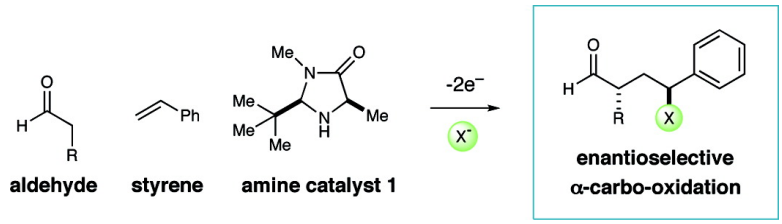
Communication

Enantioselective Organo-Singly Occupied Molecular Orbital Catalysis: The Carbo-oxidation of Styrenes

Thomas H. Graham, Casey M. Jones, Nathan T. Jui, and David W. C. MacMillan

J. Am. Chem. Soc., **2008**, 130 (49), 16494-16495 • DOI: 10.1021/ja8075633 • Publication Date (Web): 17 November 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/17/2008

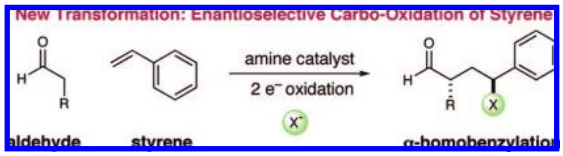
Enantioselective Organo-Singly Occupied Molecular Orbital Catalysis: The Carbo-oxidation of Styrenes

Thomas H. Graham, Casey M. Jones, Nathan T. Jui, and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544

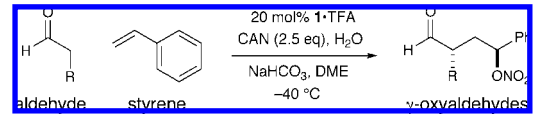
Received September 23, 2008; E-mail: dmacmill@princeton.edu

A critical objective for the continued advancement of the field of asymmetric catalysis is the design and implementation of novel activation modes that allow the invention of unprecedented transformations.[1] Recently, our laboratory introduced a new mode of organocatalytic activation, termed (singly occupied molecular orbital) SOMO catalysis,[2] that is founded upon the transient production of a 3π-electron radical-cation[3] species that can function as a generic platform of induction and reactivity. As part of these studies, we documented the first direct and enantioselective allylic alkylation,[2] enolation,[4] and vinylation[5] of aldehydes, three protocols that were not previously known in a chiral or achiral format. Continuing this theme, we recently questioned whether feedstock olefins, such as styrenes, might be exploited in this SOMO pathway to allow the enantioselective α-homobenzylation of aldehydes, a new C−C bond-forming reaction between functional groups that are generally inert to chemical combination. In this context, we disclose the first asymmetric SOMO-catalyzed carbo-oxidation of styrenes to provide γ-nitrate-α-alkyl aldehydes, a valuable synthon for the production of enantioenriched butyrolactones, pyrrolidines, and α-formyl homobenzylation adducts. Most important, this new organo-SOMO reaction allows simple styrenes to function as α-alkylation partners for aldehydes, a transformation that to our knowledge is without precedent.[6]



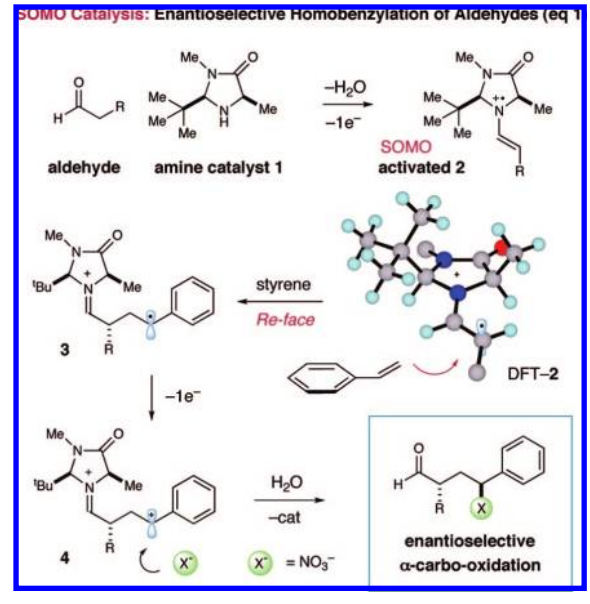
Design Plan. In our previous SOMO catalysis studies, we exploited the capacity of the aldehyde-derived radical cation DFT-**2**[7] to rapidly engage electron-rich olefins that incorporate traceless activation handles (e.g., enolsilanes, allylsilanes, vinyl trifluoroborate salts).[2,4,5] A common mechanistic feature of these coupling reactions is the transient production of a β-silyl or β-borato cation intermediate that can regioselectively collapse to render an olefinic or carbonyl containing product. With this in mind, we questioned whether a simple, nonactivated olefin, such as styrene, might also undergo addition to the radical cation DFT-**2** to form a benzylic radical **3** that upon further oxidation will generate a similar carbocation **4** (eq 1). As a key design element, the benzylic cation **4** cannot readily participate in an E1 elimination mechanism (the salient pathway of our previous studies) as the styrene precursor does not incorporate a β-activation/leaving group. Instead we hoped to capture the value of this high energy intermediate via intermolecular addition of an anionic or neutral heteroatom addend (e.g., NO_3^-, Cl^-, H_2O), a step that would create a second stereogenic center while increasing the relative molecular complexity of the alkylation product. In accord with our previous studies, we expected high levels of enantiocontrol on the basis that catalyst **1** should selectively form a SOMO-activated cation **2** (DFT-**2**) that projects the 3π-electron system away from the bulky *tert*-butyl group, while the carbon-centered radical will selectively populate an (*E*)-configuration to avoid nonbonding interactions with the catalyst framework. Moreover, the calculated structure of DFT-**2** reveals that the methyl group on the catalyst system will effectively shield the *Si*-face of the SOMO-activated π-system, leaving the *Re*-face exposed to styrene addition.

Table 1. Organocatalytic Carbo-oxidation: Aldehyde Scope



entry	R	% yield	anti:syn	% ee[a,b]
1	hexyl	91	3:1	96
2	*cyc*-hexyl	88	3:1	96
3	$(CH_2)_6C{\equiv}CEt$	94	3:1	96
4	Bn	81	3:1	96
5	$(CH_2)_3OBn$	90	3:1	95
6	4-*N*-BOC piperidinyl	82	2:1	94

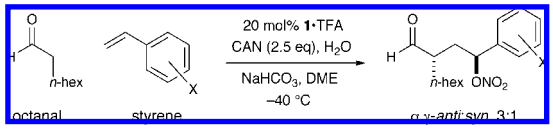
[a] Enantiomeric excess determined by chiral HPLC or SFC analysis. [b] Stereochemistry assigned by single crystal X-ray analysis or analogy.

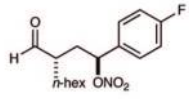
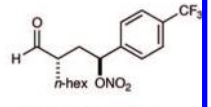
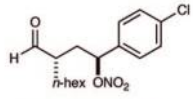
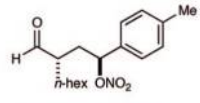
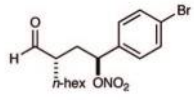
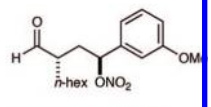
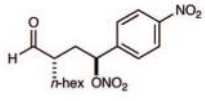
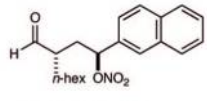
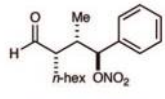
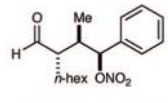


The proposed enantioselective α-formyl homobenzylation was first examined using octanal and styrene, with imidazolidinone **1** as the SOMO catalyst and ceric ammonium nitrate (CAN)[8] as the stoichiometric oxidant (Table 1, entry 1). Notably, the desired aldehyde α-alkylation was successful along with intermolecular trapping of the putative cation **4** by the nitrate anion arising from reduction of the Ce(IV) oxidant. Indeed, the resulting homoaldol-type product was formed in excellent yield and enantioselectivity, while diastereocontrol

10.1021/ja8075633 CCC: $40.75

Table 2. Organocatalytic Carbo-oxidation: Scope of the Styrene



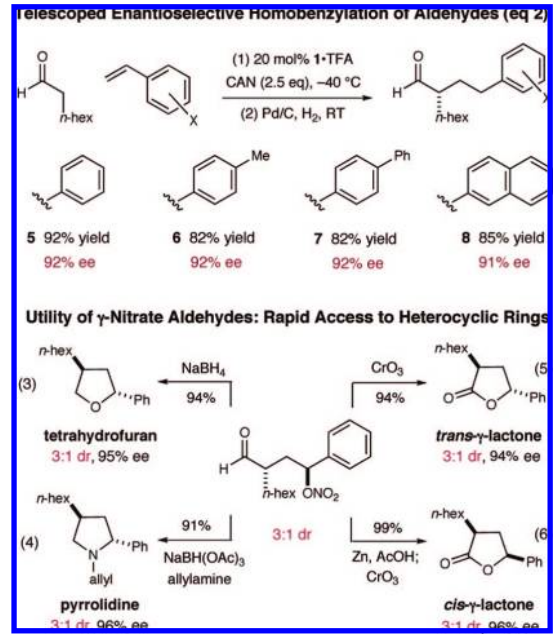
entry	product[a] (% yield, % ee[b,c])	entry	product[a] (% yield, % ee[b,c])
1	 93% yield 96% ee	2	 90% yield 96% ee
3	 92% yield 96% ee	4	 88% yield 93% ee
5	 92% yield 97% ee	6	 94% yield 96% ee
7	 95% yield 92% ee	8	 90% yield 97% ee
9[d]	 86% yield 94% ee	10[e]	 83% yield 89% ee

[a] The benzylic stereocenter was formed in all cases with 3:1 α,*γ-anti* diastereocontrol. [b] Values of ee determined by SFC or HPLC analysis. [c] Stereochemistry assigned by X-ray analysis or by analogy. [d] With *trans*-*β*-methyl styrene, dr = 6:1 α,*β-syn*. [e] With *cis*-*β*-methyl styrene, dr = 4:1 α,*β-anti*.

for the cation trapping step was moderate (~75:25 anti:syn). As revealed in Table 1, substantial variation in the steric contribution of the aldehyde component is possible (entries 1, 2 and 6, R = *n*-hexyl, *cyc*-hexyl, 4-piperidinyl, 82−91% yield, 94−96% ee). Moreover, a variety of functionalities appear to be inert to these mild oxidative conditions including alkynes, aryl rings, ethers, and carbamates (entries 3−6, 81−94% yield, 94−96% ee).

As highlighted in Table 2, a wide array of styrenes readily participate as SOMOphiles in this new catalytic carbo-oxidation (entries 1−10). For example, electron-rich and electron-deficient styrenes are readily tolerated (entries 1−8, 88−95% yield, 92−97% ee). Notably, the implementation of *β*-substituted styrenes in this coupling reaction allows the stereospecific formation of carbo-oxidation products that incorporate three stereogenic centers. As exemplified in Table 2, the use of *trans*-*β*-methyl styrene allows selective formation of the syn−anti stereochemical triad (entry 9, 6:1 dr, 94% ee), while the *cis*-*β*-methyl styrene leads to the corresponding anti−syn isomer (entry 10, 4:1 dr, 89% ee).

The utility of this new enantioselective carbo-oxidation and the accompanying *γ*-nitrate-α-alkyl aldehyde products is highlighted in eqs 2−6. First, we have found that the crude product of our SOMO catalysis step can be subjected to hydrogenation to selectively cleave the benzylic nitrate ester without reduction of the aldehyde moiety or loss in enantiopurity (eq 2).[9] This mild two-stage protocol allows the enantioselective α-homobenzylation of aldehydes using a variety of styrenyl substrates (eq 2, 82−92% yield, ≥91% ee). Second, the nitrate ester products can be utilized for the rapid construction of enantioenriched heterocyclic rings (eqs 3−6). For example, in situ treatment with sodium borohydride leads directly to tetrahydrofuran products,[10] while a reductive amination sequence using allylamine provides rapid access to optically active pyrrolidines. While direct oxidation of the aldehyde moiety provides the corresponding *trans*-*γ*-lactone, the enantioenriched *cis*-*γ*-lactone can be accessed via zinc reduction to the corresponding lactol and subsequent oxidation.[11] Notably, the stereochemical purity of the carbo-oxidation adducts is retained in all of these ring forming steps and the resulting heterocycles are readily isolated in isomerically pure form.[12]



Acknowledgment. Financial support was provided by the NIH-GMS (R01 GM078201-01-01) and kind gifts from Merck.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) MacMillan, D. W. C. *Nature* **2008**, *405*, 304.
(2) Beeson, T. D.; Mastracchio, A.; Hong, J. B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.
(3) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099.
(4) Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398.
(5) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 398.
(6) It is important to note that a noncatalytic, non-enantioselective intermolecular alkylation of malonate esters using styrene has been accomplished under oxidative conditions: Citterio, A.; Sebastiano, M.; Nicolini, R.; Santi, R. *Synlett* **1990**, 42.
(7) DFT calculations performed using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) (see ref 2).
(8) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862.
(9) (a) Auricchio, S.; Ricca, A. *Tetrahedron* **1987**, *43*, 3983. (b) Baldwin, S. W.; Long, A. *Tetrahedron Lett.* **2001**, *42*, 5343.
(10) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(11) Cainelli, G.; Manescalchi, F.; Martelli, G.; Panunzio, M.; Plessi, L. *Tetrahedron Lett.* **1985**, *26*, 3369.
(12) We were unable to separate the nitrate ester diastereomeric adducts prior to heterocyclic ring formation.

JA8075633