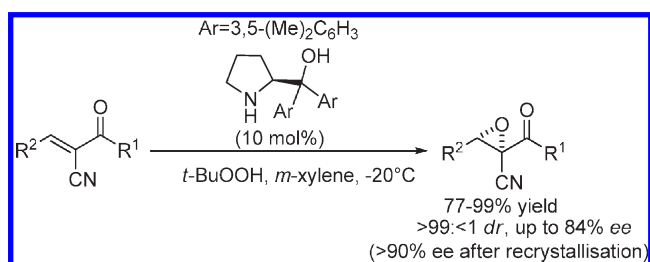# JOCNote

Organocatalytic Stereoselective Epoxidation of Trisubstituted Acrylonitriles

Claudia De Fusco, Consiglia Tedesco, and
Alessandra Lattanzi*

*Dipartimento di Chimica, Università di Salerno, Via Ponte
don Melillo, 84084, Fisciano, Italy*

lattanzi@unisa.it

The first diastereospecific and enantioselective epoxidation of *trans*-2-aroyl-3-arylacrylonitriles by means of the commercially available diaryl L-prolinol/*tert*-butyl hydroperoxide system has been developed. These diversely functionalized epoxides were obtained in excellent yield (up to 99%), complete diastereoselectivity for the *trans*-isomer, and good enantioselectivity (up to 84% ee). Highly enantioenriched epoxides can be easily obtained after a single crystallization (ee > 90%).

The asymmetric epoxidation of alkenes is a fundamental process given the pivotal role of chiral epoxides as targets of biological and pharmaceutical interest and most of all as synthetic intermediates amenable to a variety of manipulations of the epoxide ring.[1] Several electrophilic and nucleophilic chiral metal-based and organocatalytic systems have been developed to date for the epoxidation of an array of alkenes.[2] In the area of nucleophilic epoxidation of electron-poor alkenes, numerous catalytic systems are available to effect this transformation, although most of them have limited substrate scope, essentially focused on α,β-unsaturated ketones as substrates.[3] Indeed, only a few protocols are suitable for the asymmetric epoxidation of α,β-unsaturated aldehydes,[4] cyclic enones,[5] α,β-unsaturated esters,[6] amides, and derivatives thereof.[7] The lantanoids/BINOLs/*tert*-butyl[8] hydroperoxide (TBHP) and polyleucine/H_2O_2/NaOH[9] systems are likely among the most versatile protocols showing wider applicability. Surprisingly, studies have been almost exclusively restricted on the epoxidation of *trans*-disubstituted electron-poor alkenes. Hence, expanding the substrate scope of the asymmetric nucleophilic epoxidation also to trisubstituted electron-poor alkenes would be highly desirable, even in consideration of the access to versatile intermediates bearing quaternary stereocenters. To the best of our knowledge, Deng and coauthors[10] recently reported the first example of highly diastereo- and enantioselective epoxidation of *trans*-α-carbonyl-β-substitued acrylates mediated by TADDOL-derived hydroperoxide[11] (TADOOH) under basic conditions (Scheme 1).

The corresponding epoxides proved to be key compounds employed for the first asymmetric total synthesis of (−)-plicatic acid, an agent causing inflammatory and allergic reactions.[12] Over the recent years, we developed a simple and convenient

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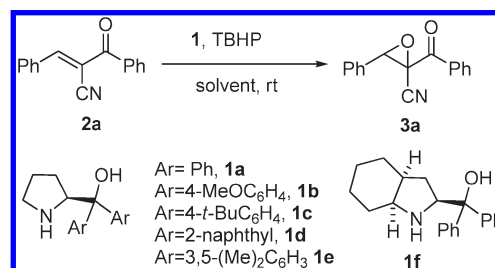(9) For selected examples, see: (a) Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed.* **1980**, *19*, 929. (b) Lasterra-Sanchéz, M. E.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1467. (c) Adger, B. M.; Barkley, J. V.; Bergeron, S.; Cappi, M. W.; Flowerdew, B. E.; Jackson, M. P.; MacCague, R.; Nugent, T. C.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3501. (d) Allen, J. V.; Drauz, K.-H.; Flood, R. W.; Roberts, S. M.; Skidmore, J. *Tetrahedron Lett.* **1999**, *40*, 5417. (e) Kelly, D. R.; Roberts, S. M. *Biopolymers* **2006**, *84*, 74.
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SCHEME 1. Trisubstituted Electron-Poor Alkenes Investigated up to Now in the Asymmetric Epoxidation
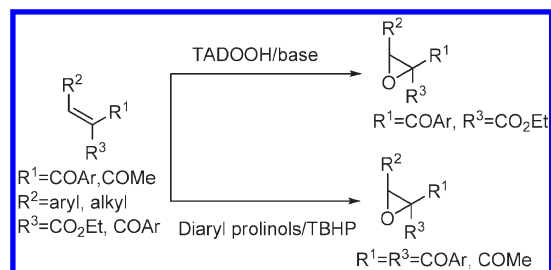
organocatalytic system for the asymmetric epoxidation of disubstituted electron-poor alkenes, such as *trans*-α,β-unsaturated ketones based on α,α-L-diaryl prolinols as promoters and *tert*-butyl hydroperoxide (TBHP) as the oxidant.[13] The *trans*-epoxides were obtained in good to high enantioselectivity. Recently, we showed that symmetrically trisubstituted electron-poor alkenes, such as acyclic and cyclic 2-arylidene-1,3-diketones, can be epoxidized by this system in high to excellent yield and up to 85% ee (Scheme 1).[14] These epoxides are pharmaceutically important building blocks and intermediates for the synthesis of densely functionalized epoxide derivatives. With this background in mind and taking into account the lack of stereoselective protocols for the epoxidation of trisubstituted electron-poor alkenes, we became interested in studying *trans*-α-carbonyl-β-substitued acrylonitriles, where both issues of diastereo- and enantioselectivity should have been addressed. The choice to introduce a cyano group in the alkene was stimulated by the fact that an ever-increasing number of important pharmaceuticals and natural products are nitrile-containing compounds and its potential usefulness as a synthetic group susceptible of further transformation to amine, aldehyde, amide, and carboxylic acid moieties.[15] Herein, we describe the first asymmetric protocol for the epoxidation of *trans*-2-aroyl-3-arylacrylonitriles[16] by using the α,α-L-diaryl prolinols/TBHP system that gives access to diversely functionalized *trans*-epoxides in excellent yield, complete diastereoselectivity, and up to 84% ee.

According to our previously established conditions for the epoxidation of α,β-unsaturated ketones,[13a] commercially

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TABLE 1. Optimization of Reaction Conditions[a]

entry	1	solvent	t (h)	yield (%)[b]	ee (%)[c]
1	**1a**	methylcyclohexane	3	99	21
2	**1b**	methylcyclohexane	6	88	43
3	**1c**	methylcyclohexane	3	99	35
4	**1d**	methylcyclohexane	3	97	48
5	**1e**	methylcyclohexane	3	96	56
6	**1f**	methylcyclohexane	4	99	2
7	**1e**	hexane	3	99	54
8	**1e**	CHCl$_3$	6	96	48
9	**1e**	toluene	3	99	57
10	**1e**	ClC$_6$H$_5$	3	99	60
11	**1e**	CF$_3$C$_6$H$_5$	3	99	58
12	**1e**	*p*-xylene	3	97	63
13	**1e**	*m*-xylene	3	99	64
14[d]	**1e**	*m*-xylene	17	69	47
15[e]	**1e**	*m*-xylene	18	99	78
16[e,f]	**1e**	*m*-xylene	18	88	71
17[g]	**1e**	*m*-xylene	48	99	74
18[h]	**1e**	toluene/*m*-xylene 1/3	60	99	73

[a]Unless otherwise noted, reactions were carried with **2a** (0.1 mmol), TBHP (1.2 equiv), **1** (30 mol %), and solvent (0.5 mL). [b]Isolated yield after flash chromatography. [c]Determined by chiral HPLC analysis. [d]Cumyl hydroperoxide was used. [e]The reaction was carried out with **2a** (0.1 mmol), TBHP (1.2 equiv), **1e** (10 mol %), and *m*-xylene (2 mL) at −20 °C. [f]Catalyst **1e** was used at 5 mol % loading. [g]The reaction was carried out with **2a** (0.1 mmol), TBHP (1.2 equiv), **1e** (20 mol %), and *m*-xylene (0.5 mL) at −30 °C. [h]The reaction was carried out with **2a** (0.1 mmol), TBHP (1.2 equiv), **1e** (10 mol %), and *m*-xylene (0.5 mL) at −60 °C.
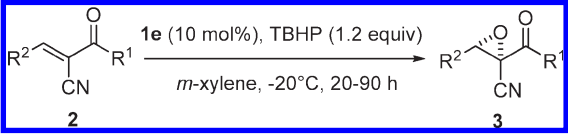
available or easily accessible α,α-L-diaryl prolinols[17] **1** were screened at 30 mol % loading in the epoxidation of model compound **2a** with TBHP at room temperature (Table 1).

Epoxide **3a** was recovered, after a short reaction time, in excellent yield exclusively as *trans*-isomer as judged by ^{1}H NMR analysis on the crude reaction mixture (entries 1−6). As expected, the asymmetric induction was significantly influenced by the type of substitution in the organocatalysts, with commercially available compound **1e** leading to the product with up to 56% ee (entry 5), whereas the bicyclic derivative **1f** proved to be completely unselective (entry 6).

Screening of nonpolar solvents showed that aromatic media were the most effective and the reaction carried out in *m*-xylene enabled the improvement of the ee value up to 64% (entry 13). Cumyl hydroperoxide afforded an inferior result with respect to TBHP (entry 14). Pleasingly, working at −20 °C with reduced catalyst loading (10 mol %) and under more diluted conditions led to the recovery of epoxide **3a** in excellent yield and 78% ee (entry 15). The use of 5 mol % of catalyst under similar conditions slightly affected the efficiency of the process (entry 16). At temperatures lower than −20 °C, the reactions proceeded with diminished enantiocontrol, likely due to an increased heterogeneity of the reaction mixture (entries 17 and 18).

With optimized conditions in hand, an array of alkenes **2** straightwardly synthesized via Knoevenagel condensation

TABLE 2. Asymmetric Epoxidation of *trans*-2-Aroyl-3-arylacrylonitriles with 1e/TBHP[a]

entry	R^1	R^2	3	yield (%)[b]	ee (%)[c]
1	Ph	Ph	3a	99 (70)	78 (94)
2	Ph	4-tBuC$_6$H$_4$	3b	92	73
3	Ph	2-CH$_3$C$_6$H$_4$	3c	77	56
4	Ph	4-BrC$_6$H$_4$	3d	99 (67)	76 (99)
5	Ph	4-CNC$_6$H$_4$	3e	99	70
6	Ph	2-naphthyl	3f	96	77
7	Ph	3-furyl	3g	99	81
8	Ph	*trans*-cinnamyl	3h	78	84
9	3-ClC$_6$H$_4$	Ph	3i	99	73
10	4-CH$_3$OC$_6$H$_4$	Ph	3j	99 (60)	79 (>99)
11	4-CH$_3$OC$_6$H$_4$	4-BrC$_6$H$_4$	3k	99	79
12	Ph	cyclohexyl	3*l*	95	48
13	Me	Ph	3m	90	83

[a]Conditions: **2** (0.2 mmol), TBHP (1.2 equiv), **1e** (10 mol %), and *m*-xylene (4 mL). [b]Isolated yield after flash chromatography; yield after crystallization in parentheses. [c]Determined by chiral HPLC analysis; ee after crystallization in parentheses.

were reacted to examine the scope of the epoxidation (Table 2). In all cases, the *trans*-epoxide was exclusively formed in high to excellent yield and good enantiocontrol with either electron-rich or electron-poor phenyl-substituted derivatives **2**. The *o*-phenyl-substituted epoxide **3c** was isolated with slightly lower ee (entry 3). Heteroaromatic and *trans*-cinnamyl alkenes **2g,h** selectively afforded the epoxides with 81% and 84% ee, respectively (entries 7 and 8). The epoxidation of the β-alkyl-substituted alkene **2l** proceeded with somewhat lower enantioselectivity (entry 12). Interestingly, the extension of the asymmetric epoxidation to α-acetyl derivatives appears plausible as compound **2m** furnished the corresponding epoxide in high yield and fairly good ee (entry 13). Epoxides **3** are solids and pleasingly a single crystallization, using hexane/isopropanol mixtures, allowed a good recovery of epoxides with ee increased to excellent values, an aspect of practical interest (Table 2, entries 1, 4, and 10).

Absolute configuration of epoxides was assigned to be 2*R*,3*S* by analogy to that determined by single crystal X-ray analysis performed on epoxide **3d** (see the Supporting Information). The stereochemical outcome of the reaction is consistent with that previously observed in the epoxidation of *trans*-disubstituted α,β-enones mediated by the same system.[13b] Although further investigations are necessary to address the mechanism of this epoxidation, on the basis of previous experimental findings[13a−c] and the known inactivity of sterically hindered carbonyl compounds toward iminium ion formation with secondary amines,[18] we suggest that compound **3e** serves as a bifunctional noncovalent promoter (Figure 1).

The establishment of an effective network of hydrogen bonds among the catalyst and the reagents would lead to the formation of a ternary complex, where the alkene is suitably positioned to undergo preferential nucleophilic attack of the *Si*-face by the oxidant.
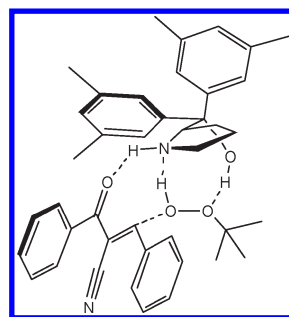
FIGURE 1. Proposed ternary complex involved in the asymmetric epoxidation.

SCHEME 2. Diastereoselective Reduction of Epoxide 3a to α,β-Epoxy Alcohol 4a
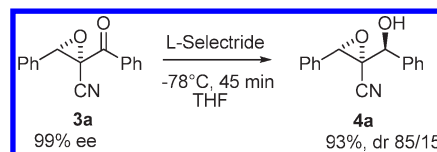
To demonstrate the synthetic utility of epoxides **3**, reduction of the carbonyl moiety of highly enantiomerically enriched **3a** was carried out with L-Selectride in THF at −78 °C (Scheme 2). The secondary alcohol **4a**, bearing three contiguous stereocenters, was obtained in 93% yield and fairly good diastereoisomeric ratio. Reduction of compound **3a** performed with other agents such as NaBH$_4$, DIBAL, and K-Selectride afforded compound **4a** with increasing 55/45, 63/37, 82/18 diastereoisomeric ratio, respectively.[19]

Although the absolute configuration of the major diastereoisomer **4a** was not determined, it is likely that the *anti*-isomer was preferentially obtained via a chelated cyclic transition state assuming the Cram chelation model[20] as previously reported in the reduction of differently substituted α,β-epoxy ketones with hydrides.[21,22] The stereoselective accesss to α,β-epoxy alcohols is a challenging but important task as these compounds are usefully exploited in the synthesis of natural products as well as of polyhydroxylated targets.[23] It is interesting to note that compounds of type **4a** are difficult to prepare via the alternative approach based on the asymmetric Sharpless epoxidation[24] of the corresponding poorly reactive 2-cyanoallylic alcohols. Indeed, only a few examples of primary 2-cyanoallylic alcohols have been epoxidized

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(22) A significant increase of diastereocontrol was observed in the reduction of compound **3a** when using chelating reducing agents such as K- and L-Selectride which would be in agreement with the chelation of the oxygen of both the epoxide and ketone moieties to the metal.

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using stoichiometric amounts of the Ti(O*i*-Pr)$_4$/L-DET/ TBHP reagent, giving the products in good to high enantio-selectivity, but in modest yield.[25]

In conclusion, the first asymmetric epoxidation of *trans*-2-aroyl-3-arylacrylonitriles has been developed by employing commercially available reagents, such as TBHP and α,α-L-diaryl prolinol **1e**. This simple and convenient protocol enables the formation of a novel class of highly functionalized epoxides with complete control of the diastereoselectivity and good level of enantioselectivity. From a practical point of view, epoxides can be recovered in excellent ee after a single crystallization.

Experimental Section

General Procedure for the Asymmetric Epoxidation. A sample vial was charged with alkene **2** (0.2 mmol) and catalyst **1e** (6.2 mg, 0.02 mmol), then *m*-xylene (4 mL). TBHP (5 M decane solution, 44 μL, 0.24 mmol) was added and the mixture was stirred at −20 °C. Upon completion by TLC (petroleum ether/diethyl ether 4:1), the solvent was removed under reduced pressure and the crude reaction mixture was directly purified by flash chromatography on silica gel eluting with petroleum ether and petroleum ether/diethyl ether mixtures (4:1) to provide the epoxide. Crystallization with *n*-hexane/*i*-PrOH at room temperature gave prismatic crystals in enantioenriched form.

3a: 49.3 mg (99%); white solid, mp 93−95 °C; after crystallization ee 94%; [α]$^{21}_{D}$ −163.4 (*c* 0.50, CHCl$_3$); ν_{max} (KBr)/cm^{-1} 3065, 1699, 1449, 1256, 1156, 760, 696; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.41 (s, 1H), 7.51−7.57 (m, 7H), 7.68−7.71 (m, 1H), 8.05 (dd, *J* = 7.9, 1.2 Hz, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 58.6, 64.2, 114.1, 126.7, 129.0, 129.1, 129.3, 130.0, 130.5, 132.8, 135.0, 186.8. Anal. Calcd for C$_{16}$H$_{11}$NO$_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 76.82; H, 4.47; N, 5.56. HPLC analysis with Chiralpak AS-H

(25) Aiai, M.; Robert, A.; Baudy-Floc'h, M.; Le Grel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2249.

column, 95:5 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 18.4 min, major enantiomer t_R = 14.0 min.

3g: 47.3 mg, (99%); yellow solid, mp 56−58 °C; [α]$^{25}_{D}$ −89.8 (*c* 0.68, CHCl$_3$), ee 81%; ν_{max} (KBr)/cm^{-1} 3139, 1701, 1598, 1268, 1166, 1024, 876, 699; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 4.32 (s, 1H), 6.63 (m, 1H), 7.53−7.56 (m, 3H), 7.68−7.72 (m, 1H), 7.76 (s, 1H), 8.05 (dd, *J* = 8.3, 1.2 Hz, 2H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 57.9, 58.7, 108.4, 114.5, 117.1, 129.1, 129.2, 132.7, 135.0, 143.6, 144.2, 186.8. Anal. Calcd for C$_{14}$H$_9$NO$_3$: C, 70.29; H, 3.79; N, 5.86. Found: C, 70.60; H, 3.82; N, 5.46. HPLC analysis with Chiralpak AS-H column, 95:5 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 27.6 min, major enantiomer t_R = 17.9 min.

3m: 33.7 mg, (90%); pale yellow solid, mp 77.3−78.9 °C; [α]$^{24}_{D}$ −188.9 (*c* 0.628, CHCl$_3$), ee 83%; ν_{max} (KBr)/cm^{-1} 3025, 2360, 1457,1127, 864, 813, 606; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 2.38 (s, 3H), 4.42 (s, 1H), 7.41−7.47 (m, 5H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.0, 59.0, 64.1, 113.4, 126.6, 128.8, 129.8, 130.4, 195.5. Anal. Calcd for C$_{11}$H$_9$NO$_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.36; H, 4.98; N, 7.63. HPLC analysis with Chiralpak AS-H column, 90:10 *n*-hexane:2-propanol, 1 mL/min, detection at 254 nm; minor enantiomer t_R = 20.6 min, major enantiomer t_R = 14.1 min.

Supporting Information Available: General experimental methods, experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for new compounds, HPLC traces, and crystallographic information file. This material is available free of charge via the Internet at http://pubs.acs.org.