Published in final edited form as:

J Am Chem Soc. 2010 April 7; 132(13): 4570–4571. doi:10.1021/ja1013536.

Iron Catalyzed Aminohydroxylation of Olefins

Kevin S. Williamson and Tehshik P. Yoon *

Department of Chemistry, University of Wisconsin–Madison, 1101 University Avenue, Madison, Wisconsin 53706

Abstract

We have discovered that *N*-sulfonyl oxaziridines react with a broad range of olefins in the presence of iron salts to afford 1,3-oxazolidines. This process provides access to 1,2-aminoalcohols with the opposite sense of regioselectivity produced from the copper-catalyzed oxyamination previously reported from our labs. Thus, either regioisomeric form of 1,2-aminoalcohols can easily be obtained from the reaction of oxaziridines with olefins, and the sense of regioselectivity can be controlled by the appropriate choice of inexpensive, non-toxic first row transition metal catalyst.

The osmium-catalyzed Sharpless aminohydroxylation^{1,2} is a powerful method for the rapid transformation of alkenes into 1,2-aminoalcohols.³ Due to the cost and toxicity of osmium salts, however, a variety of alternate methods for olefin oxyamination have been developed that utilize palladium⁴ and copper⁵ catalysts. We previously reported that *N*-sulfonyl oxaziridines (“Davis’ oxaziridines”)⁶ react with olefins in the presence of copper(II) catalysts to afford 1,3-oxazolidines.⁷ In this communication, we report that iron salts⁸ are also effective catalysts for oxaziridine-mediated oxyamination but provide the opposite regiomer outcome. Thus, the appropriate choice of inexpensive, nontoxic first-row transition metal in this transformation enables complementary access to 1,2-aminoalcohols in either regioisomeric form.

tyoon@chem.wisc.edu.

Supporting Information Available: Experimental procedures and spectral data for all new compounds are provided (36 pages, PDF format). This material is available free of charge via the Internet at <http://pubs.acs.org>.

This discovery resulted from a screen of transition metal salts that we hoped might also be effective catalysts for oxaziridine activation. We were surprised to discover that both FeBr_3 and $\text{Fe}(\text{acac})_3$ produced the previously unobserved regioisomer **2** from the reaction of oxaziridine **1a** and 4-methylstyrene (eq 1), albeit in modest yields (Table 1, entries 1–3). The efficiency of the reaction could be significantly increased upon optimization of oxaziridine structure; introduction of electron-withdrawing groups onto both the *N*-sulfonyl and *C*-aryl substituents resulted in improved yields (entries 4–7). Finally, we noticed that the reaction became noticeably exothermic upon addition of the oxaziridine to the reaction mixture, which we speculated might result in thermal decomposition of the oxaziridine. Thus, reducing the initial reaction temperature to 0 °C resulted in a further increase in the yield and reproducibility of the reaction (entry 8).

The scope of the reaction under these optimized conditions is outlined in Table 2. As in our previously reported copper-catalyzed aminohydroxylation, styrenes proved to be exceptional substrates for this aminohydroxylation reaction. Substituents at the *ortho*, *meta*, and *para* positions of the arene (entries 2–4) are easily accommodated. The reaction is also tolerant of electronic perturbation; aminohydroxylations of styrenes bearing electron-donating (entries 2–5) and electron-withdrawing substituents (entries 6–8) proceed in high yields. Styrenes bearing α and β substituents also undergo efficient aminohydroxylation (entries 9 and 10), although the latter are less reactive and require somewhat longer reaction times. Polar functional groups are also tolerated, including esters (entry 5), aryl halides (entry 6), nitro groups (entry 8), azides (entry 11) and appropriately protected alcohols and amines (entries 12 and 13).

Dienes also proved to be outstanding substrates for this reaction. Both symmetrical (entry 14) and unsymmetrical dienes (entries 15–17) react smoothly, and exclusive chemoselectivity for functionalization of the terminal olefin is observed in aminohydroxylations of monosubstituted 1,3-dienes. Finally, although enynes and aliphatic olefins proved to be significantly less reactive substrates for this transformation, synthetically useful yields of the aminohydroxylation products could be obtained under somewhat modified reaction conditions. Thus, in the presence of 5 Å molecular sieves, addition of 10 mol% of the catalyst and 4 equiv. of the oxaziridine in two portions enabled the aminohydroxylation of 1-octene and methylene cyclohexane in 57% and 53% yield, respectively (entries 18–19). Enynes react under similar conditions to afford the aminohydroxylation product in 52% yield (entry 20).

At present, the mechanism of this novel reaction is unclear, as is the origin of the complementary regioselectivity with respect to the copper-catalyzed reaction. It is evident, however, that $\text{Fe}(\text{acac})_3$ is a precatalyst and not itself the catalytically active species. The reaction between a variety of metal acetylacetonates and *N*-sulfonyl oxaziridines is rapid,⁹ and we presume that oxidation of the acac ligands is responsible for the initial exothermicity observed upon addition of oxaziridine. Consistent with the necessity of a ligand pre-oxidation step is the observation that no reaction occurs using iron complexes bearing either electronically or sterically deactivated acac ligands (e.g., $\text{Fe}(\text{F}_3\text{acac})_3$ and $\text{Fe}(\text{TMHD})_3$).¹⁰ Catalysis by the oxidized ligand itself can be ruled out by the observation that $\text{Na}(\text{acac})$ fails to promote oxyamination. Similarly, we can rule out catalysis by trace copper impurities,¹¹ as $\text{Cu}(\text{acac})_2$ produces the regioisomeric oxazolidine consistent with our previously reported copper-catalyzed methodology. We are currently conducting investigations to identify the oxidation state and coordination sphere of the catalytically active species, with the goal of identifying well-defined iron complexes that promote the aminohydroxylation reaction and are amenable to detailed mechanistic analysis.

The discovery of this iron-catalyzed aminohydroxylation is a useful synthetic advance despite our lack of mechanistic certainty. In order to highlight the complementarity of this method with the copper-catalyzed process we have previously reported, we conducted the study summarized in Scheme 1. 4-Acetoxystyrene **3** reacts with oxaziridine **1e** in the presence of a copper catalyst (2 mol% CuCl₂, 3 mol% Bu₄N⁺Cl⁻) to afford 2,4-substituted oxazolidine **4**, which can be deprotected in two steps to afford aminoalcohol **5**. On the other hand, **3** reacts with **1e** in the presence of 5 mol% Fe(acac)₃ to afford the regioisomeric 2,5-substituted oxazolidine **6** in 90% yield. Subjecting **6** to standard deprotection conditions affords the natural product (±)-octopamine, a biogenic trace amine suspected to be involved in a variety of human disease states.¹²

Thus, using oxaziridines as terminal oxidants, we have shown that 1,2-aminoalcohols are available in either regioisomeric form by vicinal oxyamination of olefins, and that the regioselectivity of this transformation can be controlled by the appropriate choice of first-row transition metal catalyst. Current studies in our lab are focusing on elucidation of the mechanism of this new iron-catalyzed process and on the development of an enantioselective variant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this research has been provided by an NSF CAREER Award (CHE-0645447) and the NIH (R01-GM084022). The NMR spectroscopy facility at UW-Madison is funded by the NIH (S10 RR04981-01) and NSF (CHE-9629688).

References

1. Sharpless KB, Chong AO, Oshima J. *J Org Chem* 1976;41:177–179.
2. For reviews of the scope of the Sharpless asymmetric aminohydroxylation and its use in synthesis, see: (a) O'Brien P. *Angew Chem Int Ed* 1999;38:326–329. (b) Nilov D, Reiser O. *Adv Synth Catal* 2002;344:1169–1173. (c) Bodkin, JA.; McLeod, MD. *J Chem Soc. Perkin, translator. Vol. 1.* 2002. p. 2733–2746.
3. Bergmeier SC. *Tetrahedron* 2000;56:2561–2571.
4. (a) Alexanian EJ, Lee C, Sorensen EJ. *J Am Chem Soc* 2005;127:7690–7691. [PubMed: 15913354] (b) Szolcsányi P, Gracza T. *Chem Commun* 2005:3948–3950. (c) Liu G, Stahl SS. *J Am Chem Soc* 2006;128:7179–7181. [PubMed: 16734468] (d) Desai LV, Sanford MS. *Angew Chem Int Ed* 2007;46:5737–5740.
5. (a) Noack M, Göttlich R. *Chem Commun* 2002:536–537. (b) Fuller PH, Kim JW, Chemler SR. *J Am Chem Soc* 2008;130:17638–17639. [PubMed: 19049311] (c) Sherman ES, Chemler SR. *Adv Synth Catal* 2009;351:467–471. [PubMed: 20126305] (d) Paderes MC, Chemler SR. *Org Lett* 2009;11:1915–1918. [PubMed: 19331361]
6. (a) Davis FA, Nadir UK, Kluger EW. *J Chem Soc, Chem Commun* 1977:25–26. (b) Davis FA, Jenkins R, Yocklovich SG. *Tetrahedron Lett* 1978;52:5171–5174.
7. (a) Michaelis DJ, Shaffer CJ, Yoon TP. *J Am Chem Soc* 2007;129:1866–1867. [PubMed: 17260993] (b) Michaelis DJ, Ischay MA, Yoon TP. *J Am Chem Soc* 2008;130:6610–6615. [PubMed: 18426204] (c) Michaelis DJ, Williamson KS, Yoon TP. *Tetrahedron* 2009;65:5118–5124. [PubMed: 20161136] (d) Benkovics T, Du J, Guzei I, Yoon TP. *J Org Chem* 2009;74:5545–5552. [PubMed: 19507883]
8. For reviews of iron catalysis in organic synthesis, see: (a) Bolm C, Legros J, Le Pailh J, Zani L. *Chem Rev* 2004;104:6217–6254. [PubMed: 15584700] (b) Enthaler S, Junge K, Beller M. *Angew Chem Int Ed* 2008;47:3317–3321. (c) Correa A, Mancheño OG, Bolm C. *Chem Soc Rev* 2008;37:1108–1117. [PubMed: 18497924] (d) Sherry BD, Fürstner A. *Acc Chem Res*

- 2008;41:1500–1511. [PubMed: 18588321] (e) Fürstner A. *Angew Chem Int Ed* 2009;48:1364–1367. (f) Czaplik WM, Mayer M, Cvengroš J, Jacobi von Wangelin A. *Chem Sus Chem* 2009;2:396–417.
9. (a) Boschelli D, Smith AB, Stringer OD, Jenkins RH, Davis FA. *Tetrahedron Lett* 1981;22:4385–4388. (b) Chen BC, Weismiller MC, Davis FA, Boschelli D, Empfield JR, Smith AB. *Tetrahedron* 1991;47:173–182. (c) Davis FA, Liu H, Chen BC, Zhou P. *Tetrahedron* 1998;54:10481–10492. (d) Ishimaru T, Shibata N, Nagai J, Nakamura S, Toru T, Kanemasa S. *J Am Chem Soc* 2006;128:16488–16489. [PubMed: 17177383]
10. F₃acac = 1,1,1-trifluoro-2,4-pentanedione; THMD = 2,2,6,6-tetramethyl-3,5-heptanedione.
11. Buchwald SL, Bolm C. *Angew Chem Int Ed* 2009;48:5586–5587.
12. Sotnikova TD, Caron MG, Gainetdinov RR. *Mol Pharmacol* 2009;76:229–235. [PubMed: 19389919]

Scheme 1a,b.

^a Reagents and conditions: (a) **1e**, 2 mol% CuCl₂, 3 mol% Bu₄N⁺Cl⁻, 77% yield; (b) HCl, H₂O, MeOH, reflux, 88% yield; (c) PhSH, K₂CO₃, 97% yield; (d) **1e**, 5 mol% Fe(acac)₃, 90% yield; (e) HClO₄, H₂O, dioxane, 80 °C, 85% yield; (f) PhSH, K₂CO₃, 77% yield. ^bAr = 2,4-Cl₂Ph.

Table 1

Optimization of reaction conditions for iron-catalyzed aminohydroxylation.

(1)

entry	catalyst	oxaziridine	SO ₂ R ^a	Ar	yield	cis:trans
1	FeCl ₃	1a	Bs	Ph	0%	--
2	FeBr ₃	1a	Bs	Ph	15%	>10:1
3	Fe(acac) ₃	1a	Bs	Ph	28%	>10:1
4	Fe(acac) ₃	1b	Ns	Ph	38%	7:1
5	Fe(acac) ₃	1c	Ns	4-ClC ₆ H ₄	44%	10:1
6	Fe(acac) ₃	1d	Ns	4-CF ₃ C ₆ H ₄	69%	4:1
7	Fe(acac) ₃	1e	Ns	2,4-Cl ₂ C ₆ H ₃	88%	3:1
8 ^b	Fe(acac) ₃	1e	Ns	2,4-Cl ₂ C ₆ H ₃	92%	4:1

^aBs = benzenesulfonyl; Ns = 4-nitrobenzenesulfonyl.

^bReaction initiated at 0 °C and then warmed to ambient temperature over 1 h.

(2)

product	time	yield ^{b,c}	cis:trans ^{b,d}
	4 h	91%	6:1
	3 h	92%	4:1
	3 h	91%	6:1
	4 h	88%	9:1
	2.5 h	90%	4:1
	4 h	82%	8:1
	5 h	84%	>10:1
	4.5 h	83%	>10:1

- R = Ph
- R = 4-MeC₆H₄
- R = 3-MeC₆H₄
- R = 2-MeC₆H₄
- R = 4-AcOC₆H₄
- R = 4-BrC₆H₄
- R = 4-CF₃C₆H₄
- R = 3-NO₂C₆H₄

(2)

time	yield ^{b,c}	cis:trans ^{b,d}
3 h	78%	5:1

product

(2)

time yield^{b,c} cis:trans^{b,d}
7 h 71% 1:1

product

(2)

product	time	yield ^{b,c}	cis:trans ^{b,d}
	6 h	82%	6:1
	4.5 h	79%	5:1
	4 h	93%	5:1
	3 h	76%	6:1
	4 h	70% ^e	5:1
	5 h	94% ^e	5:1
	11 h	83% ^e	5:1

X = N₃

X = OTIPS

X = NHTs

R = *n*-Hex

R = Ph

R = CO₂Et

(2)

product	time	yield ^{b,c}	cis:trans ^{b,d}
6 h	57%	2:1

(2)

product	time	yield ^{b,c}	cis:trans ^{b,d}
6 h	53%	--

(2)