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Iron-Catalyzed Aminohydroxylation of Olefins

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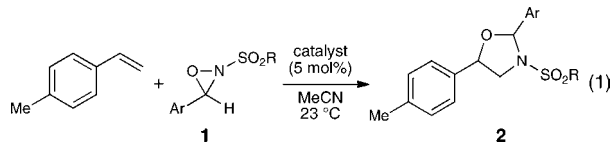
The osmium-catalyzed Sharpless aminohydroxylation[1,2] is a powerful method for the rapid transformation of alkenes into 1,2-aminoalcohols.[3] Because of the cost and toxicity of osmium salts, however, a variety of alternate methods for olefin oxyamination that utilize palladium[4] and copper[5] catalysts have been developed. 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 salts[8] are also effective catalysts for oxaziridine-mediated oxyamination but provide the opposite regiomeric 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.

This discovery resulted from screening 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 $Fe(acac)_3$ 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 was 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 accom-

Table 1. Optimization of Reaction Conditions for Iron-Catalyzed Aminohydroxylation

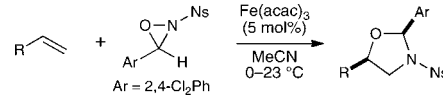


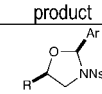
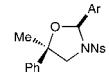
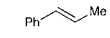
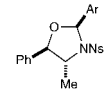
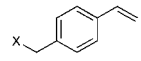
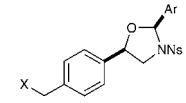
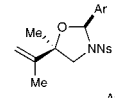
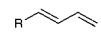
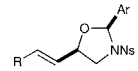
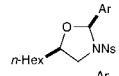
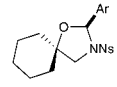
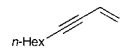
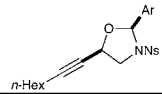
1 **2**

entry	catalyst	oxaziridine	SO_2R[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_6H_4	44%	10:1
6	$Fe(acac)_3$	**1d**	Ns	4-$CF_3C_6H_4$	69%	4:1
7	$Fe(acac)_3$	**1e**	Ns	2,4-$Cl_2C_6H_3$	88%	3:1
8[b]	$Fe(acac)_3$	**1e**	Ns	2,4-$Cl_2C_6H_3$	92%	4:1

[a] Bs = benzenesulfonyl; Ns = 4-nitrobenzenesulfonyl. [b] Reaction initiated at 0 °C and then warmed to ambient temperature over 1 h.

Table 2. Substrate Scope of the Iron-Catalyzed Aminohydroxylation[a]



entry	olefin	product	time	yield[b,c]	cis:trans[b,d]
					
1	R = Ph		4 h	91%	6:1
2	R = 4-MeC_6H_4		3 h	92%	4:1
3	R = 3-MeC_6H_4		3 h	91%	6:1
4	R = 2-MeC_6H_4		4 h	88%	9:1
5	R = 4-$AcOC_6H_4$		2.5 h	90%	4:1
6	R = 4-BrC_6H_4		4 h	82%	8:1
7[f]	R = 4-$CF_3C_6H_4$		5 h	84%	>10:1
8[f]	R = 3-$NO_2C_6H_4$		4.5 h	83%	>10:1
9			3 h	78%	5:1
10[f]			7 h	71%	1:1
					
11	X = N_3		6 h	82%	6:1
12	X = OTIPS		4.5 h	79%	5:1
13	X = NHTs		4 h	93%	5:1
14			3 h	76%	6:1
					
15	R = *n*-Hex		4 h	70%[e]	5:1
16	R = Ph		5 h	94%[e]	5:1
17[f]	R = CO_2Et		11 h	83%[e]	5:1
18[g]	*n*-Hex		6 h	57%	2:1
19[g]			6 h	53%	--
20[g]			7.5 h	52%	>10:1

[a] Unless otherwise noted, reactions were performed using 0.5 mmol of olefin, 2 equiv of oxaziridine, and 5 mol % $Fe(acac)_3$ in MeCN. [b] Data represent the averaged results of two reproducible experiments. [c] Isolated yields. [d] Ratios determined by ^1H NMR analysis of the unpurified reaction mixture. [e] >10:1 olefin selectivity. [f] Reaction conducted using 3 equiv of oxaziridine. [g] Two portions of $Fe(acac)_3$ (2 × 5 mol %) and oxaziridine (2 × 2 equiv) were added to these reactions.

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modated. 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).

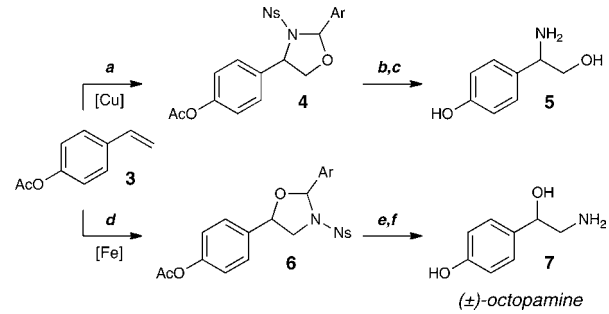
Dienes also proved to be outstanding substrates for this reaction. Both symmetrical (entry 14) and unsymmetrical dienes (entries 15−17) react smoothly, and exclusive chemoselectivity for functionalization of the terminal olefin was observed in aminohydroxylations of monosubstituted 1,3-dienes. Finally, 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 % catalyst and 4 equiv of the oxaziridine in two portions enabled the aminohydroxylation of 1-octene and methylenecyclohexane in 57 and 53% yield, respectively (entries 18 and 19). An enyne reacted 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 $Fe(acac)_3$ is a precatalyst and not itself the catalytically active species. The reactions between a variety of metal acetylacetonates and *N*-sulfonyl oxaziridines are 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 preoxidation step is the observation that no reaction occurs using an iron complex bearing either electronically or sterically deactivated acac ligands [e.g., $Fe(F_3acac)_3$ or $Fe(TMHD)_3$].[10] Catalysis by the oxidized ligand itself is ruled out by the observation that Na(acac) fails to promote oxyamination. Similarly, we can rule out catalysis by trace copper impurities,[11] as $Cu(acac)_2$ produces the regiosiomeric 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 reported previously, we conducted the study summarized in Scheme 1. 4-Acetoxystyrene (**3**) reacts with oxaziridine **1e** in the presence of a copper catalyst (2 mol % $CuCl_2$, 3 mol % $Bu_4N^+Cl^-$) 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 a first-row transition-metal catalyst. Current studies in our lab are focused on elucidation of the mechanism of this new iron-catalyzed process and the development of an enantioselective variant.

Scheme 1[a,b]



[a] Reagents and conditions: (a) **1e**, 2 mol % $CuCl_2$, 3 mol % $Bu_4N^+Cl^-$, 77% yield; (b) HCl, H_2O, MeOH, reflux, 88% yield; (c) PhSH, K_2CO_3, 97% yield; (d) **1e**, 5 mol % $Fe(acac)_3$, 90% yield; (e) $HClO_4$, H_2O, dioxane, 80 °C, 85% yield; (f) PhSH, K_2CO_3, 77% yield. [b] Ar = 2,4-Cl_2Ph.

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

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