Tetrahedron 67 (2011) 8229–8234

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stereochemical investigation of conjugate additions of carbon- and heteronucleophiles to ring-substituted nitrosocyclohexenes

Ritobroto Sengupta, Jason A. Witek, Steven M. Weinreb *

Department of Chemistry, The Pennsylvania State University, University Park, PA 16802, United States

ARTICLE INFO

Article history:
Received 8 July 2011
Received in revised form 19 August 2011
Accepted 22 August 2011
Available online 28 August 2011

Keywords:
Stereoselectivity
Michael-type additions
Enolonium ion equivalents
Organocuprate additions

ABSTRACT

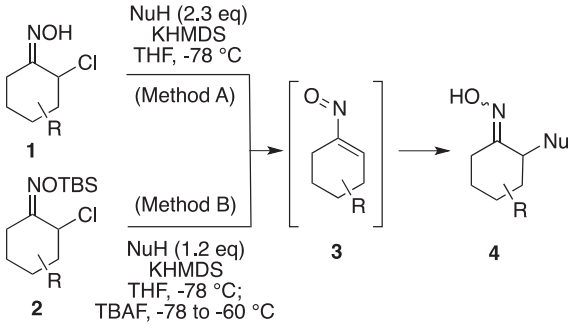
Intermolecular Michael-type conjugate additions of some in situ-generated ring-substituted nitrosocyclohexenes with both carbon- and heteronucleophiles have been found to be highly stereoselective, leading predominantly (or exclusively) to products resulting from axial attack on a half-chair conformation of the nitrosoalkene substrate.

1. Introduction and background

We have recently been involved in exploring synthetic methodology based on inter-[1] and intramolecular[2] conjugate additions of nucleophiles to highly reactive, transient nitrosoalkenes.[3] In particular, we have been interested in using this type of transformation to evaluate the synthetic potential of nitrosoalkenes as enolonium ion equivalents.[4] At the outset of these investigations it became evident to us that there are a number of fundamental stereochemical issues relevant to this type of conjugate addition that have never been addressed. For example, in a recent publication we described stereochemical studies on nucleophilic additions to acyclic nitrosoalkenes bearing a γ-stereogenic center, a process found to be highly diastereoselective, leading exclusively to the *anti* adducts.[5] We now report some new stereochemical investigations of conjugate additions of various carbon- and heteronucleophiles to cyclic systems.

2. Results and discussion

Our current studies focussed on probing the stereochemical outcome of nucleophilic additions to substituted nitrosocyclohexenes **3** to form α-substituted oxime products **4** (Scheme 1). For comparison purposes in the exploratory stages of this investigation, the requisite nitrosoalkenes **3** were generated and reacted with the nucleophile via two different procedures: (1) treatment of the α-chlorooxime **1**, formed from a ring-substituted α-chlorocyclohexanone, with 2.3 equiv of the potassium salt of the nucleophile in THF at −78 °C (Method A) and (2) the Denmark procedure[6] involving treatment of an α-chloro-*O*-silyloxime **2** with tetrabutylammonium fluoride in THF in the presence of 1.2 equiv of the potassium salt of the nucleophile (Method B).



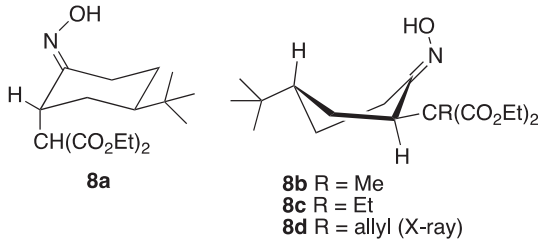
Scheme 1. Addition of nucleophiles to substituted nitrosocyclohexenes.

Initial experiments involved examining the addition of various malonate ester enolates to in situ-produced 4-*tert*-butylnitrosocyclohexene. Thus, the known[6a,7] racemic *cis*-α-chloro-4-*tert*-butylcyclohexanone oxime **5a** and the corresponding *trans*-isomer **5b** were combined with the potassium enolate of diethyl malonate (**6a**) under the conditions of Method A (see Experimental section for details) to afford exclusively *trans*-adduct **8a** (R′=H) in good

* Corresponding author. E-mail address: smw@chem.psu.edu (S.M. Weinreb).

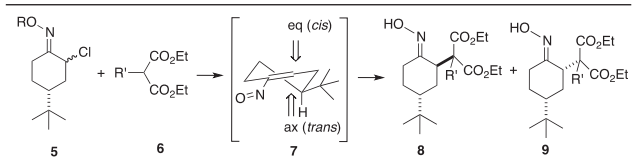
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.08.054

yields (Table 1, >20:1 **8**/**9** estimated by ^{1}H NMR). In both experiments only one oxime geometric isomer of **8a** was produced. Although we cannot definitively assign geometry in this case, the fact that we have generally observed formation of the (*E*)-oximes as the exclusive (or predominant) product in other examples (vide infra) has led us to tentatively propose this geometry for adduct **8a**. The configuration and chair conformation of **8a**, as shown in Scheme 2, were established by NMR analysis.[8] Exposure of *cis*-α-chloro-*O*-silyloxime **5c**[6a] to the Denmark conditions in the presence of diethyl malonate potassium enolate (Method B) also afforded a comparable yield of the same *trans*-adduct **8a** as the sole product. It seems reasonable that adduct **8a** is formed in all three cases via preferred axial attack[9] on the half-chair conformation of 4-*tert*-butylnitrosocyclohexene (**7**). These experiments also indicated that the stereoselectivity and yield of the addition products are independent of the precursor and method of generation of the nitrosoalkene.[6a]



Scheme 2. Configurations and conformations of malonate adducts of 4-*tert*-butylnitrosocyclohexene.

Table 1
Malonate additions to 4-*tert*-butylnitrosocyclohexene



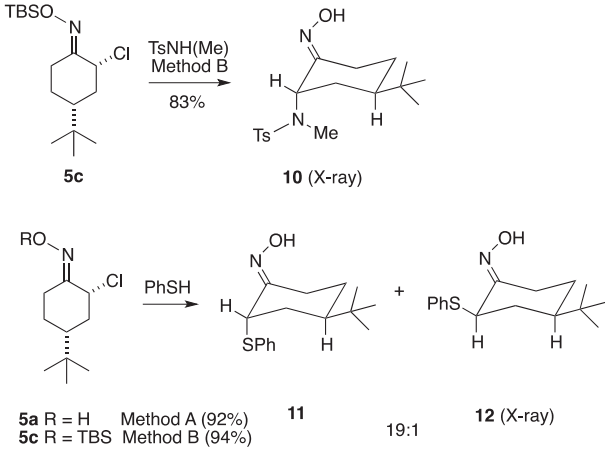
			Total Yield (**8** + **9**)	Isomer Ratio (**8** : **9**)
a R = H, α-Cl	**a** R' = H	Method A	85%	
b R = H, β-Cl		Method A	93%	only **8**
c R = TBS, α-Cl		Method B	86%	
a R = H, α-Cl	**b** R' = Me	Method A	89%	
b R = H, β-Cl		Method A	85%	6.2:1
c R = TBS, α-Cl		Method B	81%	
a R = H, α-Cl	**c** R' = Et	Method A	76%	
b R = H, β-Cl		Method A	88%	only **8**
c R = TBS, α-Cl		Method B	72%	
a R = H, α-Cl	**d** R' = allyl	Method A	89%	9.1:1
c R = TBS, α-Cl		Method B	72%	

Further studies were subsequently carried out with α-alkyl-substituted malonate nucleophiles. It was found that repeating the above experiments with oxime derivatives **5a**–**c** using α-methyl diethyl malonate (**6b**) in most runs afforded an inseparable 6.2:1 mixture of adducts (*E*)-*trans*-**8b** and (*E*)-*cis*-**9b** in good total yield. However, in one reaction conducted with oxime **5a**, only the *trans*-product **8b** was formed, thereby providing a pure sample of this material. Interestingly, the major *trans*-product **8b** apparently exists in the twist boat conformation shown in Scheme 2 as determined by 2D NMR NOE analysis of the pure isomer. We have again assumed the oxime geometry to be (*E*) in this system since the stereochemistry could not be determined unambiguously by spectral methods. The fact that **8b** is a twist boat is not too surprising since Allinger has reported that *trans*-1,3-di-*tert*-butylcyclohexane exists in this conformation.[10]

Addition of the potassium enolate of α-ethyl diethyl malonate (**6c**) to the nitrosocycloalkene derived from the three oxime derivatives **5a**–**c** as was done with malonates **6a** and **6b** also afforded a single *trans*-adduct **8c** with the (*E*)-oxime configuration. As was the case with **8b**, NMR analysis indicated that this system exists in a twist boat conformation (Scheme 2).

Finally, addition of α-allyl diethyl malonate (**6d**) to α-chlorooximes **5a** via Method A and **5c** via Method B led to an inseparable 9.1:1 mixture of (*E*)-*trans*-adduct **8d** and (*E*)-*cis*-compound **9d**. It was possible in this case to crystallize the major (*E*)-*trans* isomer **8d** from the mixture, and X-ray analysis of this compound showed it indeed to exist in a twist boat conformation and confirmed the (*E*)-oxime geometry.[11]

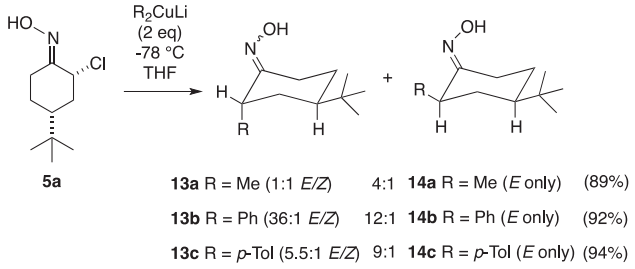
It is also possible to add heteronucleophiles to vinylnitroso compound **7** with a high degree of stereoselectivity. Therefore, *N*-methyl-*p*-toluenesulfonamide undergoes smooth axial addition to the nitrosoalkene formed from α-chloro-*O*-TBS-oxime **5c** under the conditions of Method B to afford exclusively the *trans*-(*E*)-oxime product **10** (Scheme 3). The structure and stereochemistry of this adduct were firmly established by X-ray analysis.



Scheme 3. Addition of heteronucleophiles to 4-*tert*-butylnitrosocyclohexene.

Similarly, potassium thiophenoxide undergoes highly axial-stereoselective addition to the nitrosoalkene derived from α-chlorooxime **5a** via Method A, as well as using the Denmark procedure from *O*-silyloxime **5c** (Method B).[12] Both procedures led to a chromatographically separable ~19:1 mixture of the (*E*)-*trans*-product **11** and the (*E*)-*cis* isomer **12** in high yields. The structure of the minor product **12** was confirmed by X-ray analysis.

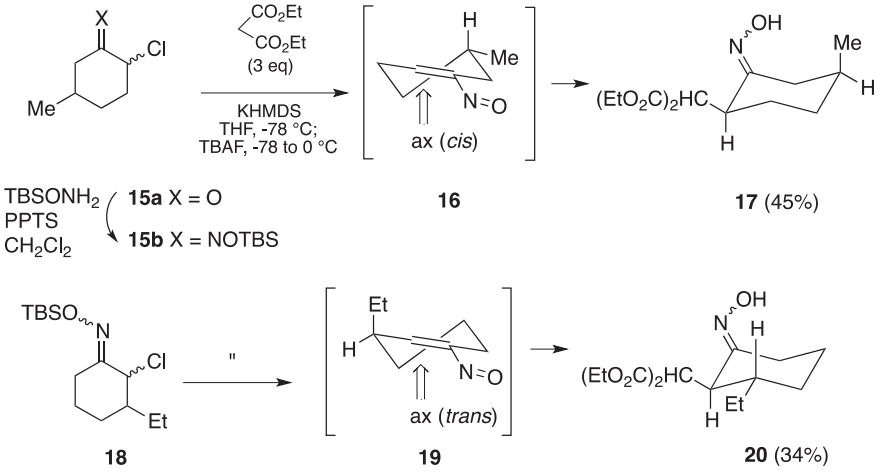
We have also investigated the stereochemistry of the addition of organocuprates to 4-*tert*-butylnitrosocyclohexene (**7**). For example, treatment of α-chlorooxime **5a** with 2 equiv of dimethylcopper lithium afforded a chromatographically separable 4:1 mixture of *trans* α-methyl product **13a** derived from axial attack on nitrosoalkene **7**, and the corresponding *cis* isomer **14a** in excellent total yield (Scheme 4). A small amount (~10%) of the reductive dechlorination product of starting oxime **5a** was also formed in this reaction. In addition, the major isomer **13a** was found to be an inseparable 1:1 mixture of (*E*/*Z*)-oxime geometric isomers,[8] whereas the minor product **14a** was exclusively (*E*) as determined by X-ray analysis. Similar but improved stereoselectivity was observed in the conjugate addition reactions with aryl cuprates. Therefore, the phenyl cuprate addition gave a 12:1 mixture of *trans*-**13b** and *cis*-**14b** in high overall yield, whereas the *p*-tolyl cuprate cleanly afforded a 9:1 mixture of **13c** and **14c**. It should also be noted that in the aryl cuprate additions



Scheme 4. Addition of cuprates to 4-*tert*-butylnitrosocyclohexene.

diastereomer and (*E*/*Z*)-oxime ratios were observed to be quite variable from run to run, probably due to equilibration during workup and/or purification. However, we have been unable to determine if similar isomerizations occurred in the malonate reactions (cf. Table 1).

Finally, we have briefly investigated the stereochemistry of the addition of diethyl malonate to some other nitrosocyclohexenes. For example, treatment of α-chloro-*O*-TBS-oxime **15b**, prepared from the corresponding known α-chloroketone **15a** (mixture of isomers),[13] with the potassium salt of diethyl malonate, followed by TBAF led to a single diastereomeric adduct **17** (yield unoptimized) (Scheme 5). This product, which is a 5:1 (*E*/*Z*) mixture of oxime isomers, has the cis-stereochemistry and conformation as shown based upon NMR analysis. The adduct **17** probably arises via axial attack by the malonate enolate on the half-chair vinylnitroso intermediate **16**.



Scheme 5. Addition of diethyl malonate to ring-substituted nitrosocyclohexenes.

Similarly, addition of malonate anion to the nitrosoalkene derived from known α-chloro-*O*-silyloxime **18**[6c] led to the *trans*-product **20** as an 11:1 (*E*/*Z*) oxime mixture. It seems reasonable that this adduct is formed via axial attack on the preferred (due to $A^{1,2}$-strain)[14] quasi-axial-ethyl half-chair nitrosoalkene **19**.

3. Conclusion

Analogous to the work described here, a number of studies have appeared probing the stereochemistry of Michael additions to cyclohexenes bearing electron-withdrawing groups, such as cyano, phenylazo, acetyl, carboxylate, etc.[15] Interestingly, with many of these Michael acceptors the preference for axial or equatorial attack varies widely depending on the particular nucleophile, solvent, and reaction conditions, as well as steric factors. In the case of the nitrosocyclohexene systems described here, axial attack is generally favored by varying degrees using a wide variety of carbon- and heteronucleophiles. It should be noted that due to the high electrophilicity of nitrosoalkenes, as well as the methods of generation of these species, we are limited to use of non-nucleophilic solvents, such as THF.

The studies outlined here further demonstrate the potential for stereospecific alkylation and arylation of nitrosoalkenes, which can act as effective enolonium ion equivalents. The product α-substituted oximes can be converted back to the parent carbonyl compounds via a plethora of methods.[16] Alternatively, these oximes could potentially be reduced to the corresponding amines or subjected to Beckmann rearrangements to afford ring-expanded lactams. We are continuing to investigate the potential of nitrosoalkenes in organic synthesis.

4. Experimental

4.1. General methods

All non-aqueous reactions were carried out under an inert argon atmosphere in flame dried glassware. Liquid reagents sensitive to air were added via a dry syringe. All solvents and reagents were obtained from commercial sources and used without further purification. EM Science silica gel 60 (230–400 mesh) was used for flash column chromatography, and silica gel 60 PF_{254} plates were used for analytical and preparative thin layer chromatography. ^1H and ^{13}C NMR experiments were performed on Bruker CDPX 300, DRX 400 or AV-III-600 MHz spectrometers. All high and low resolution mass spectral data were obtained using a Waters LCT Premier time of flight mass spectrometer (Waters Corporation, Micromass Ltd., Manchester, UK). IR spectra were measured on a Perkin–Elmer 1600 Series FTIR.

4.2. Synthesis and characterization

4.2.1. General procedures for intermolecular Michael additions of nucleophiles to in situ-generated 4-tert-butylnitrosocyclohexene. Method A: Addition of malonate and thiophenoxide nucleophiles to 4-tert-butylnitrosocyclohexene generated from α-chlorooximes **5a** *and* **5b**. A flame dried 25 mL round-bottomed flask containing a stirring bar was purged with Ar. The flask was cooled to −78 °C and charged with dry THF (3 mL). At this temperature, KHMDS (0.5 M in PhMe, 0.9 mL, 0.45 mmol) was added, followed by the

nucleophile (0.44 mmol). The mixture was stirred at −78 °C for 45 min. A solution of the α-chlorooxime **5a** or **5b** (39 mg, 0.19 mmol) in THF (1 mL) was added slowly and the mixture was stirred at −78 °C for 20 min. The reaction was quenched with saturated NH_4Cl solution and was extracted with Et_2O. The combined organics were dried over anhydrous $MgSO_4$. The residue obtained after solvent removal under reduced pressure was purified by flash column chromatography on silica gel (gradient elution using 10–20% ethyl acetate in hexanes).

Method B: Addition of malonate, sulfonamide, and thiophenoxide nucleophiles to 4-tert-butylnitrosocyclohexene generated from α-chloro-O-TBS-oxime **5c**. A flame dried 25 mL round-bottomed flask containing a stirring bar was purged with Ar. The flask was cooled to −78 °C and charged with dry THF (2 mL), followed by KHMDS (0.5 M in PhMe, 0.45 mL, 0.23 mmol). The nucleophile (0.22 mmol) was added and the mixture was stirred at −78 °C for 45 min. A solution of the α-chloro-*O*-TBS-oxime **5c** (57 mg, 0.18 mmol) in THF (1 mL) was added slowly to the reaction mixture at −78 °C, followed by the dropwise addition of TBAF (1.0 M in THF, 0.56 mL, 0.56 mmol) at this temperature. The temperature of the reaction bath was raised to −60 °C and maintained there for 20 min. The reaction was quenched with saturated NH_4Cl solution at −60 °C, removed from the cold bath, and allowed to warm to rt. The reaction mixture was extracted with Et_2O and the combined organics were dried over anhydrous $MgSO_4$. The residue obtained after solvent removal under reduced pressure was purified by flash column chromatography on silica gel (gradient elution using 10–20% ethyl acetate in hexanes).

*4.2.1.1. 2-(5-tert-Butyl-2-hydroximinocyclohexyl)-malonic acid diethyl ester (**8a**).* Method A: *cis*-**5a** (yield: 85%), *trans*-**5b** (yield: 93%). Method B: *cis*-**5c** (yield: 86%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 4.28–4.13 (m, 4H), 3.77 (d, *J*=11.5 Hz, 1H), 3.26 (dt, *J*=4.7, 11.5 Hz, 1H), 3.15 (dq, *J*=2.1, 15.6 Hz, 1H), 2.07–1.75 (m, 3H), 1.53–1.18 (m, 9H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 168.3, 160.2, 62.0, 53.7, 42.6, 40.3, 32.9, 30.0, 27.7, 25.5, 22.5, 14.6, 14.4; IR (thin film) 3460, 3307, 2954, 2872, 1731, 1655, 1249, 1179, 1149, 1102, 1032, 926 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{17}H_{30}NO_5$: 328.2124, found: 328.2127.

*4.2.1.2. 2-(5-tert-Butyl-2-hydroxyiminocyclohexyl)-2-methylmalonic acid diethyl ester (**8b**).* Method A: *cis*-**5a** (yield: 89%), *trans*-**5b** (yield: 85%). Method: B: *cis*-**5c** (yield: 81%). Product was isolated as an inseparable 6.2:1 mixture of *trans*-**8b**/*cis*-**9b**. ^{1}H NMR (300 MHz, $CDCl_3$, *cis* isomer **9b**) δ 7.38 (br s, 1H), 4.25–4.07 (m, 4H), 3.41 (dm, *J*=15.6 Hz, 1H), 3.17 (dd, *J*=3.3, 12.4 Hz, 1H), 1.93–1.58 (m, 4H), 1.54 (s, 3H), 1.43–1.16 (m, 8H), 0.85 (s, 9H). ^{1}H NMR (300 MHz, $CDCl_3$, *trans* isomer **8b**) δ 7.60 (br s, 1H), 4.25–4.07 (m, 4H), 3.33 (t, *J*=8.2 Hz, 1H), 2.71 (dm, *J*=17.4 Hz, 1H), 2.33–2.20 (m, 1H), 1.83–1.57 (m, 3H), 1.52 (s, 3H), 1.43–1.16 (m, 8H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, *trans* isomer **8b**) δ 172.0, 171.9, 160.2, 61.8, 61.7, 56.2, 43.8, 42.1, 33.5, 27.4, 26.4, 25.1, 22.0, 18.0, 14.4, 14.3; IR (thin film) 3448, 2954, 2872, 1725, 1655, 1296, 1243, 1179, 1108, 1020, 932 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{18}H_{32}NO_5$: 342.2280, found: 342.2281.

*4.2.1.3. 2-(5-tert-Butyl-2-hydroxyiminocyclohexyl)-2-ethylmalonic acid diethyl ester (**8c**).* Method A: *cis*-**5a** (yield: 76%), *trans*-**5b** (yield: 88%). Method B, *cis*-**5c** (yield: 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (br s, 1H), 4.31–4.14 (m, 4H), 3.20 (t, *J*=6.6 Hz, 1H), 2.89 (br d, *J*=14.5 Hz, 1H), 2.24–2.06 (m, 3H), 1.97–1.85 (m, 1H), 1.79–1.76 (m, 1H), 1.69–1.61 (m, 1H), 1.32–1.22 (m, 8H), 0.96–0.87 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 171.2, 160.3, 61.2, 59.7, 43.0, 42.3, 32.9, 28.3, 28.0, 27.3, 23.8, 14.2, 14.0, 9.5; IR (thin film) 3460, 2954, 2872, 1725, 1655, 1296, 1232, 1114, 1026, 955 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{19}H_{34}NO_5$: 356.2437, found: 356.2444.

*4.2.1.4. 2-Allyl-2-(5-tert-butyl-2-hydroxyiminocyclohexyl)-malonic acid diethyl ester (**8d**).* Method A: *cis*-**5a** (yield: 89%). Method B: *cis*-**5c** (yield: 72%). Product was isolated as an inseparable 9.1:1 mixture of **8d**/**9d**. X-ray quality crystals of the major *trans* isomer **8d** were obtained from the mixture by slow evaporation from acetone/ethyl acetate. ^{1}H NMR (400 MHz, $CDCl_3$, *cis* isomer **9d**) δ 7.44 (br s, 1H), 5.99–5.89 (m, 1H), 5.05 (br d, *J*=8.3 Hz, 1H), 5.03 (br s, 1H), 4.30–4.12 (m, 4H), 3.42 (br d, *J*=13.2 Hz, 1H), 2.97 (dd, *J*=5.8, 14.0 Hz, 1H), 2.91–2.65 (m, 3H), 2.09 (br d, *J*=12.4 Hz, 1H), 1.91 (br d, *J*=10.5 Hz, 1H), 1.65–1.54 (m, 1H), 1.30–1.18 (m, 8H), 0.88 (s, 9H). ^{1}H NMR (400 MHz, $CDCl_3$, *trans* isomer **8d**) δ 7.52 (br s, 1H), 5.99–5.89 (m, 1H), 5.05 (br d, *J*=8.3 Hz, 1H), 5.03 (br s, 1H), 4.30–4.12 (m, 4H), 3.16 (t, *J*=7.4 Hz, 1H), 2.91–2.65 (m, 3H), 2.29–2.17 (m, 2H), 1.75–1.57 (m, 2H), 1.30–1.18 (m, 8H), 0.87(s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, *trans* isomer **8d**) δ 171.7, 171.0, 160.3, 134.5, 118.6, 61.6, 61.5, 59.8, 43.7, 42.6, 39.8, 33.3, 27.8, 27.5, 24.6, 23.1, 14.5, 14.4; IR (thin film, **8d**/**9d** mixture) 3448, 2954, 2873, 1725, 1655, 1249, 1167, 1108, 1020, 930 cm^{-1}; HRMS-ES $[M+H]^+$ (**8d**/**9d** mixture) calcd for $C_{20}H_{34}NO_5$: 368.2437, found: 368.2422.

*4.2.1.5. N-(5-tert-Butyl-2-hydroxyiminocyclohexyl)-4,N-dimethylbenzenesulfonamide (**10**).* Method B: *cis*-**5c** (yield: 83%). X-ray quality crystals were obtained by slow evaporation from acetone/ethyl acetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.72 (d, *J*=8.1 Hz, 2H), 7.31 (d, *J*=8.1 Hz, 2H), 4.11 (t, *J*=6.0 Hz, 1H), 3.05 (dq, *J*=2.2, 15.5 Hz, 1H), 2.75 (s, 3H), 2.42 (s, 3H), 2.34–2.22 (m, 1H), 2.15–2.07 (m, 1H), 1.85 (d, *J*=10.7 Hz, 1H), 1.65–1.52 (m, 1H), 1.50–1.40 (m, 1H), 1.35–1.21 (m, 1H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 143.8, 135.0, 130.0, 128.3, 57.7, 42.4, 33.2, 33.0, 31.1, 27.5, 24.1, 23.7, 22.0; IR (thin film) 3460, 3284, 2954, 2872, 1655, 1337, 961 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{18}H_{29}N_2O_3S$: 353.1899, found: 353.1890.

*4.2.1.6. trans-4-tert-Butyl-2-phenylsulfanylcyclohexanone oxime (**11**).* Method A: *cis*-**5a** (isolated yield: 87%). Method B: *cis*-**5c** (isolated yield: 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.43 (d, *J*=7.0 Hz, 2H), 7.31–7.23 (m, 3H), 4.05 (br s, 1H), 3.25 (br d, *J*=14.6 Hz, 1H), 2.32–2.19 (m, 2H), 2.01–1.97 (m, 1H), 1.79 (br t, *J*=12.4 Hz, 1H) 1.70 (dq, *J*=4.5, 12.7 Hz, 1H), 1.20 (qd, *J*=4.2, 13.0 Hz, 1H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 134.8, 133.1, 129.3, 127.8, 50.4, 42.5, 33.9, 32.6, 27.8, 26.9, 20.8; IR (thin film) 3248, 3070, 2954, 2860, 1708, 926 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{16}H_{24}NOS$: 278.1579, found: 278.1571.

*4.2.1.7. cis-4-tert-Butyl-2-phenylsulfanylcyclohexanone oxime (**12**).* Method A: *cis*-**5a** (isolated yield: 5%). Method B: *cis*-**5c** (isolated yield: 5%). X-ray quality crystals were obtained by slow evaporation from dichloromethane/acetone, mp 142–144 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.39 (d, *J*=7.5 Hz, 2H), 7.27 (t, *J*=7.4 Hz, 2H), 7.27 (t, *J*=7.4 Hz, 1H), 3.77 (dd, *J*=4.4, 11.7 Hz, 1H), 3.47 (dt, *J*=3.9, 14.7 Hz, 1H), 2.25–2.22 (m, 1H), 1.93–1.90 (m, 1H), 1.76 (td, *J*=5.64, 13.3 Hz, 1H), 1.58–1.19 (m, 3H), 0.82 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 134.8, 131.6, 128.8, 126.8, 49.8, 47.6, 36.0, 32.6, 27.4, 26.1, 24.6; IR (thin film) 3260, 2943, 2872, 932 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{16}H_{24}NOS$: 278.1579, found: 278.1571.

4.2.2. Addition of organocuprates to 4-tert-butylnitrosocyclohexene generated from cis-α-chlorooxime **5a**. CuI powder (75 mg, 0.40 mmol) in a round-bottomed flask was dried by heating at 150 °C for 2 h under vacuum. The heating was discontinued and the flask was allowed to cool to rt under Ar. The flask was then transferred to an ice bath and charged with dry THF (1 mL). The mixture was maintained at 0 °C and a solution of the

organolithium reagent (0.80 mmol) was added slowly. A turbid green coloration was observed after addition of the first equivalent of the organolithium reagent, but the mixture turned transparent or clear tan after the addition of the second equivalent. The mixture was stirred at this temperature for 2 min and then the reaction flask was transferred to an acetone/dry-ice bath at −78 °C. A solution of the α-chlorooxime *cis*-**5a** (41 mg, 0.20 mmol) in THF (2 mL) was added slowly to this mixture at −78 °C whereby the solution turned bright yellow. The reaction mixture was stirred for 30 min at −78 °C and quenched with concentrated HCl (12.1 M, 1 mL, 12.1 mmol) at this temperature. The dry-ice bath was removed and ethylenediamine (3 mL, 45 mmol) was added to the cold mixture followed by the addition of ice-cold water (10 mL). The addition of ethylenediamine was exothermic and the flask was properly vented to prevent the buildup of pressure. The reaction mixture turned turbid blue on the initial addition of ethylenediamine and later changed to clear Prussian blue on the addition of water. Stirring was discontinued after 2 min and the organic layer was extracted with ether, dried over anhydrous $MgSO_4$ and the solvent was removed under vacuum. The product was purified by flash column chromatography on silica gel eluting with dichloromethane (100%) followed by ethyl acetate/hexanes (gradient, 10%–20% ethyl acetate in hexanes).

*4.2.2.1. trans-4-tert-Butyl-2-methylcyclohexanone oxime (**13a**).* Isolated yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$, inseparable ~1:1 mixture of oxime *Z*/*E* isomers) δ 8.75 (br s, 1H), 3.65–3.61 (m, 0.5H, *Z*), 3.15 (br d, *J*=8.7 Hz, 0.5H), 2.67–2.64 (m, 0.5H, *E*), 2.34–2.22 (m, 1H), 1.95–1.85 (m, 1.5H), 1.67–1.63 (m, 1H), 1.49–1.36 (m, 2H), 1.20–1.11 (m, 4H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, inseparable ~1:1 mixture of oxime *Z*/*E* isomers) δ 164.7, 164.6, 41.9, 41.8, 34.8, 34.0, 33.2, 32.7, 32.6, 29.0, 28.1, 27.9, 27.8, 27.0, 26.3, 21.5, 19.0, 17.2; IR (thin film) 3237, 2954, 2872, 1660, 944 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{11}H_{22}NO$: 184.1701, found: 184.1709.

*4.2.2.2. cis-4-tert-Butyl-2-methylcyclohexanone oxime (**14a**).* Isolated yield: 18%. X-ray quality crystals were obtained by slow evaporation from chloroform/ethyl acetate, mp 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (br, s, 1H), 3.44 (dm, *J*=14.0 Hz, 1H), 2.25 (m, 1H), 1.92 (dm, *J*=12.3 Hz, 2H), 1.62 (td, *J*=5.1, 14.0 Hz, 1H), 1.30 (tt, *J*=2.9, 12.0 Hz, 1H), 1.25–1.10 (m, 4H), 1.01 (q, *J*=9.4 Hz, 1H), 0.87 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 47.8, 37.9, 37.7, 32.8, 28.0, 27.3, 24.8, 17.0; IR (thin film) 3260, 2943, 2872, 1660, 932 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{11}H_{22}NO$: 184.1701, found: 184.1708.

*4.2.2.3. trans-4-tert-Butyl-2-phenylcyclohexanone oxime (**13b**).* Isolated yield: 85% as an inseparable 36:1 mixture of oxime *E*/*Z* diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$, *Z* isomer) δ 8.92 (br s, 1H), 7.40–7.24 (m, 5H), 4.93 (br s, 1H), 2.58–2.53 (m, 1H), 2.45 (br d, *J*=14.0 Hz, 1H), 1.92–1.21 (m, 5H), 0.94 (s, 9H). ^{1}H NMR (300 MHz, $CDCl_3$, *E* isomer) δ 8.92 (br s, 1H), 7.40–7.24 (m, 5H), 3.88 (br s, 1H), 3.33 (dm, *J*=12.2 Hz, 1H), 2.60 (dm, *J*=13.7 Hz, 1H), 1.92–1.6 (m, 3H), 1.50 (tm, *J*=9.3 Hz, 1H), 1.36–1.21 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, *E* isomer) δ 162.7, 141.0, 129.0, 127.7, 126.6, 44.3, 42.3, 32.9, 31.2, 27.8, 27.0, 22.5; IR (thin film) 3260, 2954, 2872, 1666, 932 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{16}H_{24}NO$: 246.1858, found: 246.1855.

*4.2.2.4. cis-4-tert-Butyl-2-phenylcyclohexanone oxime (**14b**).* Isolated yield: 7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 3.50 (dm, *J*=13.2 Hz, 1H), 3.40 (dd, *J*=4.1, 12.9 Hz, 1H), 2.12–1.98 (m, 2H), 1.79 (td, *J*=5.4, 13.9 Hz, 1H), 1.64 (q, *J*=12.4 Hz, 1H), 1.49–1.43 (m, 1H), 1.37–1.22 (m, 2H), 0.92 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 141.3, 129.1, 128.7, 127.1, 49.8, 48.1, 36.1, 33.0, 28.0, 26.9, 24.9; IR (thin film) 3247, 2950, 2868, 1668, 928 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{16}H_{24}NO$: 246.1858, found: 246.1855.

*4.2.2.5. trans-4-tert-Butyl-2-p-tolylcyclohexanone oxime (**13c**).* Isolated yield: 85% as an inseparable 5.5:1 mixture of oxime *E*/*Z* isomers. ^{1}H NMR (400 MHz, $CDCl_3$, *Z* isomer) δ 8.77 (br s, 1H), 7.19–7.14 (m, 4H), 4.84 (br s, 1H), 2.51–2.47 (m, 1H), 2.41 (dm, *J*=14.2 Hz, 1H), 2.34 (s, 3H), 2.16 (td, *J*=4.8, 13.9 Hz, 1H), 1.87–1.20 (m, 4H), 0.91 (s, 9H). ^{1}H NMR (400 MHz, $CDCl_3$, *E* isomer) δ 8.77 (br s, 1H), 7.19–7.14 (m, 4H), 3.80 (br s, 1H), 3.29 (br d, *J*=14.4 Hz, 1H), 2.55 (dm, *J*=13.7 Hz, 1H), 2.34 (s, 3H), 1.87–1.73 (m, 2H), 1.66 (td, *J*=5.1, 12.2 Hz, 1H), 1.51–1.40 (m, 1H), 1.27 (td, *J*=4.4, 12.5 Hz, 1H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, *E* isomer) δ 162.8, 137.9, 136.1, 129.8, 127.5, 43.9, 42.2, 32.9, 31.2, 27.8, 27.0, 22.4, 21.4; IR (thin film) 3237, 3107, 2942, 2872, 1655, 932 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{17}H_{26}NO$: 260.2014, found: 260.2011.

*4.2.2.6. cis-4-tert-Butyl-2-p-tolylcyclohexanone oxime (**14c**).* Isolated yield: 9%. ^{1}H NMR (400 MHz, THF-d_8) δ 10.82 (s, 1H), 7.01 (dd, *J*=7.9, 9.2 Hz, 4H), 3.49 (br d, *J*=14.4 Hz, 1H), 3.30 (dd, *J*=4.05, 12.8 Hz, 1H), 2.26 (s, 3H), 2.00–1.89 (m, 2H), 1.69–1.64 (m, 1H), 1.56 (t, *J*=12.0 Hz, 1H), 1.48–1.42 (m, 1H), 1.25–1.21 (m, 1H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, THF-d_8, compound has extremely low solubility leading to reduced signal intensity and therefore the oxime carbon peak could not be observed) δ 140.8, 136.2, 130.3, 129.4, 50.6, 49.4, 37.7, 33.7, 31.2, 28.5, 28.1, 21.7; IR (thin film) 3232, 2954, 2922, 2859, 1664, 930 cm^{-1}; HRMS-ES $[M+H]^+$ calcd for $C_{17}H_{26}NO$: 260.2014, found: 260.2011.

*4.2.2.7. 2-Chloro-5-methylcyclohexanone O-(tert-butyldimethylsilyl) oxime (**15b**).* To a stirred solution of the α-chloroketone **15a** (3.41 mmol) in CH_2Cl_2 (7 mL) and a spatula of 4 Å molecular sieves were added H_2NOTBS (529 mg, 3.41 mmol) and PPTS (spatula tip full). The reaction mixture was stirred at rt for 12 h and then filtered through a pad of Celite. The solution was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate in hexanes (5–30%) to provide the product **15b** as a clear oil (632 mg) in 67% yield as a mixture of (*E*/*Z*)-isomers and diastereomers: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.64 (br s, 0.4H), 5.50 (br s, 0.1H), 4.72 (br s, 0.4H), 4.57 (br s, 0.1H), 3.31 (t, *J*=5.7 Hz, 1H), 2.40–2.30 (m, 1H), 2.23–2.18 (m, 1H), 2.10–2.05 (m, 1H), 1.94–1.76 (m, 3H), 1.69–1.45 (m, 5H), 1.11–1.04 (m, 6H), 0.96–0.94 (m, 18H), 0.22–0.19 (m, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 162.7, 161.9, 160.7, 159.3, 66.3, 59.1, 54.5, 49.3, 47.4, 47.0, 38.7, 37.1, 35.4, 34.9, 33.6, 33.5, 32.4, 31.4, 31.3, 31.2, 29.7, 29.0, 28.4, 28.2, 27.6, 27.5, 26.6, 26.1, 25.8, 24.5, 23.5, 22.4, 22.1, 21.9, 21.2, 19.9, 18.9, 18.8, 18.2, 16.8; IR (thin film) 2955, 2858, 1744, 1461, 1252, 945 cm^{-1}; LRMS-ES$^+$ *m*/*z* (relative intensity) 276 (MH^+, 10); HRMS-ES $[M+H]^+$ calcd for $C_{13}H_{27}NOSCl$: 276.1550, found: 276.1543.

*4.2.3. General procedure for conjugate additions to ring-substituted nitrosoalkenes **16** and **19**.* To a stirred solution of diethyl malonate (**6a**, 3 mmol, 481 mg) in THF (6.5 mL) was added KHMDS (6 mL, 0.5 M in PhMe, 3 mmol) at −78 °C. The resulting solution was then stirred for 45 min at that temperature. The *O*-TBS oxime (**15b** or **18**, 1 mmol) dissolved in THF (600 μL) was added slowly over 1 min, followed by dropwise addition of TBAF (2 mL, 1.0 M in THF, 2 mmol) over 3 min. The resulting solution was immediately transferred to an ice bath and stirred for an additional 2 h. The reaction mixture was diluted with concentrated aqueous NH_4Cl and EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by flash column chromatography on silica gel eluting with a mixture of ethyl acetate in hexanes (25–40%).

*4.2.3.1. Diethyl 2-(2-(hydroxyimino)-4-methylcyclohexyl)malonate (**17**).* The product **17** was obtained as a clear oil (47 mg,

45% yield) as a 5:1 mixture of (*E*/*Z*) oxime isomers: ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.00–7.50 (br s, 1H), 4.23–4.10 (m, 4H), 3.79 (d, *J*=10.0 Hz, 0.2H), 3.71 (d, *J*=10.9 Hz), 3.20–3.13 (m, 0.3H), 3.11–3.04 (m, 1H), 2.86–2.72 (m, 0.3H), 2.56 (dd, *J*=14.1, 4.7 Hz, 1H), 2.33 (dd, *J*=14.0, 7.8 Hz, 1H), 1.93–1.74 (m, 2H), 1.72–1.61 (m, 4H), 1.44–1.37 (m, 2H), 1.30–1.19 (m, 6H), 1.01 (d, *J*=7.5 Hz, 1H), 0.96 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 168.7, 168.6, 159.3, 158.8, 61.9, 60.8, 53.8, 53.5, 41.4, 33.9, 32.0, 31.4, 30.7, 29.5, 27.7, 23.1, 23.0, 21.5, 20.6, 14.6, 14.5, 14.4, 11.8; IR (thin film) 3279, 2931, 2871, 1732, 1455, 1292, 1178, 1033, 947 cm^{-1}; LRMS-ES$^+$ *m*/*z* (relative intensity) 286 (MH^+, 36); HRMS-ES $[M+H]^+$ calcd for $C_{14}H_{25}NO_5$: 286.1654, found: 286.1649.

*4.2.3.2. Diethyl 2-(2-ethyl-6-(hydroxyimino)cyclohexyl)malonate (**20**).* The product **20** was obtained as a clear oil (18 mg, 34% yield) as a ~11:1 mixture of (*E*/*Z*) oxime isomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.10 (s, 0.1H), 4.27–4.05 (m, 4H), 3.83 (d, *J*=8.5 Hz, 1H), 3.72 (d, *J*=8.1 Hz, 0.09H), 3.13 (d, *J*=10.6 Hz, 1H), 3.01 (d, *J*=8.5 Hz, 1H), 2.01–1.92 (m, 1H), 1.81–1.74 (m, 1H), 1.73–1.61 (m, 3H), 1.60–1.49 (m, 2H), 1.48–1.39 (m, 1H), 1.36–1.21 (m, 8H), 0.92 (t, *J*=5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 159.0, 158.6, 62.0, 61.9, 54.0, 53.5, 45.4, 39.7, 25.4, 25.3, 21.8, 20.5, 14.4, 12.1, 12.0, 11.7; IR (thin film) 3278, 2960, 2874, 1732, 1456, 1262, 1034, 951 cm^{-1}; LRMS-ES$^+$ *m*/*z* (relative intensity) 300 (MH^+, 26); HRMS-ES $[M+H]^+$ calcd for $C_{15}H_{26}NO_5$: 300.1811, found: 300.1799.

Acknowledgements

We are grateful to the National Institutes of Health (GM-087733) and the National Science Foundation (CHE-0806807) for financial support of this research. We also thank Dr. H. Yennawar (Penn State Small Molecule X-Ray Cystallographic Facility) for the X-ray crystal structure determinations.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.054.

References and notes

1. Li, P.; Majireck, M. M.; Witek, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **2010**, *51*, 2032.
2. (a) Korboukh, I.; Kumar, P.; Weinreb, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 10342; (b) Kumar, P.; Li, P.; Korboukh, I.; Wang, T. L.; Yennawar, H.; Weinreb, S. M. *J. Org. Chem.* **2011**, *76*, 2094.
3. For reviews of vinylnitroso compounds see: (a) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *11*, 53; (b) Lyapkalo, I. M.; Ioffe, S. L. *Russ. Chem. Rev.* **1998**, *67*, 467.
4. For examples of enolonium ion equivalents see: (a) Sacks, C. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1975**, *97*, 7372; (b) Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935; (c) Stork, G.; Ponaras, A. A. *J. Org. Chem.* **1976**, *41*, 2937; (d) Wender, P. A.; Erhardt, J. M.; Letendre, L. J. *J. Am. Chem. Soc.* **1981**, *103*, 2114; (e) Hatcher, J. M.; Coltart, D. M. *J. Am. Chem. Soc.* **2010**, *132*, 4546; (f) Miyoshi, T.; Miyakawa, T.; Ueda, M.; Miyata, O. *Angew. Chem., Int. Ed.* **2011**, *50*, 928.
5. Witek, J. A.; Weinreb, S. M. *Org. Lett.* **2011**, *13*, 1258.
6. (a) Denmark, S. E.; Dappen, M. S. *J. Org. Chem.* **1984**, *49*, 798; (b) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741; (c) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466.
7. Malosh, C. F.; Ready, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 10240.
8. Ribeiro, D. S.; Olivato, P. R.; Rittner, R. *Magn. Reson. Chem.* **2000**, *38*, 627.
9. Eisenstein, O.; Klein, J.; Lefour, J. M. *Tetrahedron* **1979**, *35*, 225.
10. Allinger, N. L.; Freiberg, L. A. *J. Am. Chem. Soc.* **1960**, *82*, 2393.
11. Allinger, N. L.; Allinger, J.; Geller, L. E.; Djerassi, C. *J. Org. Chem.* **1960**, *25*, 6.
12. X-ray data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 833440=**8d**; CCDC 833441=**10**; CCDC 833442=**12**; CCDC 833443=**14a**.
13. For recent examples of enantioselective additions of thiols to nitrosoalkenes see: Hatcher, J. M.; Kohler, M. C.; Coltart, D. M. *Org. Lett.* **2011**, *13*, 3810.
14. Cf. Malhotra, S. K.; Moakley, D. F.; Johnson, F. *J. Chem. Soc., Chem. Commun.* **1967**, 448.
15. See for example: (a) Abramovitch, R. A.; Struble, D. L. *Tetrahedron* **1968**, *24*, 357; (b) Abramovitch, R. A.; Rogic, M. M.; Singer, S. S.; Venkateswaran, N. *J. Org. Chem.* **1972**, *37*, 3577; (c) Abramovitch, R. A.; Singer, S. S.; Rogic, M. M.; Struble, D. L. *J. Org. Chem.* **1975**, *40*, 34; (d) Alexander, C. W.; Hamdam, M. S.; Jackson, W. R. *J. Chem. Soc., Chem. Commun.* **1972**, 94; (e) Bozzini, S.; Gratton, S.; Pellizer, G.; Risaliti, A.; Stener, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 869.
16. For reviews of oxime cleavage see: (a) Corsaro, A.; Chiacchio, U.; Pistara, V. *Synthesis* **2001**, 1903; (b) Corsaro, A.; Chiacchio, U.; Pistara, V. *Curr. Org. Chem.* **2009**, *13*, 482; (c) Sahu, S.; Sahu, S.; Patel, S.; Dash, S.; Mishra, B. K. *Indian J. Chem.* **2008**, *47B*, 259.