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A Modular Approach to Polyketide Building Blocks: Cycloadditions of Nitrile Oxides and Homoallylic Alcohols

Nina Lohse-Fraefel and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Hönggerberg, HCI, H335, CH-8093 Zürich, Switzerland
carreira@org.chem.ethz.ch

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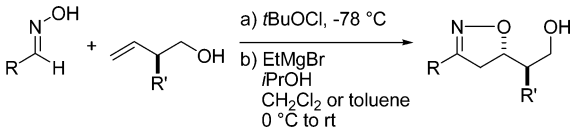
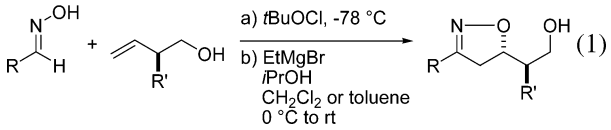
ABSTRACT



A general approach to the diastereoselective synthesis of Δ^2-isoxazolines via magnesium-mediated, hydroxyl-directed diastereoselective nitrile oxide cycloadditions of homoallylic alcohols and monoprotected homoallylic diols is disclosed. A broad spectrum of aliphatic and aromatic nitrile oxides and a variety of homoallylic alcohols participate in the cycloaddition, thus expanding the scope of polyketide building blocks that can be accessed using this strategy.

The potent biological activity and stereochemical complexity of polyketide natural products render them attractive synthetic targets; moreover, the synthesis of useful building blocks for polyketide construction is an important task in organic synthesis. Although the generally employed methods addressing this objective involve carbonyl addition reactions,[1,2] several alternative approaches have been disclosed.[3]

We have recently reported highly regio- and diastereoselective nitrile oxide cycloadditions of aliphatic chiral nitrile oxides and optically active allylic alcohols.[4,5] The efficient nitrile oxide cycloaddition permits the direct synthesis of a broad spectrum of dipropionate subunits of various stereochemical permutations, following a single reaction protocol. The utility of the prepared cycloadducts as masked aldol products[6] has been demonstrated in the applications to the total syntheses of complex natural products[7] and for the preparation of stereochemically rich pentaketides.[8,9] In this communication, we document the successful extension of this methodology to nitrile oxide cycloadditions with homoallylic alcohols (eq 1). The modular nature of the presented protocol considerably expands the constellation of protected polyketide subunits that can be attained from readily available starting materials.



(1)

The diastereoselective cycloaddition reaction of nitrile oxides and allylic alcohols has been intensively studied. By contrast,

(1) For aldol addition approaches to polyketide building blocks, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Paterson, I.; Cannon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (c) Paterson, I. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 249−297. (d) Carreira, E. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, 1999; Vol. III, pp 997−1065. (e) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 133−238.

(2) For the use of allylation, crotylation, and allenylmetal reagents in polyketide synthesis, see: (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 299−401. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 403−490. (c) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817.

(3) For recent examples, see: (a) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365. (b) Meyer, C.; Blanchard, N.; Defosseux, M.; Cossy, J. *Acc. Chem. Res.* **2003**, *36*, 766. (c) Lautens, M.; Paquin, J.-F. *Org. Lett.* **2003**, *5*, 3391. (d) Misske, A. M.; Hoffmann, H. M. R. *Chem. Eur. J.* **2000**, *6*, 3313. (e) Breit, B.; Zahn, S. K. *J. Org. Chem.* **2001**, *66*, 4870. (f) Myles, D. C.; Danishefsky, S. J. *Pure Appl. Chem.* **1989**, *61*, 1235.

(4) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082.

(5) For a lead reference, see: Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324.

(6) For the transformation of isoxazolines to the corresponding β-hydroxy ketones, see: Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

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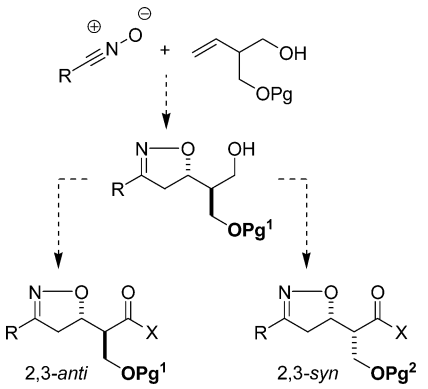
the cycloaddition reaction of the homologue has received scant attention. A recent study by Kociolek examined the cycloaddition of a single nitrile oxide, namely, that derived from benzoic acid, and as disclosed below, the structure was misassigned.[10] Importantly, with respect to our interest in developing this strategy as a general approach to polyketide building blocks, we were interested in conducting a broad study with nitrile oxides that would be useful for polyketide construction. At the outset of the investigation there were two clear problems that could be foreseen: (1) homoallylic alkoxides would be considerably less reactive than the allylic alkoxides that have been studied, and consequently (2) the use of aliphatic nitrile oxides would be precluded for use in the process as these are prone to undergo dimerization in the absence of a good olefinic coupling partner. Moreover, in the course of such studies, we aimed to overcome the inherent limitation of any highly diastereoselective reaction wherein accessing the complementary diastereomers can only be done with difficulty. Thus we wished to develop diastereoselective strategies that would provide access to the various stereochemical permutations of dipropionate subunits

Scheme 1

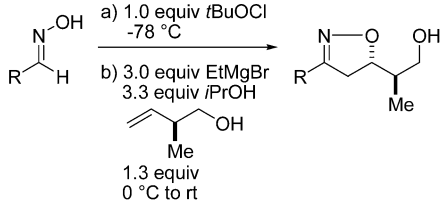


(Scheme 1), permitting divergent asymmetric synthesis from a single diastereoselective cycloaddition reaction.

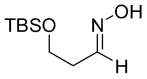
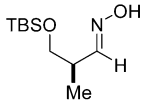
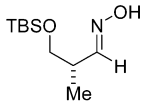
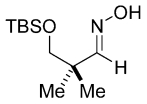
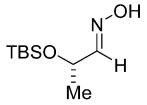
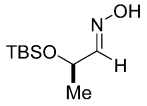
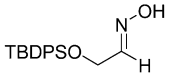
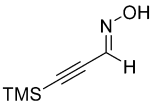
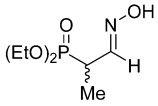
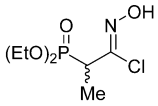
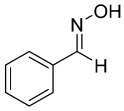
As shown in Table 1, a broad range of aliphatic and aromatic nitrile oxides smoothly undergo cycloaddition with (*S*)-2-methyl-3-butenol under conditions we have previously optimized for allylic alcohols. The nitrile oxides were usually generated in situ according to standard procedures using *t*BuOCl or NCS. For entries 8 and 11 in Table 1, the intermediate hydroximinoyl chlorides were isolated and used without further purification, and for the phosphonate-derived nitrile oxide (cf. entry 9), purification of the intermediate hydroximinoyl chloride by chromatography proved advantageous for obtaining the corresponding cycloadduct in high yield (entry 9 vs entry 10). Optimization studies revealed that best results were obtained by slow addition of the hydroximinoyl solution to the solution of alkoxides over 1−1.5 h at 0 °C. After 6 h at 0 °C, the reaction mixture was gradually allowed to warm to room temperature over 12. The densely functionalized cycloadducts were formed in 66−89% yield and *anti* diastereoselectivities (vide infra) ranging from 4:1 to 13:1.

The diastereomeric ratios were generally determined by ^{1}H or ^{13}C NMR analysis of the unpurified material unless

Table 1. Nitrile Oxide Cycloadditions with (*S*)-2-Methyl-3-butenol



(2)

entry	substrate	solvent	d.r.[a]	yield
1		CH_2Cl_2	8:1[b]	67%
2		CH_2Cl_2	7:1	83%
3		CH_2Cl_2	9:1	85%
4		toluene	4:1[b]	89%
5		toluene	6:1[c]	82%
6		toluene	5:1[c]	83%
7		toluene	10:1[c]	87%
8		toluene	5:1[b]	66%[d,e]
9		CH_2Cl_2	11:1[f]	36%
10		CH_2Cl_2	13:1[f]	71%[g]
11		CH_2Cl_2	7:1	87%[e,h]

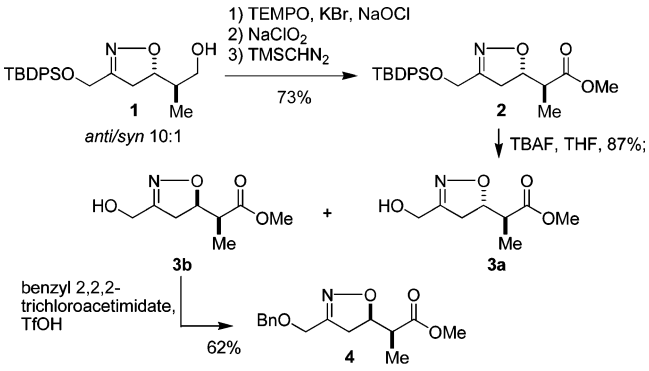
[a] Determined by ^{1}H NMR analysis of the unpurified adduct. [b] Determined after filtration over a short pad of silica gel. [c] Determined by ^{13}C NMR analysis of the unpurified adduct. [d] NCS instead of *t*BuOCl was used. [e] The intermediate hydroximinoyl chloride was isolated. [f] Determined after condensation with benzaldehyde. [g] Yield based on the hydroximinoyl chloride, which was isolated in 81% yield from the corresponding oxime. [h] 1.1 equiv of *t*BuOCl was used.

(7) Bode, J. W.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 3611.
(8) Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485.
(9) Bode, J. W.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 1587.

otherwise stated. For cycloadducts (entries 9 and 10) that incorporate a phosphonate, the unpurified reaction product was allowed to condense with benzaldehyde (DBU, LiCl, MeCN) to afford the corresponding olefin, which was then subjected to analysis by ^{1}H NMR spectrum to determine the diastereoselectivity in the cycloaddition.

The relative stereochemistry was established by conversion of cycloadduct **1** into known isoxazoline **4** (Scheme 2), for

Scheme 2. Synthesis of Isoxazoline **4**



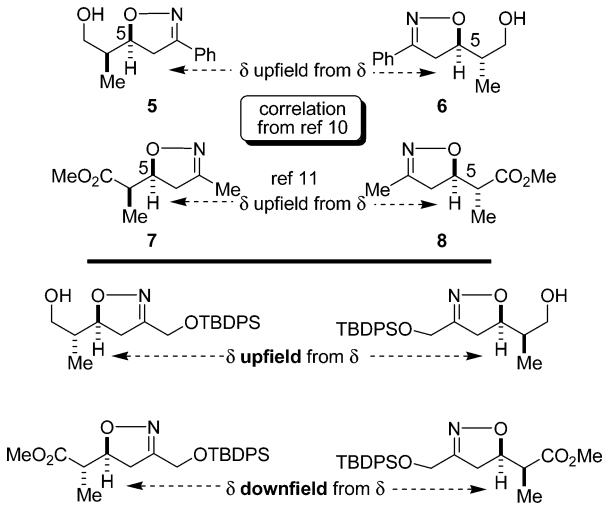
which the relative stereochemistry had been previously established.[11] Isoxazoline **1**, a 10:1 mixture of diastereomers, was readily converted to the corresponding methyl ester **2** in 70% yield (3 steps). Deprotection of the silyl ether with TBAF afforded alcohols **3a** and **3b** (87%), which were then separated. Protection of the primary alcohol in **3b** afforded benzyl ether **4** in 62% yield. Isoxazoline **4** proved identical by ^{1}H and ^{13}C NMR in all respects to the data previously reported for this compound, confirming the *syn* relationship in this minor diastereomer and therefore an *anti* relationship for the major diastereomer.[11,12]

In their studies on nitrile oxide cycloadditions with homoallylic alcohols, Kociolek and Hongfa[10] assigned the relative stereochemistry of the major product with the benzaldehyde derived nitrile oxide (**5**) as *syn* (Scheme 3). They concluded this from an analysis of ^{1}H NMR chemical shifts and coupling constants for the C_5-H signals of the two diastereomers **5** and **6**. Earlier work with related esters **7** and **8** had revealed a trend with the C_5 proton diastereomer at higher field for the *syn* adduct **7** compared to that of the *anti* stereoisomer **8**.[11]

The conversion of primary alcohol **1** into methyl ester **2** allowed us to examine the validity of such a correlation in structure assignment. For the cycloadducts possessing a primary alcohol functionality the signal for the C_5 isoxazoline proton of the major *anti* diastereomer appeared upfield to that of the corresponding signal for the minor *syn* diastereomer in the ^{1}H NMR spectrum. When the primary alcohol moiety was oxidized to the corresponding methyl ester, the opposite pattern was observed: the signal of the C_5 isoxazoline proton of the major diastereomer appeared now more downfield than the corresponding signal of the minor

(10) Kociolek, M. G.; Hongfa, C. *Tetrahedron Lett.* **2003**, *44*, 1811.
(11) Panek, J. S.; Beresis, R. T. *J. Am. Chem. Soc.* **1993**, *115*, 7898.

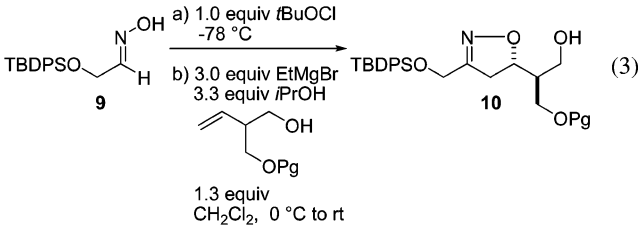
Scheme 3. Chemical Shift Correlations



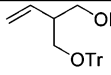
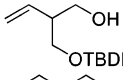
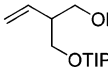
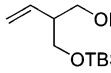
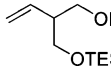
diastereomer. These results suggest that the prior stereochemical assignment is in need of reevaluation.

The protocol developed for nitrile oxide cycloadditions with homoallylic alcohols proved equally successful for monoprotected homoallylic diols (Table 2), which were

Table 2. Nitrile Oxide Cycloadditions with Monoprotected Homoallylic Diols



(3)

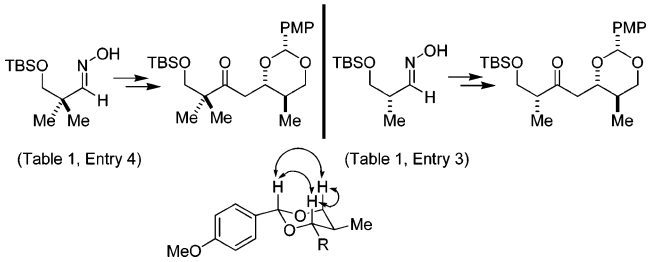
entry	monoprotected homoallylic diol	d.r.	yield
1		19:1[a]	82%
2		21:1[b]	85%
3		14:1[b]	73%
4		10:1[b]	78%
5		6:1[b]	53%

[a] Determined by ^{1}H NMR analysis of the unpurified material. [b] Determined by ^{13}C NMR analysis of the unpurified material.

readily prepared from (*Z*)-butenediol via Wittig rearrangement.[13] A variety of monoprotected homoallylic diols underwent cycloaddition with the nitrile oxide generated in situ from oxime **9**. The cycloadducts were formed in 53−

85% yield and in diastereomeric ratios ranging from 6:1 to 21:1. A positive correlation between both yield and diastereoselectivity and the steric demand of the resident protective group was observed. Best results were obtained with the bulky trityl and TBDPS protective groups (entries 1 and 2). Although the immediate cycloadducts **10** possess an *anti* relationship, the corresponding *syn* derivatives could readily be accessed by a simple orthogonal protection-deprotection sequence of the primary alcohols. It is therefore possible to secure both *syn* and *anti* diastereomers from the same set of starting materials using the identical transformation.

(12) The *anti* relationship was confirmed for two additional cycloadducts (Table 1, entries 3 and 4) via derivatization and subsequent NOE experiments, as shown below:



(13) For the synthesis for the corresponding THP derivative, see: Kozikowski, A. P.; Scripko, J. G. *J. Am. Chem. Soc*. **1984**, *106*, 353.

We have documented an alternative approach to masked polyketide building blocks via magnesium-mediated, hydroxyl-directed diastereoselective nitrile oxide cycloadditions with homoallylic alcohols and monoprotected homoallylic diols. Through the use of monoprotected homoallylic diols, not only *anti* diastereomers are accessible but the corresponding *syn*-diastereomers as well by a simple orthogonal protection-deprotection sequence. The method we describe considerably expands the type of polyketide units that can be accessed reliably through the use of nitrile-oxide cycloaddition reactions. Further studies of these reactions are ongoing, as well as applications in natural products synthesis, which will be reported as results become available.

Acknowledgment. We thank the Swiss National Science Foundation and F. Hoffmann-LaRoche for their generous support of our research program.

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

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