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Simple Primary Anilines as Iminium Catalysts for the Epoxidation of α-Substituted Acroleins

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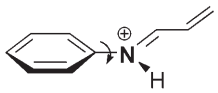
Abstract: Simple *ortho*-alkylated anilines have been shown to be excellent iminium catalysts for the epoxidation reaction of α-substituted acroleins. A range of different α-substituted acroleins give the epoxide products in good to excellent yields and good chemoselectivity.

Keywords: anilines; epoxides; iminium catalysis; organocatalysis

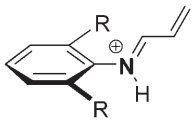
Since contemporary iminium catalysis began to thrive in the early 2000s, a single family of catalysts has dominated the field.[1] These imidazolidinone catalysts, developed by the Seebach group[2] and adopted by MacMillan for iminium catalysis,[3] are effective with α-unsubstituted substrates, but generally display low reactivity with α-substituted enals.[4] Alternative hydrazide-based catalysts from the laboratories of Tomkinson[5] and Ogilvie[6] have displayed increased reactivity towards β-substituted enals, and later discoveries by Ishihara[7] have addressed the use of α-oxygenated acroleins using more complex primary amines. From an industrial point of view, the complexity and cost of the catalysts may prohibit their use in large-scale applications, and the recyclability of the imidazolidinone catalysts appears to be limited.[8] In addition, α-substituted and α,β-disubstituted enals are often not viable partners for iminium-catalyzed transformations.

We reasoned that suitably substituted primary amines should overcome these limitations. Anilines appeared particularly attractive candidates due to their extremely low cost and ready availability. In spite of their long history in organic chemistry, anilines have been very rarely used as catalysts.[9] In fact, the parent aniline has been reported to be entirely inactive in iminium catalysis with enals.[10] Here we demonstrate that more hindered *ortho*-substituted anilines are highly versatile and chemoselective catalysts for activating α-substituted enals towards epoxidation of the double bond.

There are ample literature examples of stable imines formed from aromatic primary amines, including an isolable imine formed from aniline and cinnamaldehyde.[11] Of course, an imine that is *too* stable will not be suitable for a catalytic reaction. This might explain the low reactivity of the parent aniline. Increasing the steric hindrance of the aniline with *o*- and *m*-substitution is expected to destabilize the imine, allowing hydrolysis and regeneration of the catalyst.[12]



iminium ion conjugated with the aromatic ring: slower turnover

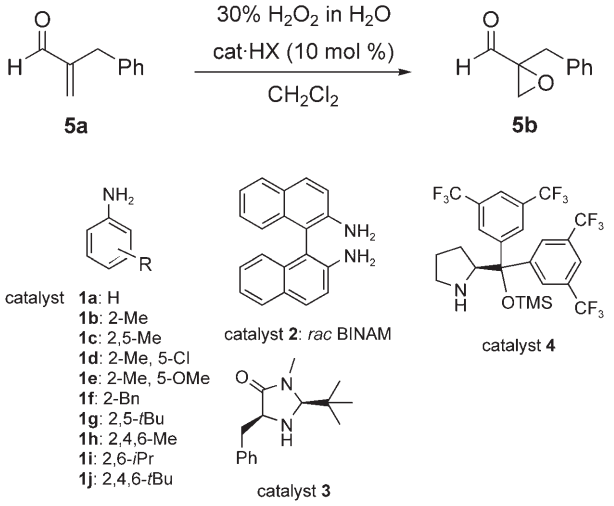


deconjugated iminium: faster turnover?

We recently disclosed a simple organocatalytic method for the preparation of α-substituted acroleins.[13] These compounds were selected as test substrates for the iminium-catalyzed epoxidation reaction.[14] Secondary amine catalysts (e.g., pyrrolidine and its derivatives, such as **4**) did not display useful levels of activity in these reactions. The parent aniline **1a** also displayed poor reactivity. Increasing the steric hindrance in the *ortho* position steadily improved the catalytic activity (Table 1). The doubly *ortho*-substituted 2,6-diisopropylaniline **1i** was identified as the most active catalyst for the epoxidation reaction.

The choice of the acid co-catalyst influenced the activity of the catalytic system in a significant manner. While very strong acids such as HCl, Tf_2NH and CH_3SO_3H failed to promote the reaction, somewhat weaker acids, diphenylphosphoric acid (DPP) and trifluoroacetic acid (TFA), were found to be the co-catalysts of choice[15]. Also, no reaction was observed in

Table 1. Catalyst screening for the epoxidation of α-substituted acroleins.



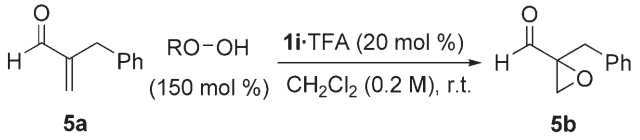
Entry	Catalyst	HX	Conversion[a] [%] (at 4.5 h)
1	**1a**	PhO, PhO, P(=O)OH (DPP)	15
2	**1b**	DPP	36[b]
3	**1c**	DPP	29[b]
4	**1d**	DPP	36
5	**1e**	DPP	22
6	**1f**	DPP	40
7	**1g**	DPP	34
8	**1h**	DPP	45[b]
9	**1i**	DPP	51–56
		TFA	62
		TFA	81[c]
		TFA	100[c,d]
10	**1j**	DPP	0
11	**2**	DPP	30
12	**4**	DPP	0

[a] Conversion by ^{1}H NMR after 4.5 h.
[b] 5.5 h.
[c] 20 mol% cat.
[d] 50 wt% H_2O_2.

the absence of acid. The conversions were further improved by the use of 20 mol% of the inexpensive catalyst and the use of more concentrated H_2O_2 (50% *vs.* 30%, entry 8).

To explore the scope and limitations of the epoxidation method, we exposed a variety of α-substituted α,β-unsaturated aldehydes to the epoxidation reaction. We first optimized the reaction conditions by defining the optimal oxidizing agent, solvent, concentration and catalysts loading.[15] As shown in Table 2, hydrogen peroxide, *t*-BuOOH (TBHP), and cumene hydroperoxide (CHP) are all suitable as oxidants. Somewhat superior rates were obtained with TBHP and CHP.[14] We selected the TBHP conditions for further study.

Table 2. Screening of oxidizing agents for the epoxidation reaction. Abbreviations: UHP: urea-hydrogen peroxide, *m*-CPBA: *m*-chloroperbenzoic acid.



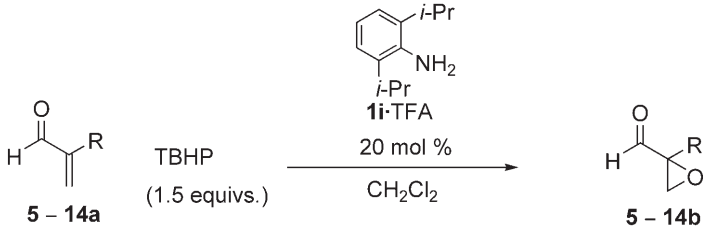
Entry	Oxidizing agent	Concentration of **5a**	Conversion[a] [%] (at 1 h)
1	30% H_2O_2	0.2 M	81[b]
2	50% H_2O_2	0.2 M	65
	50% H_2O_2	1.0 M	73
3	UHP	0.2 M	19
4	TBHP[c]	0.2 M	74
	TBHP[d]	0.2 M	67
	TBHP[c,e]	0.2 M	50
	TBHP[c]	**1.0 M**	**96**
5	*m*-CPBA	0.2 M	0
6	CHP	0.2 M	62
	CHP	1.0 M	98

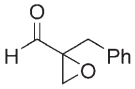
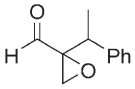
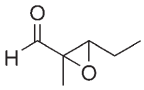
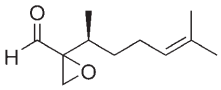
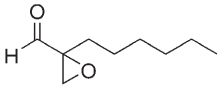
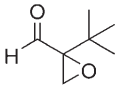
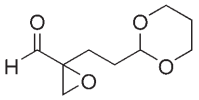
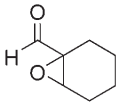
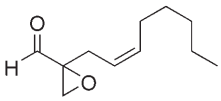
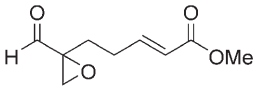
[a] Conversion by ^{1}H NMR after 1 h.
[b] 4.5 h.
[c] 5 M in isooctane.
[d] 70% in H_2O.
[e] 120 mol%.

The optimized protocol was then applied to a variety of α-substituted acroleins and enals. As shown in Table 3, a wide variety of α-substituted acroleins can be converted to the corresponding epoxides. The reaction provides the epoxide products in a clean and efficient manner, and considerable variability in the steric demands of the substrate is possible. The reaction rates are somewhat higher with acroleins containing an aromatic moiety. To our delight, the reaction can also accommodate aliphatic β-substitution (entries 3 and 9).[16] Most importantly, a number of functionalities, including acetals (entry 8) and both electron-rich and electron-deficient alkenes (entries 5, 10 and 11) are tolerated. No conjugate addition or epoxide opening products are observed. The products can be isolated either after *in situ* reduction to the epoxy alcohol or as the free aldehyde.[15]

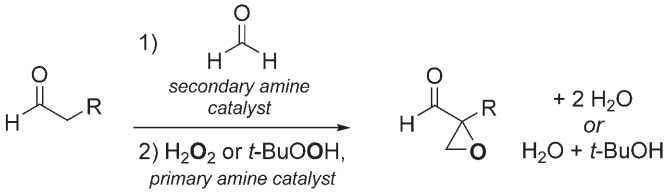
In summary, we have identified simple *ortho*-substituted anilines as efficient and readily available iminium catalysts, and have developed the first organocatalytic epoxidation of α-substituted α,β-unsaturated aldehydes. Taken together, a wide range of aldehydes can now be transformed *via* a mild two-stage protocol into corresponding oxamethylenated products, using only simple secondary amine (e.g., pyrrolidine) and primary amine (*ortho*-substituted aniline) catalysts (Scheme 1). The protocol is extremely versatile and the simplicity of these aniline catalysts should allow

Table 3. Substrate scope of the epoxidation of α-substituted α,β-unsaturated aldehydes.



Entry	Product	Time [h]	X[a] [%]	Yield[b] [%]	*dr*[c]
1	 **5b**	1.5	96	92	
2	 **6b**	1.5	100	99	2:1
3	 **7b**	2	100	83	1:1
5	 **8b**	7	89	73	3:1
6	 **9b**	3	100	67	
7	 **10b**	7	80	n.d.	
8	 **11b**	1	100	77[d]	
9	 **12b**	3.5	100	90	
10	 **13b**	1	94[e]	72 (90[e])	
11	 **14b**	2.5	99	71	

[a] Isolated yield after $NaBH_4$ reduction and FC.
[b] Conversion by ^1H NMR.
[c] Diastereomeric ratio of *anti:syn*.
[d] 120 mol% TBHP. The product was isolated as an aldehyde.
[e] Calculated based on 80% isomeric purity of the starting material.



Scheme 1. Organocatalytic oxamethylenation of aldehydes.

their incorporation into solid supported catalysts. These aniline catalysts should also find use in other iminium-catalyzed reactions, such as the Diels–Alder reaction.[17]

Full details of the Diels–Alder reaction and the development of enantioselective[18] variants of these reactions will be reported separately.

Experimental Section

General Procedure for the Epoxidation of Aldehydes

To a solution of aldehyde (0.5 mmol, 100 mol%) in CH_2Cl_2 (0.5 mL, 1.0 M) in a 2-mL vial was added catalyst **1i**·TFA (0.1 mmol, 20 mol%) and TBHP solution (5 M in isooctane, 0.75 mmol, 150 mol%) at room temperature. The mixture was allowed to stir at room temperature for 1–48 h. Acrolein (50 μL) was then added and the mixture was allowed to stir for an additional 10 min. The mixture was then poured into a solution of $NaBH_4$ in EtOH (2 mL) with a CH_2Cl_2 (1 mL) rinse. The mixture was allowed to stir for 5–10 min at 0 °C. The mixture was then quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3× 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under vacuum. The crude product thus obtained was then purified with flash chromatography (20% EtOAc in hexanes).

Alternatively, the aldehyde products were isolated directly after the addition of acrolein as above by aqueous work-up (10 mL) and extraction with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The pure epoxy aldehydes were obtained by preparative TLC or flash chromatography (10–20% EtOAc in hexanes).

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[12] Support for this model can be obtained by inspecting the X-ray crystal structures for range of iminium ions derived from anilines. A statistical study of these X-ray structures is not possible due to low number of examples, but the available data suggests that the iminium ions derived from parent aniline tend to favor conformations where the iminium ion is conjugated with the aromatic ring. *ortho*-Substituted anilines, on the other hand, tend to favor non-coplanar conformations, with the iminium ion twisted out of conjugation with the ring. See the Supporting Information for examples.

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[15] See the supporting information for details.

[16] The lack of stereocontrol in formation of **7b** can be explained by the rapid isomerisation of the double bond. This is well documented in iminium catalysis, see: a) J. W. Yang, M. T. Hechavarria Fonseca, B. List, *Angew. Chem. Int. Ed.* **2004**, *43*, 6660–6662; b) J. W. Yang, M. T. Hechavarria Fonseca, N. Vignola, B. List, *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110; c) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32–33; See also ref.[14b] for similar results.

[17] Catalyst **1i**·TFA promoted the Diels–Alder reaction between cyclopentadiene and α-benzylacrolein in 100% conversion after >3 h. See the Supporting Information

for details. In addition, catalyst **1i**·HCl promoted the Diels–Alder reaction between cyclopentadiene and cinnamaldehyde in acetonitrile in 64% conversion after 18 h.

[18] In preliminary experiments, chiral anilines have afforded the epoxidation products in up to 50% *ee*. Details of these experiments, including optimization of the protocol, will be reported separately.

