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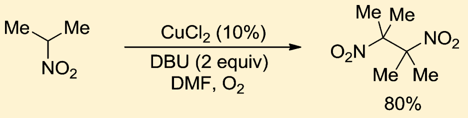
Copper-Catalyzed Homodimerization of Nitronates and Enolates under an Oxygen Atmosphere

Hien-Quang Do, Hung Tran-Vu, and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003, United States

Supporting Information

ABSTRACT: A method for copper-catalyzed oxidative dimerization of nitronates and enolates using oxygen as the terminal oxidant has been developed. Cyclization through oxidative intramolecular coupling is also feasible for both nitronates and enolates. The mild reaction conditions lead to good functional group tolerance.



Oxidative dimerization is a useful transformation for the construction of many symmetric organic molecules such as biaryls,[1a] vicinal dinitroalkanes,[1b] and 1,4-dicarbonyl compounds.[1c] In general, the presence of a stoichiometric oxidant is essential for achieving good conversions. Both organic and inorganic oxidants such as 1,2-dihaloethanes,[2a,b] benzoquinones,[2c,d] silver salts,[2e,f] copper salts,[2e,g−j,t] ceric ammonium nitrate,[2k,u,v] persulfates,[2e,f] hydrogen peroxide,[2e] iron salts,[2e,m,n] titanium salts,[2o,p] and halogens[2p,s] have been used in these transformations (Scheme 1). However, for both environmental and economic reasons, it is advantageous if those stoichiometric oxidants can be replaced by readily accessible oxygen. Although the involvement of oxygen in the oxidative dimerization of aromatic compounds has recently witnessed significant progress,[3] the oxidative homocoupling of aliphatic anions such as nitronates and enolates utilizing oxygen as terminal oxidant still remains challenging.[4a]

Scheme 1. Dimerization of Nitronates and Enolates

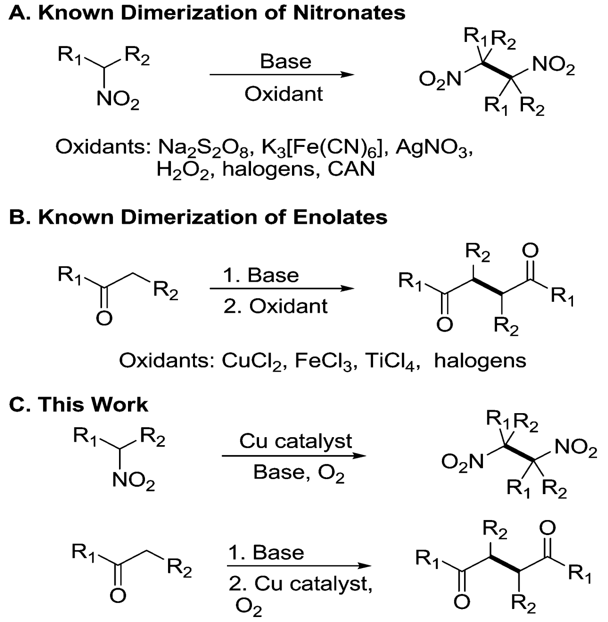
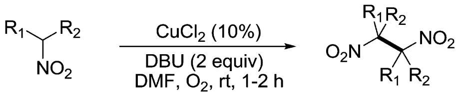
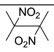
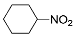
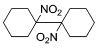
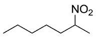
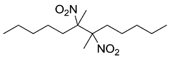
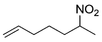
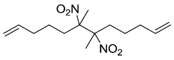
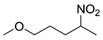
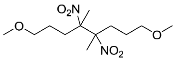
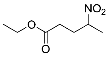
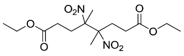
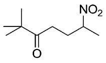
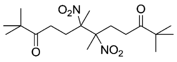
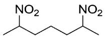
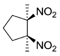


Table 1. Dimerization of Nitroalkanes[a]



entry	nitroalkane	product	yield
1			80%
2[b]			55%
3[b]			73%
4[b]			60%
5			62%
6			63%
7			46%
8[b,c]			53%

[a] Conditions: nitroalkane (1.0 mmol), DBU (2.0 mmol), $CuCl_2$ (0.1 mmol), DMF (0.8 mL), room temperature, 1−2 h. Yields are isolated yields. [b] $CuCl_2$ (0.15 mmol) was used. [c] DBU (4 mmol) was employed.

Vicinal dinitroalkanes are useful intermediates for the synthesis of vicinal diamines that are employed as ligands for transition-metal-catalyzed reactions and can be found in many biologically active compounds.[5] Moreover, the nitro group can also be converted to a wide range of important functionalities

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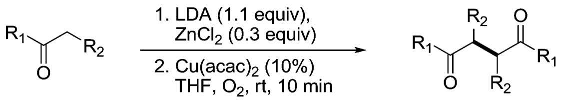
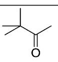
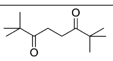
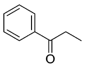
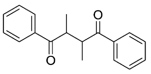
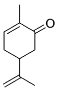
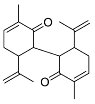
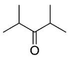
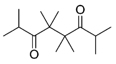
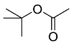
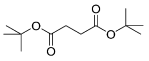
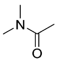
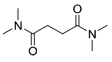
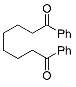
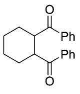
Table 2. Dimerization of Carbonyl Compounds[a]



entry	carbonyl compound	product	yield
1[c]			69%
2		 *dr* = 4:1	68%
3		 *dr* = 1.9:1	64%
4[b]			31%
5[c]			52%
6[c,b]			58%
7[b]		 *trans:cis* = 2:1	55%

[a]Conditions: carbonyl compound (1.0 mmol), LDA (1.1 mmol), $ZnCl_2$ (0.3 mmol), $Cu(acac)_2$ (0.1 mmol), THF (1.0 mL), room temperature, 10 min. Yields are isolated yields of a diastereomer mixture if applicable. [b]$Cu(acac)_2$ (0.15 equiv) was used. [c]0.5 mmol of $ZnCl_2$ was employed.

such as amine, carbonyl, nitrile, oxime, hydroxylamine, and thiol.[6]

Similarly, the 1,4-dicarbonyl moiety is ubiquitous in organic molecules, including natural products and numerous medicinal remedies.[2t] Therefore, the synthesis of vicinal dinitroalkanes and 1,4-dicarbonyl compounds is still attracting attention. We have recently developed a method for copper-catalyzed dimerization of aromatic compounds employing oxygen as the terminal oxidant.[3h] We speculated that the strategy should be applicable to the oxidative dimerization of nitronates and enolates. Our speculation was based on the fact that Cu(II)-promoted enolate dimerization as well as the oxidation of low-valent copper species to Cu(II) is well precedented.[2e−g,j,t,3h] Therefore, we set out to develop conditions for this transformation employing copper catalysis and oxygen as a terminal oxidant.

The dimerization of nitroalkanes has been intensively studied in terms of both method development and mechanism. It can be performed by both electrochemical and chemical methods.[2e,f,k−m,r,s,7] In the latter case, several equivalents of chemical oxidants are employed. Sello and Morin have recently published an elegant work on the synthesis of pimaricin-inducing factor.[2k] The authors have developed a general procedure for oxidative dimerization of various nitroalkanes using 2.2 equiv of CAN oxidant and NaH base. However, the use of NaH base requires 15-crown-5 to decomplex the sodium counterion from nitronate and ensure a good yield of the product. We reasoned that since nitroalkanes are fairly acidic ($pK_a < 16−17$),[8] milder bases could be used to generate nitronates. In addition, the higher compatibility of the base with the copper catalyst and oxygen should result in a one-step reaction. A number of bases and solvents were screened for the dimerization of 2-nitropropane under an oxygen atmosphere with 10 mol % of copper(II) chloride catalyst. Interestingly, when DBU was employed as a base, the dimerization proceeded smoothly at room temperature in most common solvents such as DMF, THF, dioxane, DCM, acetonitrile, and methanol to afford the product in good conversion.[9] The best results were obtained in DMF, and the products were isolated in excellent yields (Table 1). In addition, mild reaction conditions allow for high tolerance of functional groups. The optimized conditions were applied to dimerization of nitroalkanes bearing various functionalities. Functional groups such as ether (entry 5), ester (entry 6), and ketone (entry 7) are tolerated. The reaction was then extended to the cyclization of dinitroalkanes through an intramolecular oxidative coupling reaction. A mixture of 2,6-dinitroheptane diastereomers underwent cyclization to afford *cis*-1,2-dimethyl-1,2-dinitrocyclopentane as the sole product (entry 8). In contrast, nearly equal amounts (6/4) of *cis*- and *trans*-1,2-dimethyl-1,2-dinitrocyclopentane were observed by Jackson and Bowman in the cyclization of the same substrate.[2m]

The Nef reaction is a competing process under these conditions and is responsible for the diminished yield of some substrates by unproductive consumption of starting material.[4] The contribution of side reactions becomes significant for substrates containing at least one large alkyl group (entries 2−7). About 8% of cyclohexanone was formed in the dimerization of nitrocyclohexane (analysis by GC). In some cases, an increase of catalyst amount to 15 mol % improves the yield (entries 2, 3, 4, and 8).[10]

If two diastereoisomers can be produced, for acyclic cases they are usually generated in equal amounts (dr = 1:1, entries 3−7). The control experiments reveal that copper catalyst is essential for the formation of the product. Only a trace of dimerization product was detected if copper(II) chloride is omitted. Additionally, the reactions can be run in open vials in the air; however, substantially longer reaction times are required.[11] Unfortunately, all attempts to expand the reaction to dimerization of primary nitroalkanes led to disappointing conversions.

The dimerization of enolates is well-established and has been widely applied in organic synthesis. However, no copper-catalyzed process has yet been developed.[2g−i,n,p,t] We were interested in establishing the conditions for copper-catalyzed enolate dimerization using oxygen as the terminal oxidant. Propiophenone was chosen as the model substrate. The lithium enolate was prepared by treatment of ketone with LDA in THF at −78 °C. The resulting enolate solution was reacted with oxygen in the presence of 10% of copper(II) chloride. Only 10% conversion to the dimerization product was observed. We assumed that lithium enolate is unstable under the reaction conditions. Consequently, the enolate anion should be stabilized in the presence of oxygen. A feasible solution for this issue is the introduction of a more electrophilic zinc or magnesium salt. We were gratified to find that treatment of lithium enolate solution with 0.3 equiv of zinc chloride improves the conversion from 10% to 70%. Increasing the amount of zinc chloride additive to 1 equiv decreases the conversion. Further optimization led to the use of copper(II) acetylacetonate catalyst. The optimized conditions involve 10 mol % of Cu(acac)$_2$ catalyst, 0.3−0.5 equiv of ZnCl$_2$ additive, and 1 atm of oxygen, affording the desired product in 68% isolated yield. The conditions work well for a variety of carbonyl compounds such as ketones (Table 2, entries 1−4, 7), esters (entry 5), and amides (entry 6).

Good results can be obtained for both primary and secondary ketones (entries 1−3), although tertiary ketone afforded diminished yield, presumably due to steric effects (entry 4). For chiral or prochiral secondary ketones, two diastereoisomers are produced with preferential formation of the *syn* (*dl*) diastereoisomer (entries 2 and 3). Analogous outcomes have also been observed in stoichiometric dimerizations.[2i,n,t] The cyclization through intramolecular oxidative coupling was also successful, and a mixture of *cis*- and *trans*-1,2-dibenzoylcyclohexane was obtained if 1,8-diphenyloctane-1,8-dione was subjected to the general conditions. As expected, the *trans* isomer was formed predominantly (entry 7). In general, the yields in the catalytic reactions parallel those previously described in stoichiometric reactions.[2g−i]

In conclusion, we have developed two copper-catalyzed methods for oxidative dimerization of nitroalkanes and carbonyl compounds that employ oxygen as the terminal oxidant. Mild reaction conditions in the homocoupling of nitroalkanes lead to good functional group tolerance.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, and tables giving experimental details, data, and spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: olafs@uh.edu.

Notes

The authors declare no competing financial interest.

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(9) Please see the Supporting Information for optimization data.

(10) An increase of CuCl$_2$ loading increases the dimerization product yield; however, the effect becomes smaller with higher Cu(II) loading. Please see the Supporting Information for details.

(11) Dimerization of nitrocyclohexane in air led to 52% conversion to product in 5 h. If the reaction was run under nitrogen, 9% conversion to product was observed (15 mol % of CuCl$_2$ used). Please see the Supporting Information for details.