HETEROCYCLES, Vol. 74, 2007, pp. 743 - 761. © The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2007 Accepted, 15th November, 2007, Published online, 16th November, 2007. COM-07-S(W)59

SYNTHESIS OF NITROSOALKYL- AND AMINO-SUBSTITUTED α,β-UNSATURATED KETONES BY CLEAVAGE OF THE N-O-BOND OF BICYCLIC Δ^4-ISOXAZOLINES

Markku Lager, Paul Dietrich, Dirk Weinrich, and Karola Rück-Braun*

Technical University Berlin, Chemistry Department, Straße des 17. Juni 135, D-10623 Berlin, Germany. E-mail: krueck@chem.tu-berlin.de

Dedicated with respect and compliments to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – The N-O-bond cleavage of bicyclic Δ^4-isoxazolines prepared from five-membered cyclic nitrones was studied. Proline-derived bicyclic isoxazolines furnished exclusively acylic nitrosoalkyl-substituted α,β-unsaturated ketones upon treatment with *m*-CPBA. The nitroso compound **16** was characterized as stable diazo-dioxyde by X-ray analysis. For the N-O-bond cleavage of C3-*H*-substituted bicyclic Δ^4-isoxazolines a $Pd(PPh_3)_4$–promoted cleavage protocol in the presence of silanes furnishing enaminones is described.

INTRODUCTION

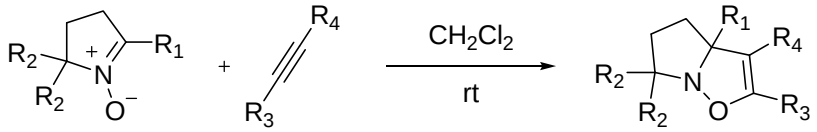
1,3-Dipolar cycloaddition reactions open up a versatile access to five-membered ring skeletons, and the cycloadducts derived from nitrones and nitrile oxides are well suited for further transformations based on reductive and oxidative N-O-bond cleavage.[1–9] This approach has been extensively used in organic synthesis starting from isoxazolidines.[10–15] Recently, we reported on cycloaddition reactions with a polymer-bound cyclic nitrone containing a piperazine-2-one skeleton, and further transformations based on N-O-bond cleavage towards the synthesis of libraries of highly functionalized piperazine-2-ones for lead structure finding.[16] During these studies we realized that the oxidative and reductive N-O-bond cleavage of bicyclic Δ^4-isoxazolines derived from nitrones and alkynes seemed to be less documented in the literature. One reason may be the thermal lability of these compounds and related cycloadducts.[18–20] We herein report on Δ^4-isoxazoline transformations of bicyclic cycloadducts derived mainly from five-membered nitrones. The *m*-CPBA oxidation of Δ^4-isoxazolines prepared from acyclic N-methylnitrones and alkynes was reported by Padwa to yield α,β-unsaturated ketones by extrusion of

nitrosomethane.[17] When oxidizing bicyclic cycloadducts containing a carboxyl-substituent in C3-position of the Δ^4-isoxazoline ring we obtained nitrosoalkyl-functionalized α,β-unsaturated ketones. Obviously, the nitroso functionality does remain in the product because of the bicyclic structure of the Δ^4-isoxazolines. The influence of the substitution pattern in C3-position on the outcome of the oxidative N-O-bond cleavage was examined. During these studies also the N-O-bond cleavage of C3-*H*-substituted Δ^4-isoxazolines was investigated. A mild protocol using $Pd(PPh_3)_4$ / $HSiR_3$ is presented yielding α,β-unsaturated aminoketones. This method appears to be a suitable alternative to other N-O-bond cleavage methods or hydrogenolytic cleavage protocols.[8–14,16,23–25]

RESULTS AND DISCUSSION

The bicyclic isoxazolines **5**–**12** were prepared from the nitrones **1**–**4**[26,27] and the corresponding alkynes in dichloromethane at room temperature using a four-fold excess of the dipolarophile.[28] All isoxazolines were obtained as single regioisomers after flash-chromatography in 44-91% yield (Table 1).

Table 1. Synthesis of Δ^4-isoxazolines via 1,3-dipolar cycloaddition

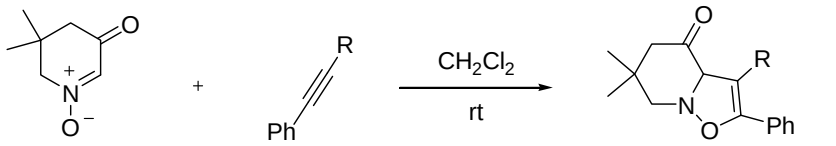


1-4 **5-12**

entry	nitrone	R_1	R_2	R_3	R_4	time	product	yield (%)[a]
1	**1**	CO_2Bn	H	Ph	CO_2Et	16 h	**5**	90
2	**1**	CO_2Bn	H	Me	CO_2Et	7 d	**6**	83
3	**2**	CO_2Me	H	Ph	CO_2Et	16 h	**7**	85
4	**3**	H	H	Ph	CO_2Et	16 h	**8**	53[b]
5	**3**	H	H	Me	CO_2Et	7 d	**9**	51[b]
6	**4**	H	Me	Ph	CO_2Et	16 h	**10**	91
7	**4**	H	Me	Me	CO_2Et	7 d	**11**	44
8	**4**	H	Me	Ph	H	7 d	**12**	86

(a) Isolated yields. (b) Overall yield over two steps including nitrone synthesis.

Similarly, the bicyclic isoxazolines **14** and **15** with an anellated six-ring were synthesized in 84% and 91% yield (Scheme 1) starting from nitrone **13**.[26,28]



13

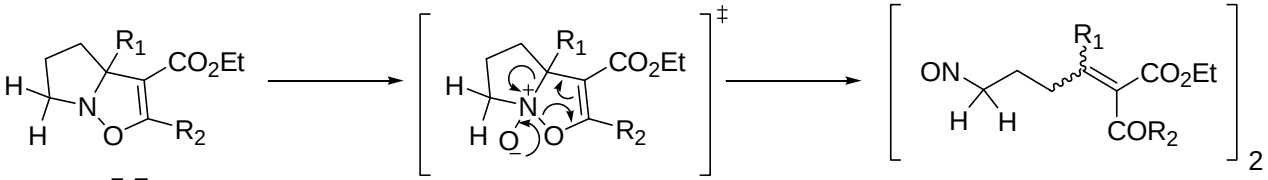
14: R = H: 84%
15: R = CO_2Et: 91%

Scheme 1. Synthesis of isoxazolines **14** and **15**

Most importantly these cycloadducts differ in their substitution pattern R_1 at position C3 of the Δ^4-isoxazoline ring (see Table 1), containing either a carboxylic ester functionality or hydrogen as substituent. Moreover the cycloadducts **10**–**12** have a α-$C(Me)_2$-group in the neighborhood of the isoxazoline nitrogen atom. Both positions are known to have an impact on N-O-bond cleavage reactions of Δ^4-isoxazolines derived from acyclic and cyclic nitrones.[15,17,19–22]

For oxidative N-O-bond cleavage the cycloadducts **5-7** (R_1 = CO_2R, Table 2) were treated with 1.1 equiv *m*-CPBA in dichloromethane at -30 °C or room temperature.

Table 2. Oxidative N-O-bond cleavage with 1.1 equiv *m*-CPBA in CH_2Cl_2



5-7 **16-18**

entry	isoxazoline	R_1	R_2	T (°C)	time	product	yield (%)[a]
1	**5**	CO_2Bn	Ph	-30	16 h	**16**	87
2	**5**	CO_2Bn	Ph	rt	5 min	**16**	85
3	**6**	CO_2Bn	Me	-30	16 h	**17**	45
4	**7**	CO_2Me	Ph	-30	16 h	**18**	85
5	**7**	CO_2Me	Ph	rt	5 min	**18**	80

(a) Isolated yields.

At -30 °C in the absence of light an immediately blue coloration of the reaction solutions was observed after the addition of *m*-CPBA, remaining for at least 30 min and disappearing within 1 h resulting in colorless solutions. When carrying out the reaction in the presence of light at room temperature no coloration was noticed. Nitroso compounds exhibit a deep generally blue coloration in solution in their monomeric state, whereas their dimers are colorless compounds.[29] Accordingly to these observations the

aliphatic nitroso compounds **16**–**18** presented in Table 2 were isolated as dimers after flash-chromatography in 45-87% yield. Dimerization to the diazo-dioxydes proceeds thermally and photochemically and can be monitored by IR-spectroscopy. The strong absorption at 1250 cm^{-1} is characteristic for the diazo-dioxyde functionality.[29] The molecular structure of compound **16** was classified by X-ray analysis (Figure 1).[30]

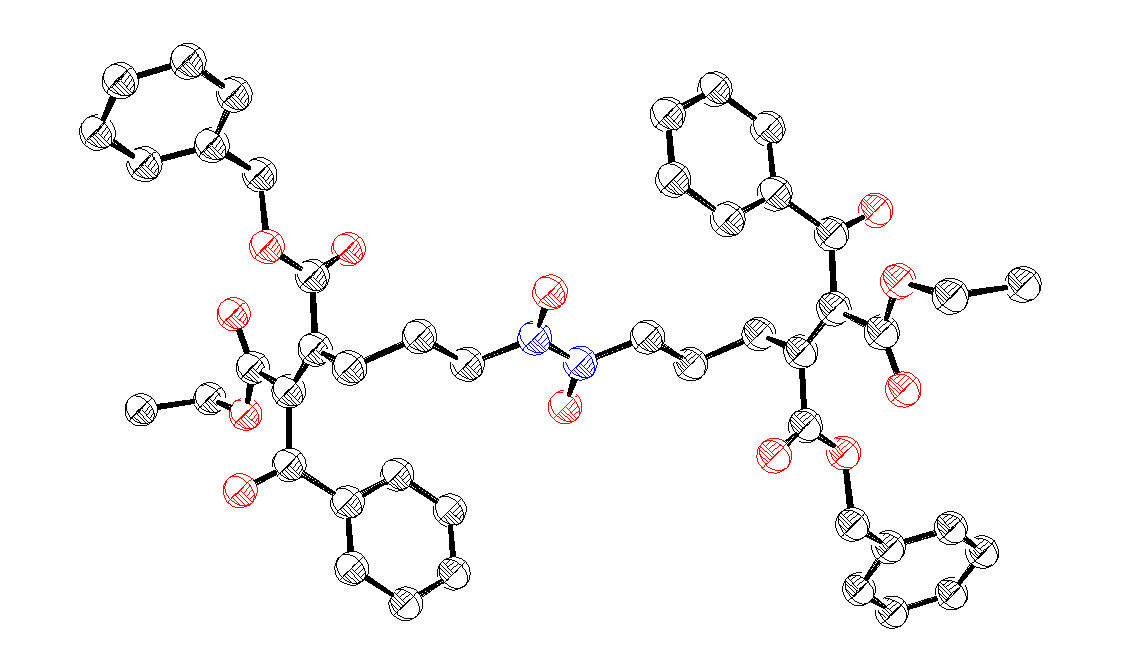
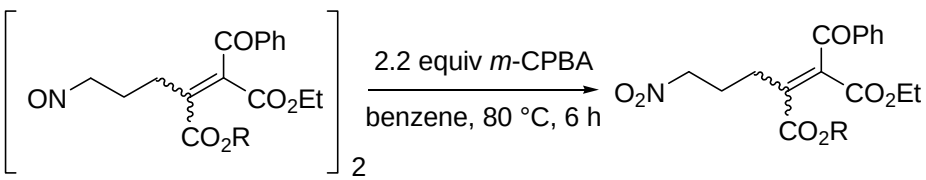


Figure 1. Crystal structure of diazo-dioxyde **16**, the ellipsoids represent 50% displacement of atoms

Under the reaction conditions employed further oxidation to the nitro compounds was not observed. Treatment of **16** and **18** with 2.2 equiv *m*-CPBA in boiling benzene resulted in the quantitative formation of the corresponding nitro compounds **19** and **20** (Scheme 2), which were also obtained by oxidation of the Δ^4-isoxazolines **5** and **7** using 3.3 equivalents *m*-CPBA in boiling benzene, without loss in yield and purity.



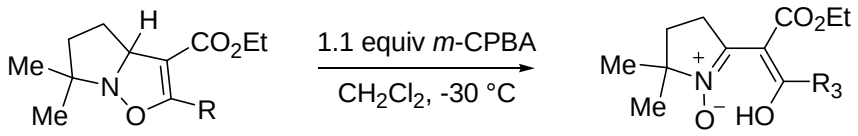
16: R = Bn
18: R = Me

19: R = Bn: 96%
20: R = Me: 91%

Scheme 2. Oxidation of the diazo-dioxydes **16** and **18**

In contrast to the results obtained with the cycloadducts **5**–**7**, decomposition was detected during the reactions of the C3-*H* substituted isoxazolines **8** and **9** (entries 4 and 5, Table 1; R_1 = H) with *m*-CPBA at -30 °C (16 h) and no isolable products were obtained. Formation of a second-generation aldonitrone could

not be detected. The bicyclic isoxazolines **10** and **11** also display a C3-*H* substituent, but in addition a α-C(Me)$_2$-group besides the nitrogen atom preventing aldonitrone formation. Oxidation of **10** and **11** furnished the "2nd generation" ketonitrones **21** and **22** in 71% and 96% yield, respectively (Scheme 3).



10: R = Ph
11: R = Me

21: R = Ph: 71%
22: R = Me: 96%

Scheme 3. Reaction of C3-*H* Δ^4-isoxazolines **10** and **11** with *m*-CPBA

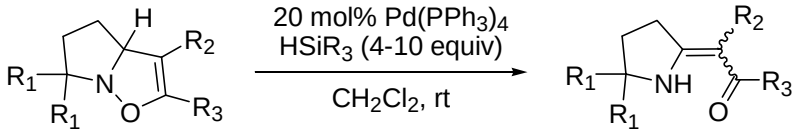
All results obtained can be well explained by oxidation of the nitrogen atom of the cycloadducts furnishing an unstable isoxazoline N-oxide intermediate (Table 2).[15,17,22] For Δ^4-isoxazolines with a C3-*H* substituent the known pathways for oxidative N-O-bond cleavage of isoxazolidines yielding aldonitrones or ketonitrones explain plausible the results.[15] However, only the ketonitrones **21** and **22** could be isolated in these studies with Δ^4-isoxazolines. In all proline-derived systems the electron-withdrawing CO_2R group at C3 is promoting the additional nitrogen-C3-bond cleavage furnishing the respective aliphatic nitroso compounds.

Functionalized α,β-unsaturated ketones are versatile building blocks for organic synthesis.[21,31–34] Therefore we extended our studies towards the preparation of pyrrolidino- and piperidino-enaminones. The preparation of β-aminoketones starting from isoxazolidines via hydrogenolytic cleavage of the N-O-bond using Pd/C is well documented in the literature.[35–36] However, hydrogenolytic cleavage is not the method of choice for the conversion of Δ^4-isoxazolines to enaminones due to the simultaneous reduction of the double bond.[19,25] Therefore we investigated alternative methods, related to a procedure published by Noyori for the palladium(0)-catalyzed cleavage of prostaglandin endoperoxides with Pd(PPh$_3$)$_4$.[37] The results obtained during formation of hydroxyketones and dioles from the endoperoxides have been interpreted by an efficient catalytic process based on the nucleophilicity of Pd(0) and the hydrogen-carrying ability of Pd(II). However, in the presence of strong oxidizing starting materials a competing Pd(0)/Pd(I) redox mechanism was postulated.[37]

Upon treatment of cycloadduct **8** with Pd(PPh$_3$)$_4$ (20 mol-%) in dichloromethane at room temperature no reaction was observed. Palladium-catalyzed reactions in the presence of silanes have been applied in the reduction of alkynes, for deprotection of benzyl esters, and the reduction of nitro compounds to hydroxylamines.[38-41] Starting from the isoxazolines **8** and **10**–**12** with Pd(PPh$_3$)$_4$ (20 mol-%) in the presence of Et$_3$SiH (4 equiv) at room temperature in dichloromethane the respective amino-substituted

α,β-unsaturated ketones were obtained. Depending on the substitution pattern of the parent isoxazolines *E*/*Z* isomeric mixtures were isolated. The results are summarized in Table 3.

Table 3. Palladium/$HSiR_3$ catalyzed N-O cleavage reactions of Δ^4-isoxazolines



8, 10-12 **23-26**

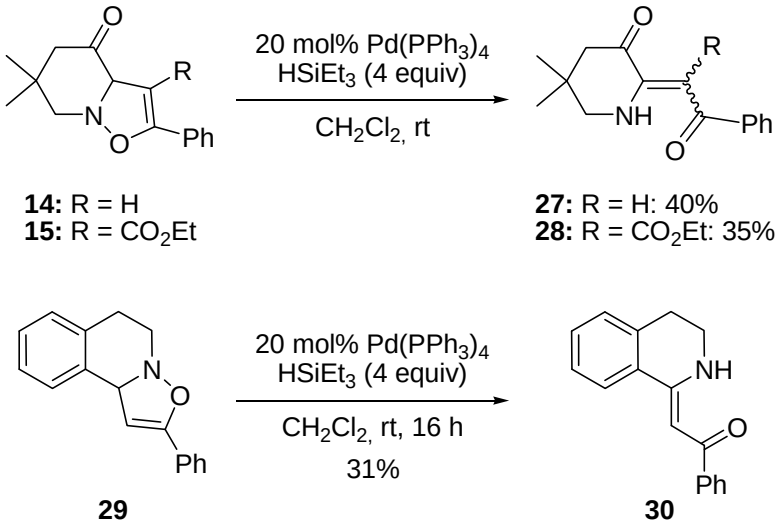
entry	educt	R_1	R_2	R_3	silane R	T	time (h)	product	yield (%)[a]
1	**8**	H	CO_2Et	Ph	Et	rt	16	**23**	10
2	**10**	Me	CO_2Et	Ph	Et	rt	16	**24**	56
3	**11**	Me	CO_2Et	Me	Et	rt	16	**25**	35
4	**12**	Me	H	Ph	Et	rt	16	**26**	69
5	**8**	H	CO_2Et	Ph	Ph	40 °C	2	**23**	70
6	**11**	Me	CO_2Et	Me	Ph	40 °C	2	**25**	53

(a) Isolated yields.

The products **24-26** were isolated in 35-69% non-optimized yield (Table 3, entries 2–4). During all reactions within 16 h the formation of Pd-black was observed. We also noticed formation of Pd-black from $Pd(PPh_3)_4$ and Et_3SiH in the absence of the isoxazoline. However, neither Pd/C nor Pd-black were found to be active catalysts for N-O-bond cleavage in the absence of silane. Moreover no product formation was detected when the isoxazolines were reacted in the presence of silane without any palladium source.

Unfortunately the yield for product **23** could not be improved when Et_3SiH was applied. As by-product the corresponding β-ketoester was observed and isolated. Therefore differently substituted silanes were investigated. Treatment of **8** with Ph_3SiH (4 equiv) and 20 mol-% $Pd(PPh_3)_4$ at room temperature for 3 d gave no conversion at all. Increasing the amount of Ph_3SiH (5 and 10 equiv) in combination with 10 mol-% of $Pd(PPh_3)_4$ at 40 °C led to incomplete conversion of the starting material after 1 d. With 10 equiv Ph_3SiH or Cl_3SiH in the presence of $Pd(PPh_3)_4$ (20 mol-%) at 40 °C complete conversion of the isoxazoline **8** and product formation was detected within 2 h. During these transformations Pd-black was not observed. When using these conditions product **23** was isolated after 2 h reaction time, filtration through a pad of Celite followed by column chromatography in 30% (Cl_3SiH) and 70% (Ph_3SiH, Table 3,

entry 5) yield, respectively. Also the yield of **25** was improved by using Ph_3SiH (Table 3, entry 6). However, starting from the isoxazolines **14**, **15** and **29** shown in Scheme 4 generally moderate yields were obtained using either Et_3SiH at room temperature (**27**: 40%, **28**: 35%, **30**: 31%) or Ph_3SiH at 40 °C.



Scheme 4. Synthesis of piperidino-enaminones **27**, **28** and **30**

So far, yields were not systematically optimized regarding work-up or purification by chromatography. The role of the silane and its substitution pattern needs further investigations. Also the influence of the solvents and of the catalytic quantity of $Pd(PPh_3)_4$ was not fully evaluated or optimized. However triethylamine proved to have no influence on the catalytic active system. Thus, for all reactions at higher temperature a competing acid- or base-catalyzed degradation of the Δ^4-isoxazolines to the enaminoketones besides the metal-mediated reaction pathway should be exluded.[42] In analogy to the catalytic process reported by Noyori for endoperoxides the N-O-bond cleavage of C3-*H*-substituted bicyclic Δ^4-isoxazolines is proposed to proceed via the reaction pathway shown in Figure 2.

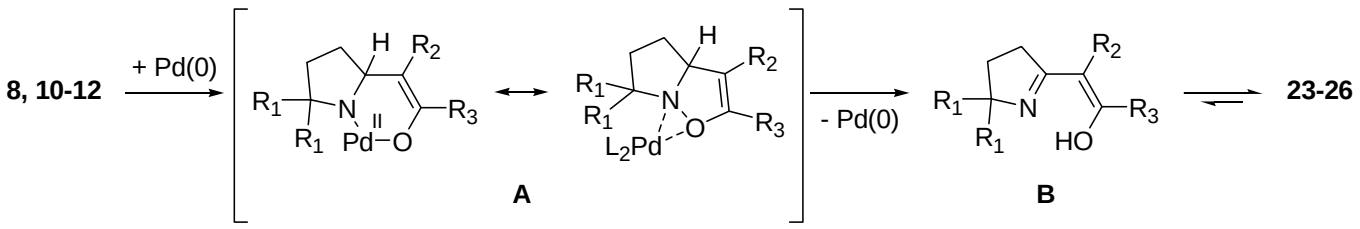


Figure 2. Proposed reaction pathway for the Pd(0)-promoted N-O-bond cleavage of C3-*H* Δ^4-isoxazolines

Starting from the initially formed intermediate **A** a formal β-elimination is furnishing the enolimines **B** followed by tautomerization to the enaminoketones.

CONCLUSION

In this paper the synthesis of aliphatic nitroso compounds containing an enone subunit is described starting from proline-derived bicyclic Δ^4-isoxazolines by oxidative N-O-bond cleavage using *m*-CPBA. Furthermore pyrrolidino- and piperidino-substituted enones are prepared from C3-*H*-substituted bicyclic Δ^4-isoxazolines by N-O-bond cleavage using $Pd(PPh_3)_4$/silane. The mild methods presented are broadening the field of applications for cycloaddition/N-O-bond cleavage protocols in organic synthesis.

EXPERIMENTAL

1. General remarks: All reactions were performed under nitrogen atmosphere. Solvents were dried before use according to standard procedures. ^{1}H-NMR spectra were recorded on a 200 MHz spectrometer and residual solvent protons were used as internal standard. All chemical shifts (δ) are given in ppm relatively to tetramethylsilan (TMS) and coupling constants (*J*) in Hz. The number of protons was determined by integration of the signals. Multiplicities of the signals were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. ^{13}C-NMR spectra were recorded at 50.3 MHz. Solvents are mentioned for the particular substances. Infrared spectra were recorded as ATR (Attenuated Total Reflectance) and are reported as wave numbers υ in cm^{-1}. The samples for high-resolution mass spectra (HR-MS) were ionized at an ionization potential of 70 eV. Nitrones **1**, **2**, **3** and **13** were prepared according to literature procedures.[26,27] Nitrone **4** and alkynes were purchased from Aldrich and used without further purification. Nitrone **3** was used without further chromatographic purification. Isoxazoline **29** was prepared according to the literature.[43] The isomeric E/Z ratios of compound **23**, **24** and **28** were determined by ^{1}H-NMR spectroscopy according to the literature.[44]

2. General procedure for the synthesis of isoxazolines 5-12 and 14–15: To a solution of the nitrone **1**–**4** or **13** in dichloromethane (CH_2Cl_2) the respective alkyne was added and the solution was stirred at the appropriate temperature until complete consumption of the nitrone (TLC-monitoring). The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel. The isoxazolines **5**–**12** and **14**–**15** were isolated as colorless viscous oils.

2.1 3a-Benzyl 3-ethyl 2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3,3a-dicarboxylate (5): The solution of nitrone **1** (3.21 g, 0.015 mol, 1 equiv) and ethyl 3-phenylpropiolate (10.44 g, 0.06 mol, 4 equiv) in CH_2Cl_2 (5 mL) was stirred for 16 h at rt. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **5** was obtained in 90% yield (5.30 g, 0.013 mol). R_f 0.48 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.88-7.28 (m, 10H), 5.34 (d, *J* = 12.68 Hz, 1H), 5.10 (d, *J* = 12.68 Hz, 1H), 4.08-3.84 (m, 2H), 3.46–3.39 (m, 2H), 2.86-2.72 (m, 1H), 2.29-2.17 (m,

1H), 1.97-1.91 (m, 2H), 1.01 (t, *J* = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 171.3, 163.6, 163.1, 135.8, 131.0, 129.3, 128.4, 128.0, 127.8, 126.8, 103.3, 83.4, 67.2, 60.3, 59.9, 35.0, 23.5, 13.8. IR (ATR, υ): 3100-2850, 1742, 1710, 1689, 1639. HR-MS Calcd for $C_{23}H_{23}NO_5$: m/e 393.1576. Found: m/e 393.1577.

2.2 3a-Benzyl 3-ethyl 2-methyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3,3a-dicarboxylate (6): The solution of nitrone **1** (3.21 g, 0.015 mol, 1 equiv) and ethyl but-2-ynoate (6.72 g, 0.06 mol, 4 equiv) in CH_2Cl_2 (5 mL) was stirred at rt for 7 d. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **6** was obtained in 83% yield (4.12 g, 0.012 mol). R_f 0.50 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.40-7.20 (m, 5H), 5.32 (d, *J* = 12.2 Hz, 1H), 5.08 (d, *J* = 12.2 Hz, 1H), 4.11-3.88 (m, 2H), 3.32-3.26 (m, 2H), 2.70-2.56 (m, 1H), 2.20 (s, 3H), 2.13-2.04 (m, 1H), 1.90-1.77 (m, 2H), 1.07 (t, *J* = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 171.4, 165.7, 163.8, 135.8, 128.3, 127.9, 127.7, 103.2, 82.0, 67.1, 60.2, 59.7, 34.4, 23.5, 14.0, 12.1. IR (ATR, υ): 3100-2850, 1739, 1704, 1651. HR-MS Calcd for $C_{18}H_{21}NO_5$: m/e 331.1419. Found: m/e 331.1423. Anal. Calcd for $C_{18}H_{21}NO_5$ (331.36): C 65.24, H 6.39, N 4.23. Found: C 65.30, H 6.11, N 4.12.

2.3 3-Ethyl 3a-methyl 2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3,3a-dicarboxylate (7): The solution of nitrone **2** (1.07 g, 0.007 mol, 1 equiv) and ethyl 3-phenylpropiolate (5.22 g, 0.03 mol, 4 equiv) in CH_2Cl_2 (5 mL) was stirred for 16 h at rt. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **7** was obtained in 85% yield (2.00 g, 0.006 mol). R_f 0.28 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.72-7.38 (m, 5H), 4.23-4.01 (m, 2H), 3.76 (s, 3H), 3.42–3.38 (m, 2H), 2.87-2.70 (m, 1H), 2.31-2.19 (m, 1H), 2.05-1.90 (m, 2H), 1.12 (t, *J* = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 172.1, 163.6, 163.1, 131.0, 129.4, 127.8, 126.9, 103.5, 83.3, 60.3, 60.0, 53.0, 35.1, 23.5, 14.0. IR (ATR, υ): 3100-2850, 1735, 1699, 1653. HR-MS Calcd for $C_{17}H_{19}NO_5$: m/e 317.1263. Found: m/e 317.1278.

2.4 Ethyl 2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (8): The solution of nitrone **3** (1.27 g, 0.015 mol, 1 equiv) and ethyl 3-phenylpropiolate (10.44 g, 0.06 mol, 4 equiv) in CH_2Cl_2 (2 mL) was stirred at rt for 16 h. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **8** was obtained in 53% yield (2.05 g, 7.91 mmol) over two steps including nitrone synthesis. R_f 0.39 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.78-7.29 (m, 5H), 4.95 (t, *J* = 4.88 Hz, 1H), 4.11 (q, *J* = 7.32 Hz, 2H), 3.58-3.47 (m, 1H), 3.21-3.07 (m, 1H), 2.13-1.99 (m, 2H), 1.87-1.73 (m, 2H), 1.16 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 163.8, 162.6, 130.6, 129.2, 127.6, 127.3, 103.5, 71.4, 59.9, 59.7, 33.4, 22.4, 14.1. IR (ATR, υ): 3100-2850, 1706, 1686,

1636. HR-MS Calcd for $C_{15}H_{17}NO_3$: m/e 259.1208. Found: m/e 259.1211.

2.5 Ethyl 2-methyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (9): The solution of nitrone **3** (1.27 g, 0.015 mol, 1 equiv) and ethyl but-2-ynoate (6.72 g, 0.06 mol, 4 equiv) in CH_2Cl_2 (2 mL) was stirred 7 d at rt. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **9** was obtained in 51% yield (1.50 g, 7.61 mmol) over two steps including nitrone synthesis. R_f 0.52 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 4.70-4.65 (m, 1H), 4.16-4.02 (m, 2H), 3.39–3.28 (m, 1H), 3.05-2.90 (m, 1H), 2.06 (s, 3H), 1.89-1.79 (m, 2H), 1.69-1.59 (m, 2H), 1.18 (t, J = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 164.5, 164.4, 103.0, 69.8, 59.7, 59.4, 32.7, 22.3, 14.2, 11.8. IR (ATR, υ): 3100-2850, 1701, 1650. HR-MS Calcd for $C_{10}H_{15}NO_3$: m/e 197.1051. Found: m/e 197.1055.

2.6 Ethyl 6,6-dimethyl-2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (10): The solution of nitrone **4** (0.41 g, 3.62 mmol, 1 equiv) and ethyl 3-phenylpropiolate (2.51 g, 14.5 mmol, 4 equiv) in CH_2Cl_2 (2 mL) was stirred at rt for 16 h. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 3:1). Compound **10** was obtained in 91% yield (0.94 g, 3.27 mmol). R_f 0.58 (pentane/EtOAc 3:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.79-7.30 (m, 5H), 4.98 (m, 1H), 4.13 (q, J = 7.32 Hz, 2H), 2.25-2.20 (m, 1H), 2.00-1.97 (m, 1H), 1.77-1.67 (m, 2H), 1.38 (s, 3H), 1.26 (t, J = 7.32 Hz, 3H), 1.14 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): (ppm) = 163.9, 161.9, 130.5, 129.3, 127.7, 127.5, 104.7, 70.6, 70.0, 59.7, 34.6, 33.4, 26.2, 23.4, 14.2. IR (ATR, υ): 3100-2850, 1705, 1688. HR-MS Calcd for $C_{17}H_{21}NO_3$: m/e 287.1521. Found: m/e 287.1522.

2.7 Ethyl 2,6,6-trimethyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole-3-carboxylate (11): The solution of nitrone **4** (1.69 g, 0.015 mol, 1 equiv) and ethyl but-2-ynoate (6.72 g, 0.06 mol, 4 equiv) in CH_2Cl_2 (2 mL) was stirred for 7 d at rt. Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 10:1). Compound **11** was obtained in 44% yield (1.50 g, 6.65 mmol). R_f 0.50 (pentane/EtOAc 10:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 4.78-4.72 (m, 1H), 4.19-4.07 (m, 2H), 2.23–2.02 (m, 1H), 2.11 (d, J = 0.98 Hz, 3H), 1.83-1.70 (m, 1H), 1.63-1.55 (m, 2H), 1.29 (s, 3H), 1.23 (t, J = 6.84 Hz, 3H), 1.05 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 164.8, 164.7, 104.4, 69.5, 69.1, 59.5, 34.4, 32.7, 26.1, 23.3, 14.4, 11.8. IR (ATR, υ): 3100-2850, 1705, 1655. HR-MS Calcd for $C_{12}H_{19}NO_3$: m/e 225.1365. Found: m/e 225.1369.

2.8 6,6-Dimethyl-2-phenyl-3a,4,5,6-tetrahydropyrrolo[1,2-*b*]isoxazole (12): The solution of nitrone **4** (0.4 g, 3.53 mmol, 1 equiv) and phenylacetylene (1.44 g, 14.4 mmol, 4 equiv) in CH_2Cl_2 (2 mL) was

stirred at rt for 7 d. Column chromatography was performed with pentane/EtOAc (20:1). Compound **12** was obtained in 86% yield (0.65 g, 3.02 mmol). R_f 0.27 (pentane/EtOAc 20:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.57-7.27 (m, 5H), 5.15 (d, *J* = 2.44 Hz, 1H), 4.81-4.76 (m, 1H), 2.17-2.00 (m, 1H), 1.80-1.56 (m, 3H), 1.38 (s, 3H), 1.14 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 152.5, 128.9, 128.5, 128.2, 125.4, 96.6, 70.3, 69.2, 34.8, 32.6, 26.9, 23.3. IR (ATR, υ): 3100-2850, 1682. HR-MS Calcd for $C_{14}H_{17}NO$: m/e 215.1310. Found: m/e 215.1310. Anal. Calcd for $C_{14}H_{17}NO$ (215.29): C 78.10, H 7.96, N 6.51. Found: C 77.99, H 7.87, N 6.37.

2.9 6,6-Dimethyl-2-phenyl-6,7-dihydro-3a*H*-isoxazolo[2,3-*a*]pyridin-4(5*H*)-one (14): Phenylacetylene (1.44 g, 14.16 mmol, 4 equiv) was added to a solution of nitrone **13** (0.50 g, 3.54 mmol, 1 equiv) in CH_2Cl_2 (2 mL) and stirred for 5 d at rt. Column chromatography was performed with pentane/EtOAc (10:1). Compound **14** was obtained in 84% yield (0.72 g, 2.96 mmol). R_f 0.40 (pentane/EtOAc 10:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.61-7.39 (m, 5H), 5.17 (d, *J* = 1.96 Hz, 1H), 4.92 (s, 1H), 3.23 (d, *J* = 10.24 Hz, 1H), 2.97 (d, *J* = 10.24 Hz, 1H), 2.27 (s, 2H), 1.06 (s, 3H), 1.02 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 206.1, 155.2, 129.4, 128.4, 128.0, 125.6, 92.1, 74.2, 61.5, 50.5, 30.6, 28.5, 25.4. IR (ATR, υ): 3400-2850, 1715, 1609. HR-MS Calcd for $C_{15}H_{17}NO_2$: m/e 243.1259. Found: m/e 243.1267.

2.10 6,6-Dimethyl-4-oxo-2-phenyl-4,5,6,7-tetrahydro-3a*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylic acid ethyl ester (15): The solution of nitrone **13** (0.5 g, 3.54 mmol, 1 equiv) and phenylpropynoic acid ethyl ester (0.79 g, 7.08 mmol, 2 equiv.) in CH_2Cl_2 (5 mL) was stirred at rt for 16 h. Flash chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **15** was obtained in 91% yield (1.21 g, 3.22 mmol). R_f 0.27 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.81-7.39 (m, 5H), 5.01 (s, 1H), 4.15-4.07 (m, 2H), 3.30 (d, *J* = 11.22 Hz, 1H), 3.18 (d, *J* = 11.22 Hz, 1H), 2.44 (d, *J* = 13.66 Hz, 1H), 2.28 (d, *J* = 13.66 Hz, 1H), 1.16 (t, *J* = 7.32 Hz, 3H), 1.07 (s, 3H), 1.03 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 204.0, 164.2, 163.1, 131.4, 129.7, 127.8, 126.8, 100.7, 73.8, 61.4, 60.4, 51.0, 33.4, 28.4, 25.5, 13.8. IR (ATR, υ): 3100-2850, 1729, 1707, 1626. HR-MS Calcd for $C_{18}H_{21}NO_4$: m/e 315.1471. Found: m/e 315.1477.

3. General procedure for the oxidative N-O-bond cleavage of isoxazolines 5-11: To a solution of the isoxazolines **5-11** in CH_2Cl_2, were added 1.1 equiv of *m*-CPBA at the temperature indicated in Table 2, and the reaction mixture was stirred until complete consumption of the starting material (TLC-monitoring, see Table 2). The reaction mixture was washed twice with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$). The solvent was removed in vacuo and the crude products **16**–**18** and **21**–**22** were purified by

column chromatography on silica gel.

3.1 4-Benzyl 1-ethyl 2-benzoyl-3-(3-nitrosopropyl)fumarate (16): Product **16** was synthesized according to the general procedure starting from isoxazoline **5** (0.56 g, 1.5 mmol, 1 equiv) and *m*-CPBA (0.29 g, 1.7 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) at a) –30 °C, 16 h or b) rt, 5 min (Table 2, entries 1–2). Column chromatography was performed with CH_2Cl_2/MeOH (40:1). Compound **16** was obtained in a) 87% yield (0.53 g, 1.30 mmol) or b) 85% yield (0.52 g, 1.27 mmol) as a white foamy solid. R_f 0.52 (CH_2Cl_2/MeOH 40:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.90-7.31 (m, 10H), 5.27 (s, 2H), 4.07-3.96 (m, 4H), 2.34 (t, J = 6.84 Hz, 2H), 2.15-1.90 (m, 2H), 1.00 (t, J = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 191.4, 166.8, 162.8, 144.6, 135.4, 134.6, 134.4, 134.0, 128.8, 128.6, 128.3, 128.2, 128.2, 67.4, 61.5, 57.0, 28.4, 22.2, 13.3. IR (ATR, υ): 3100-2850, 1724, 1672, 1536, 1243. HR-MS Calcd for $C_{23}H_{23}NO_6$ (monomer): m/e 409.1525. Found: m/e 409.1539. A suitable crystal of the dimer **16** for X-ray analysis (see Fig. 1) was obtained from a CH_2Cl_2 solution, showing the *Z*-geometry of the double bond and the *E*-configuration of the diazo-dioxyde moiety.

3.2 4-Benzyl 1-ethyl 2-acetyl-3-(3-nitrosopropyl)fumarate (17): Product **17** was synthesized according to the general procedure starting from isoxazoline **6** (0.49 g, 1.5 mmol, 1 equiv) and *m*-CPBA (0.29 g, 1.7 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) at –30 °C (16 h). Column chromatography was performed with CH_2Cl_2/MeOH (30:1). Compound **17** was obtained in 45% yield (0.23 g, 0.67 mmol) as a white foamy powder. R_f 0.20 (CH_2Cl_2/MeOH 30:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.37-7.30 (m, 5H), 5.21 (s, 2H), 4.21 (t, J = 6.82 Hz, 2H), 4.09 (q, J = 6.84 Hz, 2H), 2.48 (t, J = 7.32 Hz, 2H), 2.31 (s, 3H), 2.10-1.99 (m, 2H), 1.18 (t, J = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 198.1, 167.1, 163.9, 144.0, 136.7, 134.7, 128.6, 128.6, 67.8, 61.9, 57.6, 30.4, 28.1, 23.0, 13.8. IR (ATR, υ): 3100-2850, 1727, 1704, 1642, 1536, 1249. HR-MS Calcd for $C_{18}H_{21}NO_6$ (monomer): m/e 347.1369. Found: m/e 347.1370.

3.3 1-Ethyl 4-methyl 2-benzoyl-3-(3-nitrosopropyl)fumarate (18): Product **18** was synthesized according to the general procedure starting from isoxazoline **7** (0.47 g, 1.5 mmol, 1 equiv) and *m*-CPBA (0.29 g, 1.7 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) at a) –30 °C, 16 h or b) rt, 5 min (Table 2, entries 4–5). Column chromatography was performed with CH_2Cl_2/MeOH (40:1). Compound **18** was obtained in a) 85% yield (0.42 g, 1.27 mmol) or b) 80% yield (0.39 g, 1.19 mmol) as a yellow viscous oil. R_f 0.38 (CH_2Cl_2/MeOH 40:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 8.13-7.31 (m, 5H), 4.17-4.06 (m, 4H), 3.87 (s, 3H), 2.33 (t, J = 6.84 Hz, 2H), 2.02-1.95 (m, 2H), 1.08 (t, J = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 191.8, 167.9, 163.1, 145.3, 135.9, 134.4, 134.2, 129.2, 128.9, 61.9, 57.4, 52.7, 28.8, 22.6, 13.7. IR (ATR, υ): 3100-2850, 1720, 1672, 1643, 1536, 1230. HR-MS Calcd for $C_{17}H_{19}NO_6$ (monomer): m/e

333.1212. Found: m/e 333.1215.

3.4 5-(3-Ethoxy-1-hydroxy-3-oxo-1-phenylprop-1-en-2-yl)-2,2-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (21): Product **21** was synthesized according to the general procedure starting from isoxazoline **10** (0.10 g, 0.35 mmol, 1 equiv) and *m*-CPBA (0.066 g, 0.37 mmol, 1.1 equiv) in CH_2Cl_2 (10 mL) at –30 °C (2 h). Column chromatography was performed with CH_2Cl_2. Compound **21** was obtained in 71 % yield (0.075 g, 0.25 mmol, ratio keto/enol = 20/80 in $CDCl_3$) as a yellow viscous oil. R_f 0.13 (CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): *enol*: 13.89 (br, 1H), 7.99-7.23 (m, 5H), 3.76 (q, *J* = 7.32 Hz, 2H), 3.01 (t, *J* = 7.80 Hz, 2H), 2.02 (t, *J* = 7.80 Hz, 2H), 1.40 (s, 6H), 0.69 (t, *J* = 7.32 Hz, 3H). *keto*: 7.49-7.30 (m, 5H), 6.01 (s, 1H), 4.17 (q, *J* = 7.32 Hz, 2H), 2.76-2.60 (m, 1H), 2.39-2.23 (m, 1H), 1.94-1.65 (m, 1H), 1.34 (s, 3H), 1.20 (t, *J* = 7.32 Hz, 3H), 1.16 (s, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): *enol*: 191.9, 166.4, 155.7, 134.4, 129.4, 127.5, 127.0, 97.5, 71.2, 60.0, 33.3, 29.2, 25.2, 13.1. *keto*: 168.4, 141.5, 134.4, 134.6, 128.8, 128.4, 74.0, 61.7, 52.7, 32.0, 25.5, 25.0, 24.3, 13.8. IR (ATR, υ): 3100-2850, 1735, 1698, 1576. HR-MS Calcd for $C_{17}H_{21}NO_4$: m/e 303.1471. Found: m/e 303.1478.

3.5 5-(1-Ethoxy-3-hydroxy-1-oxobut-2-en-2-yl)-2,2-dimethyl-3,4-dihydro-2*H*-pyrrole 1-oxide (22): Product **22** was synthesized according to the general procedure starting from isoxazoline **11** (0.20 g, 0.88 mmol, 1 equiv) and *m*-CPBA (0.17 g, 0.97 mmol, 1.1 equiv) in CH_2Cl_2 (5 mL) at –30 °C (2 h). Compound **22** was obtained in 96% yield (0.20 g, 0.84 mmol, ratio keto/enol = 0/100 in $CDCl_3$) as a white foamy solid with a purity of ≥ 95% as determined by ^{1}H NMR spectroscopy. R_f 0.1 (CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 4.07 (q, *J* = 7.32 Hz, 2H), 2.94 (t, *J* = 7.80 Hz, 2H), 2.25 (s, 3H), 1.95 (t, *J* = 7.80 Hz, 2H), 1.32 (s, 6H), 1.18 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 189.0, 167.2, 156.5, 96.9, 71.1, 59.7, 33.5, 30.1, 27.1, 25.1, 14.0. IR (ATR, υ): 3100-2850, 1731, 1701, 1574. HR-MS Calcd for $C_{12}H_{19}NO_4$: m/e 241.1314. Found: m/e 241.1315.

4. General procedure for the preparation of nitro compounds 19 and 20: To a solution of a) isoxazoline **5** or **7** (1.5 mmol) or b) nitroso compound **16** or **18** (0.75 mmol) in benzene (10 mL) was added *m*-CPBA a) 4.95 mmol (3.3 equiv.) or b) 1.7 mmol (2.2 equiv.) and the reaction mixture was refluxed for 6 h at 80 °C (TLC-and NMR-monitoring). The resulting solution was washed twice with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was saturated with NaCl and extracted twice with EtOH/$CHCl_3$ (30 ml, 1:2). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuo. The crude products **19** and **20** were purified by column chromatography on silica gel with CH_2Cl_2.

4.1 4-Benzyl 1-ethyl 2-benzoyl-3-(3-nitropropyl)maleate (19): Product **19** was synthesized according

to the general procedure starting from a) isoxazoline **5** (0.56 g, 1.5 mmol, 1 equiv) and *m*-CPBA (0.85 g, 4.95 mmol, 3.3 equiv) or b) nitroso compound **16** (0.61 g, 0.75 mmol, 1 equiv) and *m*-CPBA (0.29 g, 1.7 mmol, 2.2 equiv.) in benzene (10mL) at 80 °C (6 h). Compound **19** was obtained in a) 97% yield (0.62 g, 1.46 mmol) or b) 96 % yield (0.61 g, 1.44 mmol) as a yellow viscous oil. R_f 0.39 (CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 8.15-7.34 (m, 10H), 5.29 (s, 2H), 4.26 (t, J = 7.32 Hz, 2H), 4.03 (q, J = 6.84 Hz, 2H), 2.35 (t, J = 6.84 Hz, 2H), 2.11–2.00 (m, 2H), 1.01 (t, J = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 191.7, 166.9, 162.9, 143.9, 135.5, 135.2, 134.6, 134.4, 129.0, 128.9, 128.6, 128.5, 128.5, 73.5, 67.8, 61.9, 28.1, 24.6, 13.5. IR (ATR, υ): 3100-2800, 1725, 1672, 1552. HR-MS Calcd for $C_{23}H_{23}NO_7$: m/e 425.1474. Found: m/e 425.1479.

4.2 1-Ethyl 4-methyl 2-benzoyl-3-(3-nitropropyl)maleate (20): Product **20** was synthesized according to the general procedure starting from a) isoxazoline **7** (0.47 g, 1.5 mmol, 1 equiv) and *m*-CPBA (0.85 g, 4.95 mmol, 3.3 equiv) or b) nitroso compound **18** (0.25 g, 0.75 mmol, 1 equiv) and *m*-CPBA (0.29 g, 1.7 mmol, 2.2 equiv) in benzene (10 mL) at 80 °C (6 h). Compound **20** was obtained in a) 93 % yield (0.49 g, 1.40 mmol) or b) 91% yield (0.48 g, 1.37 mmol) as a yellow viscous oil. R_f = 0.73 (CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 7.90-7.43 (m, 5H), 4.33 (t, J = 6.84 Hz, 2H), 4.12 (q, J = 6.84 Hz, 2H), 3.87 (s, 3H), 2.36 (t, J = 7.80 Hz, 2H), 2.31–2.11 (m, 2H), 1.08 (t, J = 6.84 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 191.8, 167.7, 163.0, 144.3, 135.7, 135.1, 134.5, 129.0, 128.8, 73.7, 62.0, 52.8, 28.2, 24.7, 13.7. IR (ATR, υ): 3063-2848, 1725, 1672, 1552, 1247. HR-MS Calcd for $C_{17}H_{19}O_7N$: m/e 350.1239 (MH^+). Found: m/e 350.1249 (MH^+).

5. General procedure for the palladium-/silane-catalyzed synthesis of enaminones 23–28 and 30: An oven-dried flask was charged with CH_2Cl_2 (2 mL), isoxazoline, Pd-catalyst (20 mol%) and silane (4-10 equiv). The flask was evacuated and backfilled with nitrogen. The reaction mixture was either stirred at rt or 40°C until complete consumption of the starting material (TLC monitoring). After filtration through a pad of Celite the solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel. All enaminones were isolated as viscous oils.

5.1 Ethyl 3-oxo-3-phenyl-2-(pyrrolidin-2-ylidene)-propanoate (23): Following the general procedure isoxazoline **8** (130 mg, 0.5 mmol, 1 equiv), $Pd(PPh_3)_4$ (115 mg, 0.10 mmol, 0.2 equiv) and $HSiEt_3$ (233 mg, 2.0 mmol, 4 equiv) were used at rt (16 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **23** was obtained in 10% yield (13 mg, 0.05 mmol) as a viscous oil. The application of isoxazoline **8** (130 mg, 0.5 mmol, 1 equiv), $Pd(PPh_3)_4$ (115 mg, 0.10 mmol, 0.2 equiv) and $HSiCl_3$ (677 mg, 5 mmol, 10 equiv) at 40 °C (2 h) followed by column

chromatography with pentane/EtOAc (gradient from 20:1 to 5:1) yielded 30% (39 mg, 0.15 mmol) of **23**. The application of isoxazoline **8** (130 mg, 0.5 mmol, 1 equiv), $Pd(PPh_3)_4$ (115 mg, 0.10 mmol, 0.2 equiv) and $HSiPh_3$ (1.3 g, 5 mmol, 10 equiv.) at 40 °C (2 h) followed by column chromatography pentane/EtOAc (gradient from 20:1 to 5:1) gave **23** in 70% yield (90 mg, 0.35 mmol) as a mixture of *E*:*Z* isomers (*E*:*Z* ratio = 71:29, ^{1}H-NMR of the purified product). R_f 0.39 (pentane/EtOAc 5/1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): *E*-isomer: 10.96 (br, 1H), 7.54-7.28 (m, 5H), 3.79 (q, *J* = 7.32 Hz, 2H), 3.20 (t, *J* = 7.80 Hz, 2H), 2.04 (t, *J* = 7.32 Hz, 2H), 0.70 (t, *J* = 7.32 Hz, 3H). *Z*-isomer: 9.34 (br, 1H), 7.55-7.28 (m, 5H), 3.81 (q, *J* = 7.32 Hz, 2H), 3.10 (t, *J* = 7.80 Hz, 2H), 2.10 (t, *J* = 7.32 Hz, 2H), 0.70 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): *E*-isomer: 194.8, 174.1, 169.2, 143.6, 129.3, 127.5, 126.5, 97.9, 59.3, 48.0, 33.9, 21.0, 13.3. *Z*-isomer: 195.1, 173.4, 170.1, 143.0, 130.3, 127.8, 127.5, 95.5, 58.9, 47.4, 33.3, 21.7, 13.4. IR (ATR, υ): 3300-3200, 3100-2850, 1688, 1660, 1597, 1578. HR-MS Calcd for $C_{15}H_{17}NO_3$: m/e 259.1208. Found: m/e 259.1210. Anal. Calcd for $C_{15}H_{17}NO_3$ (259.30): C 69.48, H 6.61, N 5.40. Found: C 69.20, H 6.60, N 5.16.

5.2 Ethyl 2-(5,5-dimethylpyrrolidin-2-ylidene)-3-oxo-3-phenylpropanoate (24): According to the general procedure isoxazoline **10** (130 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv) were used at rt (16 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **24** was isolated in 56% yield (72 mg, 0.25 mmol) as a mixture of *E*:*Z* isomers (*E*:*Z* ratio = 72:28, ^{1}H-NMR of the purified product). R_f 0.17 (pentane/EtOAc 6:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): *E*-isomer: 10.88 (br, 1H), 7.55-7.28 (m, 5H), 3.79 (q, *J* = 7.32 Hz, 2H), 3.24 (t, *J* = 7.8 Hz, 2H), 1.91 (t, *J* = 7.32 Hz, 2H), 1.36 (s, 6H), 0.69 (t, *J* = 7.32 Hz, 3H). *Z*-isomer: 9.25 (br, 1H), 7.55-7.28 (m, 5H), 3.83 (q, *J* = 7.32 Hz, 2H), 3.18 (t, *J* = 7.8 Hz, 2H), 1.85 (t, *J* = 7.32 Hz, 2H), 1.35 (s, 6H), 0.70 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): *E*-isomer: 194.8, 171.9, 169.4, 143.7, 129.4, 127.5, 126.7, 97.4, 63.4, 59.4, 35.5, 33.6, 28.5, 13.4. *Z*-isomer: 195.2, 171.5, 170.3, 143.2, 130.4, 127.9, 127.6, 94.9, 62.6, 58.9, 36.0, 33.1, 28.4, 13.5. IR (ATR, υ): 3300-3200, 3100-2850, 1688, 1660, 1597, 1578. HR-MS Calcd for $C_{17}H_{21}NO_3$: m/e 287.1521. Found: m/e 287.1522.

5.3 (*E*)-Ethyl 2-(5,5-dimethylpyrrolidin-2-ylidene)-3-oxobutanoate (25): Following the general procedure isoxazoline **11** (101 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv) were used at rt (16 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **25** was obtained in 35% yield (35 mg, 0.16 mmol) as *E* isomer. The application of isoxazoline **11** (136 mg, 0.6 mmol, 1 equiv), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol, 0.2 equiv) and $HSiPh_3$ (1.56 g, 6 mmol, 10 equiv.) at 40 °C (2 h) followed by column chromatography with pentane/EtOAc (gradient from 20:1 to 5:1) yielded 53% (72 mg, 0.32 mmol) of **25**

as *E*-isomer. R_f 0.17 (pentane/EtOAC 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 11.56 (br., 1H), 4.17 (q, *J* = 7.32 Hz, 2H), 3.17 (t, *J* = 7.32 Hz, 2H), 2.38 (s, 3H), 1.81 (t, *J* = 7.8 Hz, 2H), 1.32 (s, 6H), 1.26 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 197.7, 172.9, 168.8, 97.4, 63.1, 59.4, 35.3, 34.7, 30.8, 28.4, 14.4. IR (ATR, υ): 3300-3200, 3100-2850, 1688, 1658, 1597, 1577. HR-MS Calcd for $C_{12}H_{19}NO_3$: m/e 225.1365. Found: m/e 225.1366.

5.4 (*Z*)-2-(5,5-Dimethylpyrrolidin-2-ylidene)-1-phenylethanone (26): Following the general procedure isoxazoline **12** (96 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv) were used at rt (16 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 6:1). Compound **26** was obtained in 69% yield (67 mg, 0.31 mmol) as *Z*-isomer. R_f 0.46 (pentane/EtOAc 6:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 10.19 (br., 1H), 7.87-7.83 (m, 2H), 7.39-7.35 (m, 3H), 5.69 (s, 1H), 2.79 (t, *J* = 7.82 Hz, 2H), 1.84 (t, *J* = 7.82 Hz, 2H), 1.34 (s, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 187.8, 167.2, 140.2, 130.4, 128.1, 126.9, 85.8, 62.7, 35.6, 32.4, 28.6. IR (ATR, υ): 3260, 3100-2850, 1613, 1580, 1528. HR-MS Calcd for $C_{14}H_{17}NO$: m/e 215.1310. Found: m/e 215.1310. Anal. Calcd for $C_{14}H_{17}NO$ (215.29): C 78.10, H 7.96, N 6.51. Found: C 77.79, H 7.80, N 6.31.

5.5 (*Z*)-5,5-Dimethyl-2-(2-oxo-2-phenylethylidene)piperidin-3-one (27): According to the general procedure isoxazoline **14** (109 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv.) were used at rt (3.5 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **27** was obtained in 40% (43 mg, 0.18 mmol) as *Z*-isomer. R_f 0.53 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 10.98 (br, 1H), 7.94-7.40 (m, 5H), 6.55 (s, 1H), 3.30 (d, *J* = 2.92 Hz, 2H), 2.48 (s, 2H), 1.10 (s, 6H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): 194.5, 191.2, 150.4, 143.4, 131.5, 128.3, 127.2, 88.4, 52.3, 50.9, 32.6, 26.2. IR (ATR, υ): 3300, 3100-2850, 1714, 1610. HR-MS Calcd for $C_{15}H_{17}NO_2$: m/e 243.1259. Found: m/e 243.1260.

5.6 Ethyl 2-(5,5-dimethyl-3-oxopiperidin-2-ylidene)-3-oxo-3-phenylpropanoate (28): Following the general procedure isoxazoline **15** (141 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv) were used at rt (5 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **28** was obtained in 35% yield (49 mg, 0.16 mmol). According to the general procedure isoxazoline **15** (189 mg, 0.6 mmol, 1 equiv), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol, 0.2 equiv) and $HSiPh_3$ (1.56 g, 6 mmol, 10 equiv.) were used at 40 °C (2 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **28** was isolated in 35% yield (66 mg, 0.21 mmol) as a mixture of *E*:*Z* isomers (*E*:*Z* ratio = 7:93, ^{1}H-NMR of the purified product). R_f 0.39 (pentane/EtOAc 5:1). ^{1}H NMR (200 MHz, $CDCl_3$, δ): *E*-isomer: 11.79

(br, 1H), 7.87-7.34 (m, 5H), 3.98 (q, *J* = 7.32 Hz, 2H), 3.34 (d, *J* = 1.96 Hz, 2H), 2.55 (s, 2H), 1.21 (s, 6H), 0.99 (t, *J* = 7.32 Hz, 3H). *Z*-isomer: 9.25 (br, 1H), 7.87-7.34 (m, 5H), 4.06 (q, *J* = 7.33 Hz, 2H), 3.28 (d, *J* = 2.44 Hz, 2H), 2.37 (s, 2H), 1.07 (s, 6H), 1.03 (t, *J* = 7.32 Hz, 3H). ^{13}C-NMR (50.3 MHz, $CDCl_3$, δ): *E*-isomer: 194.6, 169.3, 153.1, 141.2, 130.1, 127.9, 126.6, 102.9, 61.1, 52.7, 51.2, 33.4, 26.4, 13.5. *Z*-isomer: 193.9, 168.6, 149.5, 138.9, 132.1, 128.7, 128.5, 99.4, 60.1, 52.6, 51.2, 32.5, 26.2, 14.0. IR (ATR, υ): 3500-3200, 3100-2850, 1738, 1648, 1628, 1597. HR-MS Calcd for $C_{18}H_{21}NO_4$: m/e 315.1471. Found: m/e 315.1471.

5.7 (*Z*)-2-(3,4-Dihydroisoquinolin-1(2*H*)-ylidene)-1-phenylethanone (30): Following the general procedure isoxazoline **29** (112 mg, 0.45 mmol, 1 equiv), $Pd(PPh_3)_4$ (108 mg, 0.09 mmol, 0.2 equiv) and $HSiEt_3$ (208 mg, 1.8 mmol, 4 equiv) were used at rt (16 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1). Compound **30** was obtained in 31% yield (34 mg, 0.14 mmol). According to the general procedure isoxazoline **29** (150 mg, 0.6 mmol, 1 equiv), $Pd(PPh_3)_4$ (139 mg, 0.12 mmol, 0.2 equiv) and $HSiPh_3$ (1.56 g, 6 mmol, 10 equiv.) were used at 40 °C (2 h). Column chromatography was performed with pentane/EtOAc (gradient from 20:1 to 5:1) yielded **30** in 30% (44 mg, 0.18 mmol) as *Z*-isomer. R_f 0.25 (pentane/EtOAc 5:1). ^{1}H-NMR (200 MHz, $CDCl_3$, δ): 11.79 (br, 1H), 7.95-7.21 (m, 9 H), 6.33 (s, 1H), 3.54 (dt, *J* = 5.86 Hz, *J* = 3.42 Hz, 2H), 2.95 (t, *J* = 6.82 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$, δ): 188.8, 158.5, 141.0, 136.7, 131.2, 130.5, 129.4, 128.3, 128.2, 127.2, 126.9, 125.6, 87.0, 38.6, 28.4. IR (ATR, υ): 3100-2850, 1706, 1686, 1636. HR-MS Calcd for $C_{17}H_{15}NO$: m/e 249.1154. Found: m/e 249.1155.

ACKNOWLEDGEMENTS

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

REFERENCES (AND NOTES)

1. K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863.
2. S. Kobayashi and K. A. Jørgensen, 'Cycloaddition Reactions in Organic Synthesis', Wiley-VCH, Weinheim, Germany, 2002.
3. A. Padwa and W. H. Pearson, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products', Vol. 1, ed. by A. Padwa, John Wiley & Sons Inc., New York, 2002.
4. T. H. E. Freysoldt, F. Wierschem, and K. Rück-Braun, *Chem. Soc. Rev.*, 2005, **34**, 507.
5. H. M. I. Osborn, N. Gemmell, and L. M. Harwood, *J. Chem. Soc.*, *Perkin Trans. 1*, 2002, 2419.

6. J. Revuelta, S. Cicchi, A. Goti, and A. Brandi, *Synthesis*, 2007, 485.
7. P. Merino, *Science of Synthesis*, 2004, **27**, 511.
8. D. H. Churykau, V. G. Zinovich, and O. G. Kulinkovich, *Synlett*, 2004, 1949.
9. S. H. Jung, J. E. Lee, and H. Y. Koh, *Bull. Korean Chem. Soc.*, 1998, **19**, 33.
10. J. Revuelta, S. Cicchi, and A. Brandi, *Tetrahedron Lett.*, 2004, **45**, 8375.
11. B. M. Trost, L. S. Chupak, and T. Lübbers, *J. Am. Chem. Soc.*, 1998, **120**, 1732.
12. S. Cicchi, A. Goti, A. Brandi, A. Guarna, and F. De Sarlo, *Tetrahedron Lett*., 1990, **31**, 3351.
13. N. R. Natale, *Tetrahedron Lett.*, 1982, **23**, 5009.
14. B. Westermann, A. Walter, U. Flörke, and H.-J. Altenbach, *Org. Lett.*, 2001, **3**, 1375.
15. Sk. A. Ali and M. I. M. Wazeer, *Tetrahedron*, 1993, **49**, 4339; Sk. A. Ali and H. A. Al-Muallem, *Tetrahedron*, 1993, **49**, 7373.
16. F. Wierschem and K. Rück-Braun, *Eur. J. Org. Chem.*, 2004, **11**, 2321; F. Wierschem and K. Rück-Braun, *Z. Naturforsch.*, 2006, **61**, 431.
17. A. Padwa, D. Kline, and J. Perumattam, *Tetrahedron Lett.*, 1987, **28**, 913; A. Padwa, U. Chiacchio, D. N. Kline, and J. Perumattam, *J. Org. Chem.*, 1988, **53**, 2238.
18. G. Schmidt, H.-U. Stracke, and E. Winterfeldt, *Chem Ber.*, 1970, **103**, 3196.
19. J. P. Freeman, *Chem Rev.*, 1983, **83**, 241.
20. A. Liguori, R. Ottana, G. Romeo, G. Sindona, and N. Uccella, *Tetrahedron*, 1988, **44**, 1255.
21. O. Tsuge and M. Noguchi, *Chem. Lett.*, 1977, 749.
22. U. Chiacchio, A. Rescifina, M. A. Chiacchio, G. Romeo, and R. Romeo, *J. Org. Chem.*, 2003, **68**, 3718.
23. O. Tamura, K. Gotanda, J. Yoshino, Y. Morita, R. Terashima, M. Kikushi, T. Miyawaki, N. Mita, M. Yamashita, H. Ishibashi, and M. Sakamoto, *J. Org. Chem.*, 2000, **65**, 8544.
24. J. Marcus, J. Brussee, and A. V. D. Gen, *Eur. J. Org. Chem.*, 1998, 2513.
25. S. Chandrasekhar, B. Nagendra Babu, M. Ahmed, V. Reddy, P. Srihari, B. Jagadeesh, and A. Prabhakar, *Synlett*, 2004, 1303.
26. S. I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda, and S. Watanabe, *J. Org. Chem.*, 1990, **95**, 1736.
27. R. C. Bernotas, J. S. Sabol, L. Sing, and D. Friedrich, *Synlett*, 1999, 653.
28. M. Lager, PhD thesis, TU Berlin, 2005.
29. K. Vancik, V. Simunic-Meznaric, I. Caleta, E. Mestrovic, S. Milovac, K. Mlinaric-Majerski, and J. Veljkovic, *J. Phys. Chem. B.*, 2002, **106**, 1576; S. K. Quek, I. M. Lyapkalo, and H. V. Huynh, *Synthesis*, 2006, 1423; D. H. Churykau and O. K. Kulinkovich, *Synlett*, 2006, 3427.
30. The X-ray structure of compound **16** was measured at the Technical University Berlin on an *AXS Bruker* 3-circle-diffractometer with Mo-K_α-radiation with graphite monochromator. The structure

was solved by direct methods using the program SHELXS-97 and refined against F2 on all data by full-matrix least squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically. $C_{46}H_{46}N_2O_{12}$, *Mr* = 818.88, crystal size: 0.14 mm × 0.31 mm × 0.44 mm, triclinic, space group P-1, *a* = 1028.47 (5) pm, *b* = 1051.28 (5) pm, *c* = 1181.67 (6) pm, α = 69.1620 (10)°, β = 65.011 (2)°, γ = 83.142 (2)°, *V* = 1.08157 (9) nm^3, Z = 2, ρ_{calcd} = 1.251 $mg \cdot m^{-3}$, F(000) = 428, λ = 71.073 pm, *T* = 293(2) K, μ (MoK_α) = 0.091 mm^{-1}. Total number of reflections measured 6585, unique reflections 3705 (R_{int} = 0.0620). Data/restraints/parameters 3705/0/272, data collection range 2.02° ≤ θ ≤ 25°. Final *R* indices: *R*1 = 0.0693, w*R*2 = 0.1597 on data with $I > 2\sigma(I)$ and *R*1 = 0.1057, w*R*2 = 0.1857 on all data; goodness of fit *S* = 1.062; extinction coefficient 0.014(4); largest difference peak and hole: 328 and -202 $e \cdot nm^{-3}$. CCDC 668051 contains crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.ac.uk/data_request/cif.

31. J. P. Michael, C. B. de Konig, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. M. W. Krause, A. S. Parsons, S. C. Pelly, and T. V. Stanbury, *Pure Appl. Chem.*, 1999, **71**, 979.
32. A.-Z. A. Elassar and A. A. El-Khair, *Tetrahedron*, 2003, **59**, 8463.
33. B. Stanovnik and J. Svete, *Chem. Rev.*, 2004, **104**, 2433.
34. T. J. Sommer, *Synthesis*, 2004, 161.
35. V. Mancuso and C. Hootele, *Tetrahedron Lett.*, 1988, **46**, 5917.
36. P. Aschwanden, L. Kvaernø, R. W. Geisser, F. Kleinbeck, and E. M. Carreira, *Org. Lett.*, 2005, **7**, 5741.
37. M. Suzuki, N. Hamanaka, and R. Noyori, *J. Am. Chem. Soc.*, 1981, **103**, 5606; M. Suzuki, Y. Oda, N. Hamanaka, and R. Noyori, *Heterocycles*, 1990, **30**, 517.
38. F. Sato, 'Handbook of Organopalladium Chemistry for Organic Synthesis', ed. by E.-i. Negishi and A. deMeijere, John Wiley & Sons, New York, 2002, pp. 2759–2765.
39. J. P. Kocienski, 'Protecting Groups: Thieme Foundations of Organic Chemistry', ed. by D. Enders, R. Noyori, and B. M. Trost, Thieme, New York, 1994.
40. R. J. Rahaim Jr. and R. E. Maleczka Jr., *Synthesis*, 2006, 3316.
41. M. Sakaitani, K. Hori, and Y. Ohfune, *Tetrahedron Lett.*, 1988, **29**, 2983.
42. R. C. F. Jones, J. N. Martin, P. Smith, T. Gelbrich, M. E. Light, and M. B. Hursthouse, *Chem. Commun.*, 2000, 1949.
43. R. Huisgen and K. Niklas, *Heterocycles*, 1984, **22**, 21.
44. G. Dannhardt and A. Bauer, *Pharmazie*, 1996, **51**, 805.