removal procedure as described earlier) under nitrogen atmosphere is sufficient to bring about the observed reactivities. Mechanistically, a pathway involving the formation of an enolate intermediate from anionically accelerated [1,5] hydrogen shift—an event that was previously shown by Giomi and co-workers[11] to thermally operate only at high temperatures in closely related molecular contexts—represents an attractive possibility, while it is also likely that the process involves the deprotonation at the benzylic position by an external pre-formed sodium alkoxide species and subsequent allylic shift and protonation. These scenarios require no participation of air oxygen, but allylic alcohol oxidation may competitively operate as neither of them could economically accommodate the observed enone formations and isomerizations (see **28** in Scheme 5).

2.5. Direct oxidative amidation of aryl aldehydes

These novel reactivities of this simple aerobic oxidation system prompted us to explore further its potential in oxidizing hydroxyl groups in labile *N,O*-hemiacetal species thereby yielding directly oxidative amidation products (Scheme 11). Indeed, using picolinealdehyde as a model substrate, it was found that the corresponding amide **70** was readily obtained in 55% yield under standard NaH/O_2 conditions. The detection of pyridin-2-ylmethanol as the major reduction by-product inspired the employment of the bulkier and hydride-free base NaHMDS at a lower temperature to suppress the competing aldehyde reduction pathway. Indeed, a much higher yield of 93% was obtained. The yield of **70** was further improved to 95% when KHMDS was used. With this optimal $KHMDS/O_2$ condition, a variety of aromatic and hetero-aromatic aldehydes **67** readily coupled with their secondary amine partners **68** to give the desired amides **69**, i.e., products **70**–**86**, in usually good-to-high yields and within just a few hours, demonstrating an impressive level of efficiency and simplicity.[12] This simple yet unusual direct amide synthesis protocol constitutes a very useful and appealing complement to various transition metal complexes-catalyzed oxidative amidation technologies.[13]



Scheme 11. Direct oxidative amidation of aryl aldehydes.

3. Conclusion

In summary, the novel reactivities and mechanisms uncovered here on a broad range of aerobic alcohol oxidations, allylic alcohol isomerizations and oxidations, cyclopropyl alcohol fragmentations, and direct aldehyde oxidative amidations collectively add new dimensions of synthetic utilities of this simplest oxidation system, they are proven to be very robust yet had not previously been fully realized and systematically explored. The advantages of these transition metal-free methodologies, as already highlighted in the preparations of some important pharmaceutical and fine chemical compounds, are very significant in terms of material accessibility, operational simplicity, and environmental and pharmaceutical compatibility. It therefore might well be anticipated that these findings will invite favorable consideration from the synthetic community and thus stimulate their wide-spreading applications in appropriate synthetic contexts, particularly in the economic and sustainable preparation of pharmaceutically meaningful compounds.[14]

4. Experimental

4.1. General experimental

Reagents were purchased at the highest commercial quality from Acros and Aldrich and used without further purification unless otherwise noted. Sodium hydride was purchased from Aldrich, 60% dispersion in mineral oil and used without further purification unless otherwise noted. Anhydrous THF was freshly distilled from a benzophenone ketyl still. Yields refer to chromatographically purified compounds, unless otherwise stated. Silica gel (ZCX-II, 200–300 mesh) used for flash column chromatography was purchased from Qing Dao Ocean Chemical Industry Co. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Brüker Advance 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), or Brüker Advance 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometer. Mass spectrometric data were obtained using ABI-Q Star Elite high resolution mass spectrometer.

4.2. Aerobic oxidation of secondary aryl alcohols

A round-bottom flask that was flame-dried and cooled under dry air or oxygen atmosphere was charged with alcohol **6** or **33** (0.5 mmol) and THF (2.5 mL). After stirring at 0 °C for 5 min, NaH powder (1 mmol, 2 equiv) was added in one portion, and the mixture was allowed to warm to room temperature. The reaction was quenched by addition of saturated NH_4Cl (2 mL) after the indicated time, extracted with EtOAc (10 mL×2), and washed by brine (15 mL). The combined organic phase was dried over $MgSO_4$, the solvent was removed under *vacuum*, and the residue was purified by flash chromatography on silica gel to give the desired ketone product **7** and **34**.

For isolations of acids **8** and **35**/**36**: the combined aqueous phase was acidified with 2 M HCl, and then extracted with EtOAc (10 mL×2) and washed by brine (15 mL). The combined organic phase was dried over Na_2SO_4, the solvent was removed under *vacuum* to give acid product that can be further purified by flash chromatography on silica gel.

4.3. Conversion of allylic alcohols to saturated ketones

To a round-bottom flask that was flame-dried and cooled under nitrogen were added allylic alcohol **51** (0.5 mmol) and THF (2.5 mL). After stirring at 0 °C for 5 min, NaH powder (1 mmol, 2 equiv) was added in one portion, the mixture was then allowed to warm to room temperature. The reaction was quenched by addition of saturated NH_4Cl (2 mL) after the indicated time, extracted with EtOAc (10 mL×2), and washed by brine (15 mL). The combined organic phase was dried over $MgSO_4$, the solvent was removed under *vacuum*, and the residue was purified by flash chromatography on silica gel to give the desired ketone product **52**.

4.4. Direct oxidative amidation of aryl aldehydes

Procedure ***A***: To a round-bottom flask that was flame-dried and cooled under nitrogen were added THF (3 mL), aromatic aldehyde **67** (0.5 mmol), and amine **68** (2 mmol, 4 equiv). After stirring for 30 min at room temperature, the reaction system was cooled to −78 °C and after another 10 min, the flask was collected to an oxygen balloon, NaHMDS (2 M in THF, 0.75 mL, 1.5 mmol, 3 equiv) or KHMDS (0.5 M in toluene, 3 mL, 1.5 mmol, 3 equiv) was added dropwise via a syringe. The reaction mixture was then allowed to warm slowly to an indicated temperature. Upon completion at the indicated time, the reaction was quenched by addition of saturated NH_4Cl (3 mL) and extracted with EtOAc (15 mL×2). The combined organic layer was washed by brine (15 mL) and dried over $MgSO_4$. The solvent was removed under *vacuum*, and the residue was purified by flash chromatography on silica gel to give the amide product **69**.

Procedure ***B***: To a round-bottom flask that was flame-dried and cooled under oxygen were added THF (2 mL), amine **68** (2 mmol, 4 equiv), and KHMDS (0.5 M in toluene, 3 mL, 1.5 mmol, 3 equiv). After stirring at room temperature for 1 h, aldehyde **67** (0.5 mmol) in THF (1 mL) was added dropwise. The reaction was monitored by TLC until the aldehyde was completely consumed. The reaction was quenched by addition of saturated NH_4Cl (3 mL), extracted with EtOAc (15 mL×2), and washed by brine (15 mL). The combined organic phase was dried over $MgSO_4$. The solvent was removed under *vacuum*, and the residue was purified by flash chromatography on silica gel to give the amide product **69**.

Acknowledgements

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Supplementary data

Detailed experimental procedures, compound characterization data, and copies of ^{1}H and ^{13}C NMR spectra. Supplementary data

related to this article can be found online at doi:10.1016/j.tet.2011.03.052.

References and notes

1. (a) Bäckvall, J.-E. *Modern Oxidation Methods*; Wiley-VCH: New York, NY, 2004; (b) Tojo, G.; Fernandez, M. *Oxidation of Alcohols to Aldehydes and Ketones*; Springer: Berlin, 2006; (c) Ley, S. V.; *Comprehensive Organic Synthesis*, 3rd ed.; Pergamon: Oxford, 1999; Vol. 7, Chapter 2, pp 252–327; (d) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086 and references cited therein. For latest reports on new alcohol oxidation systems, see: (e) Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251; (f) Zeynizadeh, B.; Lotfi, P. *Asian J. Chem.* **2009**, *21*, 3617; (g) Cao, H.-T.; Gree, R. *Tetrahedron Lett.* **2009**, *50*, 1493; (h) Zhan, B.-Z.; Thompson, A. *Tetrahedron* **2004**, *60*, 2917.
2. Pd-systems: (a) Stahl, S. S. *Science* **2005**, *309*, 1824; (b) Popp, B. V.; Stahl, S. S. *Top. Organomet. Chem.* **2007**, *22*, 149; (c) Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348 and references cited therein; (d) Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766; (e) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343 and references cited therein; (f) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475; (g) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725; (h) Bagdanoff, J. T.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 353; (i) Yamada, T.; Higano, S.; Yano, T.; Yamashita, Y. *Chem. Lett.* **2009**, *38*, 40 Ru-systems: (j) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Chem.—Asian J.* **2008**, *3*, 1479; (k) Iwasa, S.; Morita, K.; Tajima, K.; Fakhruddin, A.; Nishiyama, H. *Chem. Lett.* **2002**, *3*, 284; (l) Venkatesan, S.; Kumar, A. S.; Lee, J.-F.; Chan, T.-S.; Zen, J.-M. *Chem. Commun.* **2009**, 1912; (m) Sato, T.; Kamanoya, T. *Catal. Commun.* **2009**, *10*, 1095; (n) Csjernyik, G.; Ell, A. H.; Fadini, L.; Pugin, B.; Bäckvall, J.-E. *J. Org. Chem.* **2002**, *67*, 1657 Fe-systems: (o) Kim, S. K.; Sastri, C. V.; Seo, M. S.; Kim, J.; Nam, W. *J. Am. Chem. Soc.* **2005**, *127*, 4178; (p) Wang, N.-W.; Liu, R.-H.; Chen, J.-P.; Liang, X.-M. *Chem. Commun.* **2005**, 5322 Cu-systems: (q) Striegler, S. *Tetrahedron* **2006**, *62*, 9109; (r) Jiang, N.; Ragauskas, A. J. *J. Org. Chem.* **2006**, *71*, 7087; (s) Jiang, N.; Ragauskas, A. J. *Org. Lett.* **2005**, *7*, 3689; (t) Lorber, C. Y.; Smidt, S. P.; Osborn, J. A. *Eur. J. Org. Chem.* **2000**, *4*, 655 Pt-systems: (u) Wang, T.; Xiao, C.-X.; Yan, L.; Xu, L.; Luo, J.; Shou, H.; Kou, Y.; Liu, H.-C. *Chem. Commun.* **2007**, 4375 Au-system: (v) Li, H.-R.; Guan, B.-T.; Wang, W.-J.; Xing, D.; Fang, Z.; Wan, X.-B.; Yang, L.-P.; Shi, Z.-J. *Tetrahedron* **2007**, *63*, 8430 Ir- and Rh-systems: (w) Arita, S.; Koike, T.; Kayaki, Y.; Ikariya, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2447.
3. Immobilized-metal systems: (a) Matsumoto, T.; Ueno, M.; Wang, N.-W.; Kobayashi, S. *Chem.—Asian J.* **2008**, *3*, 239; (b) Kobayashi, S.; Miyamura, H.; Akiyama, R.; Ishida, T. *J. Am. Chem. Soc.* **2005**, *127*, 9251; (c) Miyamura, H.; Akiyama, R.; Ishida, T.; Matsubara, R.; Kobayashi, S. *Tetrahedron* **2005**, *61*, 12177; (d) Yang, G.-Y.; Zhu, W.-M.; Zhang, P.-K.; Xue, H.-Z.; Wang, W.; Tian, J.-S.; Song, M.-P. *Adv. Synth. Catal.* **2008**, *350*, 542 Transition-metal-free systems: (e) Liu, R.-H.; Liang, X.-M.; Dong, C.-Y.; Hu, X.-Q. *J. Am. Chem. Soc.* **2004**, *126*, 4112; (f) Kuang, Y.-B.; Islam, N. M.; Nabae, Y.; Hayakawa, T.; Kakimoto, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1 Biomimetic systems: (g) Piera, J.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506; (h) Sharma, U. K.; Sharma, N.; Kumar, R.; Kumar, R.; Sinha, A. K. *Org. Lett.* **2009**, *11*, 4846.
4. (a) Doering, W. E.; Cortes, G.; Knox, L. H. *J. Am. Chem. Soc.* **1947**, *69*, 1700; (b) Doering, W. E.; Chanley, J. D. *J. Am. Chem. Soc.* **1946**, *68*, 586.
5. Doering, W. E.; Haines, R. W. *J. Am. Chem. Soc.* **1954**, *76*, 482.
6. (a) Lewis, G. E. *J. Org. Chem.* **1965**, *30*, 2433; (b) Ohta, S.; Tachi, T.; Okamoto, M. *Synthesis* **1983**, *4*, 291; (c) Kruszewska, A.; Wilczewska, A. Z.; Wojtkielewicz, A.; Morzycki, J. W. *Pol. J. Chem.* **2006**, *80*, 611; (d) Siu, T.; Qin, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4713.
7. Berre, A. L. *Bull. Soc. Chim. Fr.* **1961**, 1543.
8. Holland, H. L.; Daum, U.; Riemland, E. *Tetrahedron Lett.* **1981**, *22*, 5127.
9. Leffler, J. E. *Chem. Rev.* **1949**, *45*, 385.
10. (a) Blanchard, J. U.S. Patent 6,441,165 B2. (b) Quallich, G. J. *Chirality* **2005**, *17*, S120; (c) Huesler, R.; Kirchmayr, A.; Rutsch, W. U.S. Patent 4,559,371. (d) Shenzhen UV-ChemTech, Chinese Patent publication No. 200910106950.
11. Giomi, D.; Piacenti, M.; Brandi, A. *Tetrahedron Lett.* **2004**, *45*, 2113.
12. With the substrate stoichiometry employed (aryl aldehyde 67 as the limiting material) and the product yields obtained, the Oppenauer-type oxidation pathways using the aldehydes themselves as oxidants are unlikely to occur in these systems. For relevant reference, see: Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425.
13. For excellent reviews, see: (a) Eloue-Kovi, K.; Wolf, C. *Chem.—Eur. J.* **2008**, *14*, 6302; (b) Furuyama, T. *Yuki Gosei Kagaku Kyokaishi* **2008**, *66*, 1005 For various protocols on oxidative amidation of aldehydes, see: (c) Cho, C.-C.; Liu, J.-N.; Chien, C.-H.; Shie, J.-J.; Chen, Y.-C.; Fang, J.-M. *J. Org. Chem.* **2009**, *74*, 1549; (d) Nordstrém, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672; (e) Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**, *21*, 3619; (f) Fang, C.; Qian, W.-X.; Bao, W.-L. *Synlett* **2008**, 2529; (g) Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *49*, 5732; (h) Seo, S.-Y.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317; (i) Gao, J.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 2955; (j) Ekoue-Kovi, K.; Wolf, C. *Org. Lett.* **2007**, *9*, 3429; (k) Yoo, W.-J.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064; (l) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, *3*, 523; (m) Enders, D.; Amaya, A. S.; Pierre, F. *New J. Chem.* **1999**, *23*, 261; (n) Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237; (o) Ojima, I. *Chem. Rev.* **1988**, *88*, 1011; (p) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, *6*, 474; (q) Nakagawa, K.; Onoue, H.; Minami, K.; Mineo, S. *Yakugaku Zasshi* **1975**, *95*, 1167; (r) Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1971**, 733 Zhu and co-workers recently reported an efficient one-carbon homologation protocol converting aldehydes into their corresponding amides: (s) Bonne, D.; Dekhane, M.; Zhu, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 6926.
14. Following our earlier and later retracted disclosure at *J. Am. Chem. Soc.* **2009**, doi:10.1021/ja904224y ASAP three publications investigating the oxidation reactivities of Na/O_2 and NaH, respectively, have subsequently appeared; (a) Zhou, L.-H.; Yu, X.-Q.; Pu, L. *Tetrahedron Lett.* **2010**, *51*, 475; (b) Joo, C.; Kang, S.; Kim, S. M.; Han, H.; Yang, J. W. *Tetrahedron Lett.* **2010**, *51*, 6006; (c) Kang, S.; Joo, C.; Kim, S. M.; Han, H.; Yang, J. W. *Tetrahedron Lett.* **2010**, doi:10.1016/j.tetlet.2010.11.079 ASAP.