Tetrahedron 70 (2014) 3377–3384

Contents lists available at ScienceDirect

Tetrahedron

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

Selective syntheses of 2*H*-1,3-oxazines and 1*H*-pyrrol-3(2*H*)-ones via temperature-dependent Rh(II)-carbenoid-mediated 2*H*-azirine-ring expansion

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ARTICLE INFO

Article history:
Received 21 January 2014
Received in revised form 17 March 2014
Accepted 31 March 2014
Available online 4 April 2014

Dedicated to Professor Armin de Meijere on the occasion of his 75th birthday

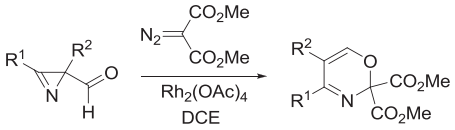
Keywords:
Azirines
Diazo compounds
Carbenoids
Ylides
Heterocyclizations

ABSTRACT

The Rh(II)-catalyzed reaction of 2-carbonyl-substituted 2*H*-azirines with ethyl 2-cyano-2-diazoacetate or 2-diazo-3,3,3-trifluoropropionate provides an easy access to 2*H*-1,3-oxazines and 1*H*-pyrrol-3(2*H*)-ones. These compounds can be selectively prepared from the same starting material using temperature as the only varied parameter. The 2-azabuta-1,3-diene intermediate, a common precursor for both heterocyclic products, isomerizes into 2*H*-1,3-oxazine under kinetic control, while 1*H*-pyrrol-3(2*H*)-one is the sole product of the reaction at elevated temperatures. According to DFT-calculations a one-atom oxazine ring contraction involving ring-opening to a 2-azabuta-1,3-diene intermediate, followed by a 1,5- and 1,2-prototropic shift leads to the consecutive formation of imidoylketene and azomethine ylide, which then further undergo cyclization to the pyrrole derivative.

1. Introduction

2*H*-Azirines are effective heterocyclic building blocks used for the synthesis of larger heterocycles: pyrroles, indoles, azaindoles, oxazoles, azepines, and others.[1] These syntheses involve catalytic or thermal azirine ring-opening across an N–C or C–C bond followed by cyclization, (4+2)-, (3+2)-cycloadditions to a C=N bond or addition of electrophiles to a nitrogen lone pair followed by a three-membered ring opening. In particular, the reactions of azirines with electrophilic metallo carbenoids, derived from diazo compounds can result in a one-, two- or three-atom ring expansion via formal insertion of carbene[2–4] or carbonylcarbene moieties and this provides a short synthetic route to 4–6-membered nitrogen heterocycles, such as azetes, pyrroles, and 2*H*-1,4-oxazines. In the last case a three-atom C–C–O fragment of a carbenoid is formally inserted into azirine to form a 1,4-oxazine ring. Recently we reported a new example of a three-atom ring expansion of 2*H*-azirines to 2*H*-1,3-oxazines by the $Rh_2(OAc)_4$-catalyzed reaction with dimethyl diazomalonate (Scheme 1).[5] This process was found to be characteristic of 2*H*-azirines having a formyl group in the 2-position. The formyl group, along with a carbon atom of the carbenoid, becomes incorporated into a 1,3-oxazine ring.



Scheme 1. $Rh_2(OAc)_4$-catalyzed reaction of azirine-2-carbaldehydes with dimethyl diazomalonate.

Functionalized non-fused 2*H*-1,3-oxazines containing a hemiaminal structural unit are of interest as appropriate building blocks for the synthesis of various nitrogenated compounds, in particular, aminoalcohols and azetidines.[6] 1,3-Oxazines having no heteroatomic substituent at C-2 are not readily available compounds, though several methods for their preparation involving both cyclic and acyclic precursors are known: phosphine-mediated reaction of ynones with 2-azido alcohols,[7] condensation of 4-amino-1-azabutadienes with esters of glyoxylic acid,[6] thermal ring-contraction of 1,4-diazepines,[8] reaction of β-carbonyl-substituted enamines with orthoesters,[9] rhodium-catalyzed coupling of isoxazoles with diazocarbonyl compounds,[10] and base-induced decomposition of isoxazolium salts.[11] These procedures are limited to

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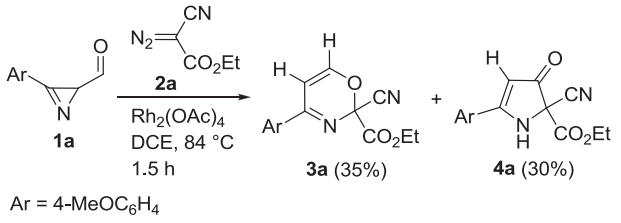
http://dx.doi.org/10.1016/j.tet.2014.03.101

those 1,3-oxazines having a restricted range of substituents and this prompted us to search for new synthetic methods. Due to the availability of diazocarbonyl compounds and 2-carbonyl-substituted 2*H*-azirines[12] the recently found Rh(II)-catalyzed reaction of these compounds deserve attention as a promising approach to 2*H*-1,3-oxazines with electron-withdrawing substitutes at C-2. To broaden the scope of the reaction, an examination of the reactivity of cyano- and trifluoromethyl-containing diazo compounds towards various 2-carbonyl-substituted azirines was carried out. In the course of this work a new synthetic application of the reaction was discovered: a two-atom azirine ring expansion to 1*H*-pyrrol-3(2*H*)-ones. Its mechanism was investigated by using DFT-calculations.

2. Results and discussion

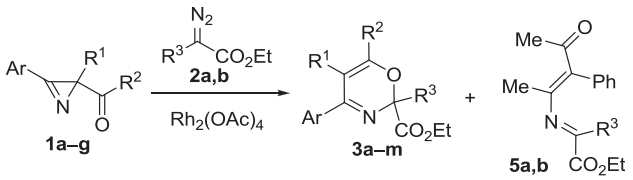
2.1. Syntheses of 1,3-2*H*-oxazines and 1*H*-pyrrol-3(2*H*)-ones from 2*H*-azirines

Aiming to broaden the scope of the carbenoid-mediated three-atom ring expansion of 2*H*-azirine-2-carbaldehydes **1** to the 2*H*-1,3-oxazine system we focused on diazo compounds **2a**,**b** as carbenoid sources transferring cyano and trifluoromethyl groups into the target heterocycle. The reaction of azirine **1a** with ethyl diazocyanoacetate **2a** was carried out under standard conditions using $Rh_2(OAc)_4$ as a catalyst in refluxing 1,2-dichloroethane (DCE). Unexpectedly, along with the expected oxazine **3a** (35%), pyrrolinone **4a** (30%) was also isolated (Scheme 2). It was also found that the latter is formed from oxazine **3a** under refluxing in DCE and hence the ratio **4a**/**3a** is increased with the increase of heating time. Fortunately, performing the reaction at a lower temperature (dichloromethane, DCM, 40 °C) avoided the thermal isomerization



Scheme 2. $Rh_2(OAc)_4$-catalyzed reaction of azirine **1a** with diazo compound **2a**.

of oxazine **3a**, and it was isolated in 69% yield as sole product. Under these conditions oxazines **3b**–**e** were synthesized in 60–70% yield (Scheme 3, Table 1). According to the ^{1}H NMR spectra of the reaction mixtures ($CHBr_2CHBr_2$ as an internal standard) the conversion of azirines **3** was 84–89%. The use of an excess of diazo compound to raise the conversion leads, however, to a decrease in the oxazine yield.



Scheme 3. Synthesis of 2*H*-1,3-oxazines **3a**–**m**.

2-Acetyl-substituted azirine **1g** reacts in a similar way to give oxazine **3l**, bearing a methyl group at atom C-6, in 60% yield. But in this case the formation of azadiene **5a**, in trace amounts (6% on consumed azirine **1g**), was also detected by ^{1}H NMR spectroscopy.

Table 1
The yields of 2*H*-1,3-oxazines **3a**–**k**

Azirine	Diazo compound	Ar	R^1	R^2	R^3	Reaction conditions	Oxazine **3**	Yield of **3**, %
1a	**2a**	4-$MeOC_6H_4$	H	H	CN	DCM, 40 °C	**3a**	69
1b	**2a**	Ph	H	H	CN	DCM, 40 °C	**3b**	70
1c	**2a**	4-MeC_6H_4	H	H	CN	DCM, 40 °C	**3c**	70
1d	**2a**	4-ClC_6H_4	H	H	CN	DCM, 40 °C	**3d**	67
1e	**2a**	Ph	Me	H	CN	DCM, 40 °C	**3e**	60
1f	**2a**	Ph	Ph	H	CN	TFT, 103 °C	**3f**	31[a]
1a	**2b**	4-$MeOC_6H_4$	H	H	CF_3	DCE, 84 °C	**3g**	78
1b	**2b**	Ph	H	H	CF_3	DCE, 84 °C	**3h**	81
1c	**2b**	4-MeC_6H_4	H	H	CF_3	DCE, 84 °C	**3i**	76
1d	**2b**	4-ClC_6H_4	H	H	CF_3	DCE, 84 °C	**3j**	73
1e	**2b**	Ph	Me	H	CF_3	DCE, 84 °C	**3k**	78
1g	**2a**	Me	Ph	Me	CN	DCM, 40 °C	**3l**	60[b]
1g	**2b**	Me	Ph	Me	CF_3	DCE, 84 °C	**3m**	38[c]

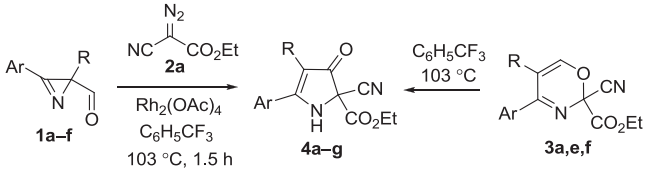
[a] Ethyl 2-cyano-3-oxo-4,5-diphenyl-2,3-dihydro-1*H*-pyrrole-2-carboxylate **4f** was also isolated in 19% yield.
[b] According to the ^{1}H NMR spectrum of the reaction mixture ethyl 2-cyano-2-[(*E*)-4-oxo-3-phenylpent-2-en-2-ylimino]acetate **5a** was also formed (**3l**/**5a** ratio 12:1).
[c] According to the ^{1}H NMR spectrum of the reaction mixture ethyl 3,3,3-trifluoro-2-[(*E*)-4-oxo-3-phenylpent-2-en-2-ylimino]propanoate **5b** was also formed (**3m**/**5b** ratio 2:1).

There are several methods for the preparation of *N*-benzyl,[13] *N*-methyl[14] and *N*-unsubstituted[15] 1*H*-pyrrol-3(2*H*)ones with 2-alkyl, 2-aryl or 2-alkoxycarbonyl substituents.[16] The thermal one-atom 1,3-oxazine ring contraction reaction provides an easy access to *N*-unsubstituted 1*H*-pyrrol-3(2*H*)-ones bearing a CN or CF_3 group in the position 2. The pyrrolinones **4a**,**e**,**f** with a cyano group in the 2-position were shown to be formed quantitatively from the corresponding oxazines **3a**,**e**,**f** in refluxing α,α,α-trifluorotoluene (TFT) (Scheme 4, Table 2, entries 2, 7, 9). Moreover they can be successfully prepared from 3-arylazirines **1a**–**d** and diazo compound **2a** without isolation of the intermediate oxazine **3** (Scheme 4, Table 2, entries 1, 3–5).

Table 2
Syntheses of pyrrolinones **4a**–**g** from 2*H*-azirines **1a**–**f** and oxazines **3a**,**e**,**f**

Entry	Starting compounds	Ar	R	Yield of **4**, %
1	**1a**+**2a**	4-$MeOC_6H_4$	H	60 (**4a**)
2	**3a**	4-$MeOC_6H_4$	H	100 (**4a**)
3	**1b**+**2a**	Ph	H	60 (**4b**)
4	**1c**+**2a**	4-MeC_6H_4	H	64 (**4c**)
5	**1d**+**2a**	4-ClC_6H_4	H	59 (**4d**)
6	**1e**+**2a**	Ph	Me	36[a] (**4e**)
7	**3e**	Ph	Me	100 (**4e**)
8	**1f**+**2a**	Ph	Ph	19[b] (**4f**)
9	**3f**	Ph	Ph	100 (**4f**)

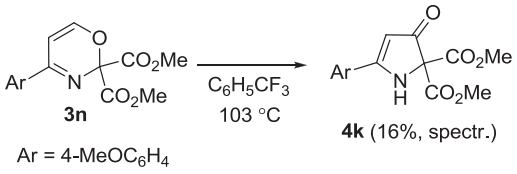
[a] According to the ^{1}H NMR spectrum ethyl 2-cyano-5-methyl-4-phenyl-2*H*-1,3-oxazine-2-carboxylate **3e** was also formed in 17% yield.
[b] Oxazine **3f** was also isolated in 31% yield.



Scheme 4. Syntheses of pyrrolinones **4a**–**g**.

Oxazine **3l** with a methyl group at the C-2 atom is thermally stable towards isomerization.

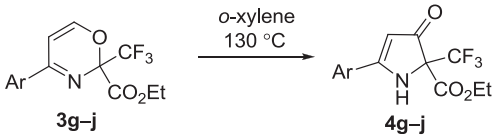
Oxazine **3n**, derived from azirine **1a** and dimethyl diazomalonate **2c**, does not undergo visible changes in DCE at 84 °C (Scheme 5), but refluxing in TFT (103 °C) gave pyrrolinone **4k** in 16% according to ^{1}H NMR spectroscopy: 3.89 (s, 6H, 2× CO_2CH_3), 3.90 (s,



Scheme 5. Isomerization of oxazine **3n** to pyrrolinone **4k**.

3H, CH_3O), 5.55 (s, 1H, H-4), 5.91 (br s, 1H, N–H), 7.01 (d, 2H, *J*=8.9 Hz, ArH), 7.67 (d, 2H, *J*=8.9 Hz, ArH). This compound is prone to decomposition during silica gel chromatography and all attempts to isolate it by chromatography failed.

Changing one of the CO_2Me groups in **3n** for a trifluoromethyl group leads to a further increase in the stability of the oxazine: only heating at 130 °C in *o*-xylene for 3.5 h results in a full conversion of **3g** to pyrrolinone **4g**, which was isolated in 43% yield using chromatography on silica gel (Scheme 6). Under these conditions oxazines **3h**–**j** were isomerized to compounds **4h**–**j** in moderate yields (Table 3). Pyrrolinones **4** could be obtained from the corresponding azirines **1** without isolation of the intermediate oxazines **3**. Thus, the compound **4g** was obtained in 21% yield by decomposition of diazo compound **2c** in the presence of azirine **1a** and $Rh_2(OAc)_4$ in TFT at 90 °C followed by additional heating of the reaction mixture at 135 °C for 3 h.



Scheme 6. Isomerization of oxazines **3g**–**j** to pyrrolinones **4g**–**j**.

Table 3
Synthesis of pyrrolinones **4g**–**j** from oxazines **3g**–**j**

Oxazine	Ar	Pyrrolinone **4**	Yield of **4**, %
3g	4-$MeOC_6H_4$	**4g**	43
1h	Ph	**4h**	34
1i	4-MeC_6H_4	**4i**	18
1j	4-ClC_6H_4	**4j**	11

The structures of compounds **4a**–**j** were verified by ^1H and ^{13}C NMR, IR spectroscopy, and mass-spectrometry and the structure of **4e** was confirmed by X-ray analysis (Fig. 1).

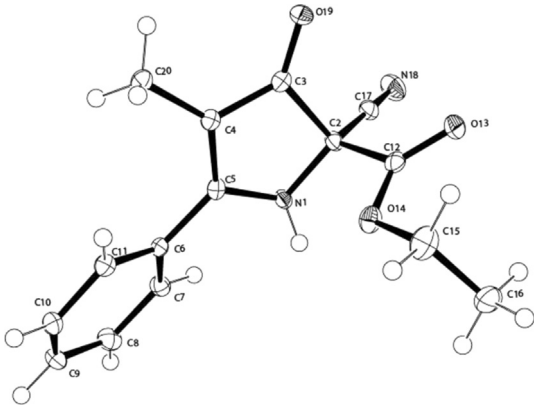
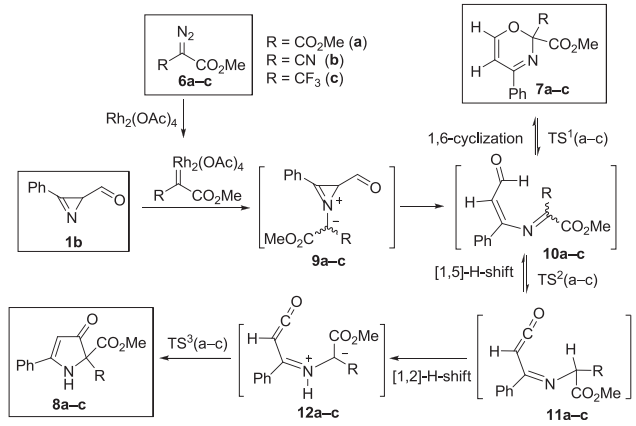


Fig. 1. X-ray structure of compound **4e**.

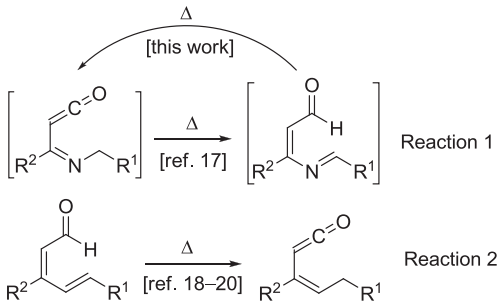
2.2. Theoretical calculations and reaction mechanism

Previous computational studies on the mechanism of formation of 2*H*-1,3-oxazine **7** in the Rh(II)-catalyzed reaction of azirine-2-carbaldehydes **1** with dimethyl diazomalonate **6a** demonstrated that it involves consecutive generation of azirinium ylide **9**, ring opening to 2-azabuta-1,3-diene **10** followed by a 1,6-π-electrocyclization.[5] The selective isomerization of azirinium ylide to azadiene with the C=C bond in *Z* configuration, which is favorable for further 1,6-cyclization, was predicted by DFT-calculations. For the 1,3-oxazine-pyrrolin-3-one isomerization **7**→**8** proceeding at elevated temperatures we proposed the mechanism involving reversible oxazine **7** ring-opening to 2-azabutadiene **10** (4-azapenta-2,4-dienal), 1,5-H-shift to imidoylketene **11**, 1,2-H-shift to the NH-azomethine ylide followed by cyclization (Scheme 7).

To the best of our knowledge the isomerization of 4-azapenta-2,4-dienals to iminoketenes is unknown but the back reaction proceeding via a [1,5]-H-shift was postulated in a gas-phase pyrolysis of *N*-alkylaminomethylene derivatives of Meldrum's acid to 4-azapenta-2,4-dienals (Scheme 8, reaction 1).[17] It was also proposed that a [1,5]-H-shift of the formyl hydrogen proceeds under isomerization of penta-2,4-dienals to vinylketenes (Scheme 8, reaction 2).[18] Later the 'ketenic' mechanism was confirmed by quantum-chemical calculations for the rearrangement of Zincke aldehydes.[19] The sigmatropic shift of this type can be realized under milder conditions for penta-2,4-dienals bearing an electron-withdrawing ester group at C-3.[20]



Scheme 7. Proposed mechanism for the formation of pyrrolinones **8**.



Scheme 8. Penta-2,4-dienal—ketene isomerization.

To verify the supposed mechanistic scheme we performed a computational evaluation of free energies of transition states of the key steps of the oxazine-pyrrolinone isomerization. Because of the dramatic influence of a C-2 substituent in the 1,3-oxazine on the

rate of this transformation, the substrates **7a**–**c** bearing CO_2Me, CN, and CF_3 in this position were included into consideration (Scheme 7). The geometries of oxazines **7a**–**c**, azadienes **10a**, *E*,*Z*-, *Z*,*Z*-**10b**,**c**, imidoylketenes **11a**–**c**, ylides **12a**–**c**, pyrrolinones **8a**–**c** as well as the transition states of ring opening of oxazines **7** (TS^1(a–c)), the [1,5]-H-shift in azabutadienes **10** (TS^2(a–c)), and cyclization of ylides **12** (TS^3(a–c)) to pyrrolinones **8a**–**c** were optimized at the DFT mPWB1K/6-31+G(d,p) level[21] using the PCM solvent model for toluene. The energy of the most stable conformation of oxazines **7a**–**c**, azadienes **10 a**–**c**, imidoylketenes **11a**–**c**, and azomethine ylides **12a**–**c** were used in the calculations of the activation free energies (Fig. 2).

lower temperatures.[25] The high acidity of **11a** in comparison with **11b**,**c** makes the stage of the formation of ylide **12a** exothermic, while 1,2-shifts in imidoylketenes **11b**,**c** are endothermic processes (Fig. 2).

Attempts to trap the intermediate azomethine ylide by accomplishing the reaction of azirine **1a** with diazo compound **2a** in the presence of *N*-(4-bromophenyl)maleimide, as a dipolar trap failed, probably, due to the very low activation barrier (8.2 kcal/mol) for its cyclization to pyrrolinone **7a**.

The suggested mechanistic scheme involving a [1,5]-prototropic shift as one of the stages reasonably explains the enhanced thermal stability of 6-methyl-substituted oxazine **3l**, which thermally pro-

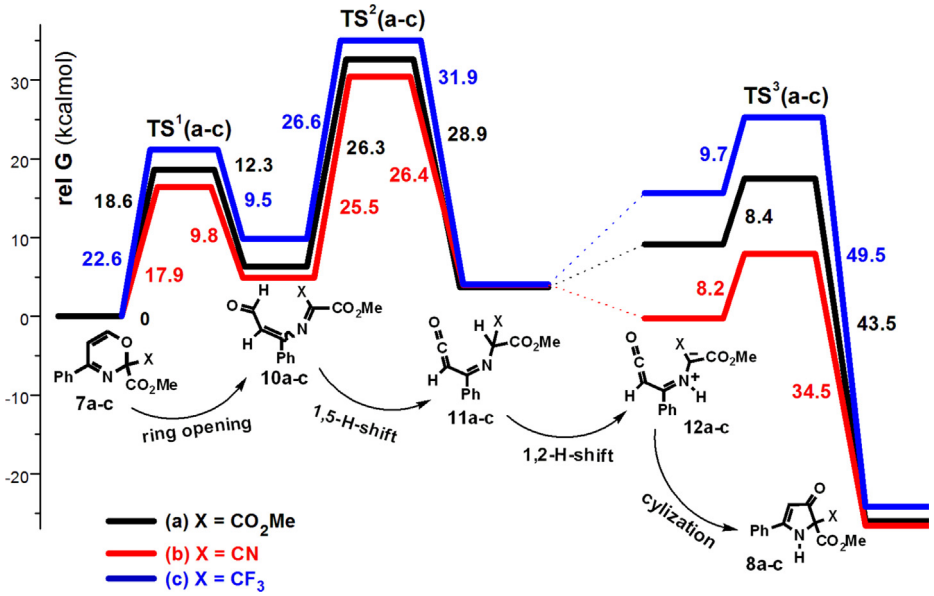


Fig. 2. Energy profiles (DFT mPWB1K/6-31+G(d,p), kcal/mol, 375.15 K) for the isomerization of oxazines **7a**–**c** to pyrrolinones **8a**–**c** in toluene.

As follows from Fig. 2 the activation barriers for ring-opening of oxazines **7a**–**c** are sufficiently low (17.9–22.6 kcal/mol) and can be overcome at room temperature. Ring-opening of oxazines **7a**–**c** is facilitated when the C-2 substituent changes from CF_3 to CO_2Me, and then to CN. Azadienes **10** in all cases are sufficiently less stable compounds than their cyclic isomers **7** and can exist only as short-lived intermediates. The activation barriers for the [1,5]-H-shift in azadienes **10** (25.5–26.6 kcal/mol) practically do not depend on the substituents R (Scheme 5). However the transition state energy for this stage appreciably increases in the order of substituents $CN<CO_2Me<CF_3$ (30.4, 32.6, 35.0 kcal/mol) and this is in good agreement with the experimentally observed relationship between the temperature needed for isomerization and the character of the substituent at C-2 in the oxazine.

The 1,2-H-shift in imidoylketene **11**, which gives rise to azomethine ylide **12**, is an intermolecular process[22] and a reliable evaluation of its activation barrier is a rather difficult problem due to the uncertainty in the nature of the reaction promoter. It is known that the imine—azomethine ylide prototropy is catalyzed both by acids and bases[22] including such weak bases as the starting imines and the final cycloaddition products of azomethine ylides.[23] Most probably, the barriers for 1,2-H-prototropy in imidoylketens are lower than those for the 1,5-H-prototropy, giving rise to azadienes **10a**–**c**, due to the higher acidity of compounds **11a**–**c**. It is well known that the facility with which the NH-azomethine ylide is formed depends upon the CH-acidity of the starting imine,[22] and prototropy for iminomalonates usually occurs at 70 °C[24] or even at

duces the 2-azadiene intermediate without the hydrogen atom able to migrate.

3. Conclusions

In conclusion, 2*H*-1,3-oxazines and 1*H*-pyrrol-3(2*H*)-ones can be easily synthesized by the Rh(II)-catalyzed reaction of 2-carbonyl-substituted 2*H*-azirines with ethyl 2-cyano-2-diazo acetate or 2-diazo-3,3,3-trifluoropropionate using temperature as the only controlled variable. The 2-azabutadiene intermediate, a common precursor for both heterocyclic products, isomerizes into 2*H*-1,3-oxazine under kinetic control, while 1*H*-pyrrol-3(2*H*)-one is the sole product of the reaction at elevated temperatures. According to DFT-calculations the one-atom oxazine ring contraction involves the ring-opening to the 2-azabuta-1,3-diene derivative, a 1,5-/1,2-prototropic shift cascade via the formation of imidoylketene and NH-azomethine ylide followed by cyclization.

4. Experimental section

4.1. General methods

Melting points were determined on a hot stage microscope and are uncorrected. ^1H (300 or 400 MHz) and ^{13}C (75 or 100 MHz) NMR spectra were determined in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane.

Electrospray ionization mass spectra were measured on a Bruker micrOTOF mass spectrometer. IR spectra were recorded on a SPECORD M80 spectrometer for tablets in KBr or solutions in $CHCl_3$. Single crystal X-ray data were collected on an Agilent Technologies Xcalibur Eos diffractometer and measured at a temperature of 100 K using monochromated Mo *Kα* radiation. An empirical absorption correction was applied in CrysAlisPro program complex using spherical harmonics implemented in Scale 3 Abspackslaling algorithm. The structure has been solved by direct methods using the SHELX-97 program incorporated in the OLEX2 program package. Positions of H atoms were modeled using the 'riding' model. Crystallographic data for the structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-970742 (for **4e**). Silica gel Merck 60 was used for column chromatography. Thin-layer chromatography (TLC) was conducted on alumina sheets precoated with SiO_2 ALUGRAM SIL G/UV254. Compounds **1a**–**f**,[12e] **1g**,[26] **2a**,[27] and **2b**[28] were prepared by the reported procedures.

4.2. Calculation details

All calculations were performed with the mPWB1K density functional method by using the Gaussian 09[29] suite of quantum chemical programs. Geometry optimizations of intermediates, transition states, reactants, and products in toluene were performed at the DFT mPWB1K/6-31+G(d,p) level using the PCM model. Stationary points on the respective potential-energy surfaces were characterized at the same level of theory by evaluating the corresponding Hessian indices. Careful verification of the unique imaginary frequencies for transition states was carried out to check whether the frequency indeed pertains to the desired reaction coordinate.

4.3. Synthesis of oxazines 3a–e, g–l

*4.3.1. General procedure A (for oxazines **3a**–**e**, **l**).* A solution of diazo compound **2a** (69.5 mg, 0.5 mmol) in anhydrous dichloromethane (DCM) (1 mL) was added in one portion to a stirred solution of azirine **1a**–**f** (0.5 mmol) and $Rh_2(OAc)_4$ (1 mol %) in anhydrous DCM (1 mL) at reflux under an argon atmosphere, and the mixture was stirred at this temperature for 10 min. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (eluent hexane/EtOAc) to give compound **3a**–**e**, **l**.

*4.3.2. General procedure B (for oxazines **3g**–**k**).* A solution of diazo compound **2b** (218 mg, 1.2 mmol) in anhydrous 1,2-dichloroethane (DCE) (5 mL) was added using a syringe during 1.5 h to a stirred solution of azirine **1a**–**f** (1.0 mmol) and $Rh_2(OAc)_4$ (1 mol %) in anhydrous DCE (3 mL) at reflux under an argon atmosphere, and the mixture was stirred at this temperature for an additional 5 min. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (eluent hexane/EtOAc) to give compound **3g**–**k**.

*4.3.3. Ethyl 2-cyano-4-(4-methoxyphenyl)-2H-1,3-oxazine-2-carboxylate (**3a**).* Compound **3a** was prepared according to procedure A, using DCM as solvent, from azirine **1a** (75 mg, 0.43 mmol) and diazo compound **2a** (60 mg, 0.43 mmol) as a yellowish oil (85 mg, 69%). IR (KBr): 3085, 2985, 2940, 2840, 2240, 1760, 1605, 1635, 1605, 1515, 1260, 1220, 1105 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.1 Hz, CH_3), 3.87 (s, 3H, CH_3O), 4.48 (q, 2H, J=7.1 Hz, CH_2), 6.37 (d, 1H, J=5.9 Hz, H-5), 6.96 (d, 2H, J=8.5 Hz, ArH), 7.19 (br s, 1H, H-5), 7.86 (d, 2H, J=8.5 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 55.4 (CH_3O), 64.1 (CH_2), 101.4 (C-5), 114.0, 126.7, 129.2 (Ar), 151.8 (C-6), 162.5, 162.96, 163.05 (C-6, C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}N_2O_4$, 287.1026; found 287.1032. If the reaction of azirine **1a** (150 mg, 0.9 mmol) with diazo compound **2a** (119 mg, 0.9 mmol) in the presence of $Rh_2(OAc)_4$ (1 mol %) is carried out according to procedure A in refluxing DCE instead of DCM then after chromatographic purification oxazine **3a** (86 mg, 35%) and pyrrolinone **4a** (73 mg, 30%) were formed.

*4.3.4. Ethyl 2-cyano-4-phenyl-2H-1,3-oxazine-2-carboxylate (**3b**).* Compound **3b** was prepared according to general procedure A, using DCM as a solvent, from azirine **1b** (75 mg, 0.52 mmol) and diazo compound **2a** (72 mg, 0.52 mmol) as a yellowish solid (92 mg, 70%). Mp 50–52 °C (hexane/Et_2O). R_f=0.27 (25% EtOAc/hexane). IR (KBr): 3100, 3085, 2995, 2240, 1745, 1625, 1520, 1315, 1225, 1100, 1025 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, 3H, J=7.1 Hz, CH_3), 4.48 (q, 2H, J=7.1 Hz, CH_2), 6.39 (d, 1H, J=5.9 Hz, H-5), 7.21 (br s, 1H, H-6), 7.44–7.58 (m, 3H, ArH), 7.88 (d, 2H, J=7.3 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 64.2 (CH_2), 84.6 (C-2), 101.6 (C-5), 113.8 (CN), 127.3, 128.7, 132.2, 134.2 (Ar), 152.0 (C-6), 162.7, 163.6 (C-4, C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{14}H_{12}N_2NaO_3$, 279.0740; found 279.0730.

*4.3.5. Ethyl 2-cyano-4-(4-methylphenyl)-2H-1,3-oxazine-2-carboxylate (**3c**).* Compound **3c** was prepared according to general procedure A, using DCM as solvent, from azirine **1c** (75 mg, 0.47 mmol) and diazo compound **2a** (65 mg, 0.47 mmol) as a yellowish solid (89 mg, 70%). Mp 51–53 °C (hexane/Et_2O). IR (KBr): 3115, 3045, 2990, 2240, 1770, 1630, 1530, 1520, 1305, 1275, 1105, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, 3H, J=7.1 Hz, CH_3), 2.42 (s, 3H, CH_3), 4.48 (q, 2H, J=7.1 Hz, CH_2), 6.38 (d, 1H, J=5.9 Hz, H-5), 7.20 (br s, 1H, H-6), 7.27 (d, 2H, J=7.9 Hz, ArH), 7.78 (d, 2H, J=7.9 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.5 (CH_3), 64.2 (CH_2), 101.6 (C-5), 113.9 (CN), 127.3, 129.4, 131.5, 143.0 (Ar), 151.7 (C-6), 162.9, 163.3 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}N_2O_3$, 271.1077; found 271.1074.

*4.3.6. Ethyl 4-(4-chlorophenyl)-2-cyano-2H-1,3-oxazine-2-carboxylate (**3d**).* Compound **3d** was prepared according to general procedure A, using DCM as solvent, from azirine **1d** (75 mg, 0.42 mmol) and diazo compound **2a** (58 mg, 0.42 mmol) as a yellowish solid (82 mg, 67%). Mp 50–54 °C (hexane/Et_2O). R_f=0.29 (25% EtOAc/hexane). IR (KBr): 3120, 2985, 2935, 2240, 1775, 1630, 1450, 1310, 1273, 1124, 1110, 1050 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.45 (t, 3H, J=7.1 Hz, CH_3), 4.48 (q, 2H, J=7.1 Hz, CH_2), 6.35 (d, 1H, J=5.9 Hz, H-5), 7.20 (br s, 1H, H-6), 7.44 (d, 2H, J=8.5 Hz, ArH), 7.83 (d, 2H, J=8.5 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 64.3 (CH_2), 101.2 (C-5), 113.7 (CN), 128.7, 129.0, 132.6, 138.7 (Ar), 152.4 (C-6), 162.6, 162.7 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{14}H_{12}{}^{35}ClN_2O_3$, 291.0531; found 291.0532.

*4.3.7. Ethyl 2-cyano-5-methyl-4-phenyl-2H-1,3-oxazine-2-carboxylate (**3e**).* Compound **3e** was prepared according to general procedure A, using DCM as solvent, from azirine **1e** (80 mg, 0.5 mmol) and diazo compound **2a** (70 mg, 0.5 mmol) as a yellowish oil (82 mg, 60%). IR (KBr): 3065, 2985, 2940, 1740, 1605, 1495, 1445, 1382, 1195, 1015 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, 3H, J=7.1 Hz, CH_3), 1.89 (s, 3H, CH_3), 4.41–4.50 (m, 2H, CH_2), 6.96 (s, 1H, H-6), 7.45–7.51 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 14.1 (CH_3), 64.2 (CH_2), 84.1 (C-2), 112.5, 114.1 (Ar, CN), 128.1, 128.4, 130.5, 135.4 (Ar), 147.6 (C-6), 162.9, 169.9 (C-4, C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{15}H_{14}N_2NaO_3$, 293.0897; found 293.0892.

*4.3.8. Ethyl 2-cyano-4,5-diphenyl-2H-1,3-oxazine-2-carboxylate (**3f**).* Compound **3f** was prepared according to general procedure C (see below), using anhydrous TFT (5 mL) as solvent, from azirine **1f** (75 mg, 0.34 mmol) and diazo compound **2b** (47 mg, 0.34 mmol)

as a yellowish oil (35 mg, 31%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, 3H, J=7.1 Hz, CH_3), 4.42 (q, 2H, J=7.1 Hz, CH_2), 7.07 (s, 1H, H-6), 7.15–7.51 (m, 10H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 64.7 (CH_2), 112.8 (CN), 123.2, 125.5, 128.3, 128.4, 128.7, 128.8, 130.5, 139.0, 131.2, 144.4, 154.7, 162.3 (C-4, C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{20}H_{16}N_2NaO_3$, 355.1053; found 355.1054.

*4.3.9. Ethyl 4-(4-methoxyphenyl)-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3g**).* Compound **3g** was prepared according to general procedure B, using DCE as solvent, from azirine **1a** (200 mg, 1.14 mmol) and diazo compound **2b** (250 mg, 1.37 mmol) as a yellowish solid (293 mg, 78%). Mp 69–71 °C (hexane/Et_2O). R_f=0.33 (25% EtOAc/hexane). IR (KBr): 3055, 3000, 2975, 2950, 1755, 1635, 1610, 1540, 1515, 1420, 1325, 1254, 1225, 1195, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, 3H, J=7.1 Hz, CH_3), 3.85 (s, 3H, CH_3O), 4.28–4.41 (m, 2H, CH_2), 6.07 (d, 1H, J=5.9 Hz, H-5), 6.93–6.97 (m, 2H, ArH), 7.08 (d, 1H, J=5.9 Hz, H-6), 7.86–7.90 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 55.3 (CH_3O), 63.0 (CH_2), 90.2 (q, J=32 Hz, C-2), 98.8 (C-5), 113.9 (Ar), 121.1 (q, J=285 Hz, CF_3), 127.5, 128.9 (Ar), 151.9 (C-6), 161.0, 162.6, 164.4 (Ar, C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}F_3NO_4$, 330.0948; found 330.0946.

*4.3.10. Ethyl 4-phenyl-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3h**).* Compound **3h** was prepared according to general procedure B, using DCE as solvent, from azirine **1b** (100 mg, 0.69 mmol) and diazo compound **2b** (188 mg, 1.03 mmol) as a colorless solid (167 mg, 81%). Mp 49–51°C (hexane/Et_2O). R_f=0.42 (25% EtOAc/hexane). IR (KBr): 3095, 2995, 2950, 2915, 1745, 1635, 1535, 1335, 1260, 1230, 1195, 1070, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, 3H, J=7.1 Hz, CH_3), 4.30–4.43 (m, 2H, CH_2), 6.10 (d, 1H, J=5.9 Hz, H-5), 7.12 (d, 1H, J=5.9 Hz H-6), 7.44–7.56 (m, 3H, ArH), 7.88–7.92 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 63.2 (CH_2), 90.2 (q, J=32 Hz, C-2), 99.0 (C-5), 121.1 (q, J=285 Hz, CF_3), 127.1, 128.6, 131.8, 135.0 (Ar), 152.2 (C-6), 162.1, 164.1 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{14}H_{13}F_3NO_3$, 300.0842; found 300.0836.

*4.3.11. Ethyl 4-(4-methylphenyl)-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3i**).* Compound **3i** was prepared according to general procedure B, using DCE as solvent, from azirine **1c** (75 mg, 0.47 mmol) and diazo compound **2b** (103 mg, 0.57 mmol) as a yellowish solid (112 mg, 76%). Mp 83–85 °C (hexane/Et_2O). R_f=0.47 (25% EtOAc/hexane). IR (KBr): 3090, 2995, 1745, 1635, 1535, 1425, 1285, 1260, 1235, 1195, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.1 Hz, CH_3), 2.41 (s, 3H, CH_3), 4.28–4.42 (m, 2H, CH_2), 6.08 (d, 1H, J=5.8 Hz, H-5), 7.10 (d, 1H, J=5.8 Hz, H-6), 7.26 (d, 2H, ArH), 7.80 (d, 2H, J=8.1 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.4 (CH_3), 63.1 (CH_2), 90.3 (q, J=31.5 Hz, C^2), 99.0 (C-5), 121.1 (q, J=285 Hz, CF_3), 127.1, 129.3, 132.2, 142.3 (Ar), 152.0 (C-6), 161.8, 164.3 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}F_3NO_3$, 314.0999; found 314.1005.

*4.3.12. Ethyl 4-(4-chlorophenyl)-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3j**).* Compound **3j** was prepared according to general procedure B, using DCE as solvent, from azirine **1d** (155 mg, 0.86 mmol) and diazo compound **2b** (189 mg, 1.04 mmol) as a yellowish solid (210 mg, 73%). Mp 52–54 °C (hexane/Et_2O). IR (KBr): 3095, 2985, 1760, 1640, 1595, 1575, 1540, 1423, 1325, 1280, 1245, 1205, 1078, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, 3H, J=7.15 Hz, CH_3), 4.29–4.42 (m, 2H, CH_2), 6.04 (d, 1H, J=5.9 Hz, H-5), 7.12 (d, 1H, J=5.9 Hz, H-6), 7.41 (d, 2H, J=8.6 Hz, ArH), 7.824 (d, 2H, J=8.6 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 63.3 (CH_2), 90.2 (q, J=32.0 Hz, C-2), 98.6 (C-5), 121.0 (q, J=285 Hz, CF_3), 128.5, 128.9, 133.3, 138.1 (Ar), 152.6 (C-6), 161.1, 164.0 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{14}H_{12}{}^{35}ClF_3NO_3$, 334.0452; found 334.0448.

*4.3.13. Ethyl 5-methyl-4-phenyl-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3k**).* Compound **3k** was prepared according to general procedure B, using DCE as solvent, from azirine **1e** (150 mg, 0.94 mmol) and diazo compound **2b** (206 mg, 1.13 mmol) as a yellowish solid (229 mg, 78%). Mp 34–36 °C (hexane/Et_2O). R_f=0.47 (25% EtOAc/hexane). IR (KBr): 3075, 2980, 1740, 1660, 1550, 1445, 1375, 1195, 1095, 1032 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=7.1 Hz, CH_3), 1.75 (d, 3H, J=1.2 Hz, CH_3), 4.38 (q, 2H, J=7.1 Hz, CH_2), 6.86 (d, 1H, J=1.2 Hz, C-5), 7.40–7.53 (m, 5H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 14.0 (CH_3), 63.1 (CH_2), 89.6 (q, J=31.8 Hz, C-2), 109.8 (C-5), 121.1 (q, J=285 Hz, CF_3), 128.0, 128.3, 130.0, 136.3 (Ar), 147.9 (C-6), 164.6, 168.1 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}F_3NO_3$, 314.0999; found 314.0993.

*4.3.14. Ethyl 2-cyano-4,6-dimethyl-5-phenyl-2H-1,3-oxazine-2-carboxylate (**3l**).* Compound **3l** was prepared according to general procedure A from azirine **1g** (100 mg, 0.58 mmol) and diazo compound **2a** (80 mg, 0.58 mmol). A mixture of oxazine **3l** and ethyl 2-cyano-2-[(*E*)-4-oxo-3-phenylpent-2-en-2-ylimino]acetate **5a** in 12:1 ratio (107 mg, 65%) was isolated. Pure oxazine **3l** (98 mg, 60%) was obtained as a yellow solid by crystallization from hexane/Et_2O (2:1). Compound **3l**. Mp 43–45 °C (hexane/Et_2O). R_f=0.33 (25% EtOAc/hexane). IR (KBr): 3030, 2985, 2935, 2235, 1775, 1650, 1555, 1425, 1310, 1250, 1115, 1070 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (t, 3H, J=7.1 Hz, CH_3), 1.92 C (s, 3H, CH_3), 1.94 (s, 3H, CH_3), 4.45–4.54 (m, 2H, CH_2), 7.19–7.21 (m, 2H, ArH), 7.39–7.46 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 17.0 (CHH_3), 23.5 (CH_3), 64.2 (CH_2), 84.0 (C-2), 114.5 (CN), 116.8, 128.2, 128.9, 130.2, 133.4 (C-5, Ar), 157.8 (C-6), 163.3, 169.3 (C-4, C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{16}H_{16}N_2NaO_3$, 307.1053; found 307.1054.

*4.3.15. Ethyl 4,6-dimethyl-5-phenyl-2-trifluoromethyl-2H-1,3-oxazine-2-carboxylate (**3m**).* Compound **3m** was prepared according to general procedure B, using DCE as solvent, from azirine **1g** (150 mg, 0.87 mmol) and diazo compound **2b** (189 mg, 1.04 mmol). A mixture of oxazine **3m** and ethyl 3,3,3-trifluoro-2-[(*E*)-4-oxo-3-phenylpent-2-en-2-ylimino]propanoate **5b** in 2:1 ratio (186 mg, 66%) was isolated. Pure oxazine **3m** (108 mg, 38%) was obtained as a colorless solid after refluxing this mixture in *o*-xylene for 3 h followed by chromatographic purification on silica gel (eluent hexane/EtOAc). Mp 61–63 °C (hexane/Et_2O). R_f=0.52 (25% EtOAc/hexane). IR (KBr): 3070, 3010, 2985, 1750, 1655, 1570, 1495, 1380, 1335, 1245, 1190, 1130, 1070, 1045, 1020 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, 3H, J=7.1 Hz, CH_3), 1.89 (s, 3H, CH_3), 1.91 (s, 3H, CH_3), 4.25–4.47 (m, 2H, CH_2), 7.08–7.11 (m, 2H, ArH), 7.32–7.39 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 17.1 (CH_3), 23.6 (CH_3), 63.0 (CH_2), 89.6 (q, J=31.4 Hz, C-2), 114.9 (C-5), 121.5 (q, J=285 Hz, CF_3), 127.9, 128.7, 130.2, 134.0 (Ar), 158.2 (C-6), 164.9, 167.4 (C-4, C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{16}H_{17}F_3NO_3$, 328.1155; found 328.1157. Compound **5b** (not separated), R_f=0.52 (25% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J=7.3 Hz, CH_3), 2.03 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 4.30 (q, J=7.3 Hz, CH_2), 7.01–7.11 (m, 2H, ArH), 7.29–7.43 (m, 3H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 18.5 (CH_3), 31.0 (CH_3), 63.1 (CH_2), 117.5 (q, J=279 Hz, CF_3), 127.7, 128.7, 129.4, 136.1 (Ar), 144.7 (q, J=37 Hz), 153.1, 155.9, 164.1 (C=O), 199.4 (C=O).

4.4. Syntheses of pyrrolinones 4a–f

4.4.1. General procedure C. A solution of diazo compound **2a** (0.5 mmol) in anhydrous TFT (5 mL) was added using a syringe over 1.5 h to a stirred solution of azirine **1a**–**f** (0.5 mmol) and $Rh_2(OAc)_4$ (2.2 mg, 1 mol %) in anhydrous TFT (5 mL) at reflux under an argon

atmosphere and the mixture was stirred at this temperature for additional 5 min. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel (eluent hexane/EtOAc) to give compound **4a**–**f**.

*4.4.2. Ethyl 2-cyano-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**4a**).* Compound **4a** was prepared according to procedure C from azirine **1a** (75 mg, 0.43 mmol) and diazo compound **2a** (60 mg, 0.43 mmol) as a yellowish oil (73 mg, 60%). R_f=0.36 (50% EtOAc/hexane). IR (KBr): 3260, 2985, 2925, 2850, 1755, 1665, 1605, 1580, 1555, 1495, 1465, 1270, 1185, 1160, 1020 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.1 Hz, CH_3), 3.91 (3H, CH_3O), 4.40 (q, 2H, J=7.1 Hz, CH_2), 5.56 (s, 1H, C-4), 6.24 (s, 1H, NH), 7.03 (d, 2H, J=8.8 Hz, ArH), 7.69 (d, 2H, J=8.8 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 55.6 (CH_3O), 64.8 (CH_2), 65.4 (C-2), 94.8 (C-4), 113.7 (CN), 114.8, 120.7, 129.2 (Ar), 161.7, 164.0, 178.0 (Ar, C-5, C=O), 185.8 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}N_2O_4$, 287.1026; found 287.1038. Compound **4a** was obtained in quantitative yield by refluxing a solution of oxazine **3a** in anhydrous TFT for 1 h.

*4.4.3. Ethyl 2-cyano-3-oxo-5-phenyl-2,3-dihydro-1H-pyrrole-2-carboxylate (**4b**).* Compound **4b** was prepared according to procedure C from azirine **1b** (75 mg, 0.52 mmol) and diazo compound **2a** (72 mg, 0.52 mmol) as a yellowish solid (79 mg, 60%). Mp 115–118 °C (Et_2O). R_f=0.45 (50% EtOAc/hexane). IR (KBr): 3300, 2985, 1750, 1680, 1545, 1490, 1475, 1250, 1150, 1075 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, 3H, J=7.1 Hz, CH_3), 4.41 (q, 2H, J=7.1 Hz, CH_2), 5.65 (s, 1H, C-4), 6.17 (s, 1H, NH), 7.54–7.75 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 65.0 (CH_2), 65.4 (C-2), 96.4 (C-4), 113.4 (CN), 127.1, 128.6, 129.4, 133.6 (Ar), 161.4, 178.5 (C-5, C=O), 186.0 (C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{14}H_{12}N_2NaO_3$, 279.0740; found 279.0733.

*4.4.4. Ethyl 2-cyano-5-(4-methylphenyl)-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**4c**).* Compound **4c** was prepared according to procedure C from azirine **1c** (75 mg, 0.47 mmol) and diazo compound **2a** (66 mg, 0.47 mmol) as a yellowish solid (82 mg, 64%). Mp 102–104 °C (Et_2O). R_f=0.49 (50% EtOAc/hexane). IR (KBr): 3290, 2985, 2935, 1760, 1680, 1615, 1580, 1555, 1465, 1251, 1190, 1155, 1015, 970 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, 3H, J=7.1 Hz, CH_3), 2.46 (s, 3H, CH_3), 4.40 (q, 2H, J=7.1 Hz, CH_2), 5.61 (s, 1H, C-4), 6.19 (s, 1H, NH), 7.35 (d, 2H, J=7.8 Hz, ArH), 7.62 (d, 2H, J=7.8 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.7 (CH_3), 64.9 (CH_2), 65.4 (C-2), 95.6 (C-4), 113.5 (CN), 125.7, 127.1, 130.1, 144.7 (Ar), 161.5, 178.5 (C-5, C=O), 186.0 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}N_2O_3$, 271.1077; found 271.1083.

*4.4.5. Ethyl 5-(4-chlorophenyl)-2-cyano-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**4d**).* Compound **4d** was prepared according to procedure C from azirine (75 mg, 0.42 mmol) and diazo compound **2a** (58 mg, 0.42 mmol) as a yellowish solid (72 mg, 59%). Mp 150–153 °C (Et_2O). R_f=0.56 (50% EtOAc/hexane). IR (KBr): 3280, 2980, 1760, 1680, 1600, 1580, 1545, 1485, 1465, 1235, 1155, 1095, 1015 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 1.22 (t, 3H, J=7.1 Hz, CH_3), 4.30 (q, 2H, J=7.1 Hz, CH_2), 5.91 (s, 1H, C-4), 7.72 (d, 2H, J=8.5 Hz, ArH), 7.94 (d, 2H, J=8.5 Hz, ArH), 9.71 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 65.1 (CH_2), 65.5 (C-2), 96.6 (C-4), 113.3 (CN), 127.0, 128.4, 129.8, 140.0 (Ar), 161.3, 177.2 (C-5, C=O), 186.0 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{14}H_{12}{}^{35}ClN_2O_3$, 291.0531; found 291.0533.

*4.4.6. Ethyl 2-cyano-4-methyl-5-phenyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**4e**).* Compound **4e** was prepared according to procedure C from azirine **1e** (80 mg, 0.5 mmol) and diazo compound **2a** (70 mg, 0.5 mmol) as a yellowish solid (49 mg, 36%). According to ^1H NMR spectroscopy oxazine **3e** was detected in the reaction mixture in 17% yield. Compound **4e**. Mp 164–165 °C (Et_2O). R_f=0.55 (50% EtOAc/hexane). IR (KBr): 3385, 3060, 2980, 1745, 1665, 1605, 1580, 1560, 1465, 1245, 1196, 1080, 950 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, 3H, J=7.1 Hz, CH_3), 1.94 (s 3H, CH_3), 4.42 (q, 2H, J=7.1 Hz, CH_2), 5.27 (s, 1H, NH), 7.55–7.71 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 8.04 (CH_3), 13.9 (CH_3), 64.1 (C-2), 65.0 (CH_2), 107.3 (C-4), 113.7 (CN), 127.9, 129.2, 130.4, 132.2 (Ar), 161.6, 174.4 (C-5, C=O), 187.7 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}N_2O_3$, 271.1077; found 271.1080. Crystal data (CCDC-970742): $C_{15}H_{14}N_2O_3$, M=270.28, monoclinic, space group $P21/n$, a=11.3003(5), b=9.3561(3), c=12.7239(4) Å, α=90, β=96.244(4), γ=90°, V=1337.24(9) $Å^3$, Z=4, T=100 K, μ(Mo Kα)=0.095 mm^{-1}, 6519 reflections measured, 3075 unique (R_{int}=0.0208) were used in all calculations. The final R_1 was 0.0385 ($2519>2\sigma(I)$) and wR_2 was 0.0898 (all data). Compound **4e** was obtained in quantitative yield by refluxing a solution of oxazine **3e** in anhydrous TFT for 5 h.

*4.4.7. Ethyl 2-cyano-4,5-diphenyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**4f**).* Compound **4f** was prepared according to procedure C from azirine **1f** (75 mg, 0.34 mmol) and diazo compound **2a** (47 mg, 0.34 mmol) as a yellowish oil (22 mg, 19%). R_f=0.58 (50% EtOAc/hexane). IR (KBr): 3290, 3060, 2985, 2925, 2250, 1755, 1655, 1605, 1550, 1485, 1440, 1245, 1180, 1075, 980 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.44 (t, 3H, J=7.1 Hz, CH_3), 4.46 (q, 2H, J=7.1 Hz, CH_2), 5.68 (s, 1H, NH), 7.21–7.55 (m, 10H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 64.6 (C-2), 65.1 (CH_2), 111.4 (C-4), 113.5 (CN), 127.5, 128.4, 128.5, 129.1, 129.2, 129.3, 129.9, 132.5 (Ar), 161.4, 174.6 (C-5, C=O), 185.2 (C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{20}H_{16}N_2NaO_3$, 355.1053; found: 355.1055. Compound **4f** was obtained in quantitative yield by refluxing a solution of oxazine **3f** in anhydrous TFT for 12 h.

4.5. Syntheses of pyrrolinones 4g–j

4.5.1. General procedure. A solution of oxazine **3g**–**j** (100 mg) in anhydrous *o*-xylene was stirred under heating at 130 °C for 3.5 h. The solvent was evaporated in vacuo and the residue purified by column chromatography on silica gel (eluent EtOAc/hexane) to give pyrrolinones **4g**–**j**.

*4.5.2. Ethyl 5-(4-methoxyphenyl)-3-oxo-2-(trifluoromethyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (**4g**).* Yield 43%. Yellowish solid. Mp 118–120 °C (hexane/Et_2O). R_f=0.44 (50% EtOAc/hexane). IR (KBr): 3230, 3010, 2940, 2845, 1760, 1670, 1605, 1555, 1505, 1270, 1180, 998 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, 3H, J=7.1 Hz, CH_3), 3.92 (s, 3H, CH_3O), 4.31–4.49 (m, 2H, CH_2), 5.62 (s, 1H, C-4), 5.73 (s, 1H, NH), 7.04 (d, 2H, J=8.9 Hz, ArH), 7.71 (d, 2H, J=8.9 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 55.6 (CH_3O), 64.0 (CH_2), 72.5 (q, J=28.7 Hz, C-2), 98.0 (C-4), 114.6 (Ar), 121.4 (q, J=283 Hz, CF_3), 121.4, 129.0 (Ar), 162.1, 163.7, 177.6 (Ar, C=O, C-5), 187.3 (C=O). HRMS (ESI-TOF, $[M+Na]^+$): calcd for $C_{15}H_{14}F_3NNaO_4$, 352.0767; found: 352.0769.

Compound **4g** was also obtained according to procedure C from azirine **1a** (100 mg, 0.57 mmol), diazo compound **2c** (125 mg, 0.69 mmol), and $Rh_2(OAc)_4$ (3 mg, 1 mol %) at 90 °C. After completion of the decomposition of the diazo compound the flask was closed with a stopper, which was fixed so as to keep a slight excess pressure and the reaction mixture was stirred at 135 °C for 3 h. The solvent was evaporated in vacuo, and the residue was purified by column chromatography on silica gel (eluent hexane/EtOAc) to give compound **4g** (39 mg, 21%).

*4.5.3. Ethyl 3-oxo-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (**4h**).* Yield 34%. Yellowish oil. R_f=0.49 (50% EtOAc/hexane). IR (KBr): 3270, 2985, 2855, 1760, 1675, 1605, 1555,

1495, 1475, 1295, 1250, 1175, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, 3H, J=7.1 Hz, CH_3), 4.32–4.45 (m, 2H, CH_2), 5.68 (s, 1H, C-4), 5.95 (s, 1H, NH), 7.52–7.64 (m, 3H, ArH), 7.73–7.76 (m, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 64.1 (CH_2), 72.6 (q, J=28.8 Hz, C-2), 99.3 (C-4), 121.3 (q, J=283 Hz, CF_3), 127.0, 129.2, 129.3, 133.2 (Ar), 161.9, 178.1 (C=O, C-5), 187.6 (C=O). HRMS (ESI-TOF, $[M+K]^+$): calcd for $C_{14}H_{12}F_3KNO_3$, 338.0401; found: 338.0399.

*4.5.4. Ethyl 5-(4-methylphenyl)-3-oxo-2-(trifluoromethyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (**4i**).* Yield 18%. Yellowish oil. R_f=0.56 (50% EtOAc/hexane). IR ($CHCl_3$): 3375, 3040, 1760, 1735, 1700, 1615, 1590, 1560, 1510, 1300, 1175 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, J=7.1 Hz, CH_3), 2.47 (s, 3H, CH_3), 4.32–4.47 (m, 2H, CH_2), 5.65 (s, 1H, C-4), 5.83 (s, 1H, NH), 7.35 (d, 2H, J=8.1 Hz, Ar), 7.64 (d, 2H, J=8.1 Hz, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 21.7 (CH_3), 64.1 (CH_2), 72.5 (q, J=28.9 Hz, C-2), 98.8 (C-4), 121.1 (q, J=283 Hz, CF_3), 126.3, 127.0, 130.0, 144.2 (Ar), 162.0, 178.1 (C=O, C-5), 187.5 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{15}H_{15}F_3NO_3$, 314.0999; found: 314.0995.

*4.5.5. Ethyl 5-(4-chlorophenyl)-3-oxo-2-(trifluoromethyl)-2,3-dihydro-1H-pyrrole-2-carboxylate (**4j**).* Yield 11%. Yellowish solid. Mp 134–137 °C (hexane/Et_2O). R_f=0.59 (50% EtOAc/hexane). IR ($CHCl_3$): 3375, 3040, 1760, 1735, 1705, 1605, 1585, 1560, 1490, 1300, 1180 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, 3H, J=7.1 Hz, CH_3), 4.33–4.48 (m, 2H, CH_2), 5.67 (s, 1H, C-4), 5.79 (s, 1H, NH), 7.53 (d, 2H, J=8.5 Hz, ArH), 7.69 (d, 2H, J=8.5 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9 (CH_3), 64.3 (CH_2), 72.7 (q, J=28.9 Hz, C-2), 99.9 (C-4), 121.2 (q, J=283 Hz, CF_3), 127.7, 128.3, 129.7, 139.5 (Ar), 161.8, 176.8, (C=O, C-5), 187.5 (C=O). HRMS (ESI-TOF, $[M+H]^+$): calcd for $C_{14}H_{12}{}^{35}ClF_3NO_3$, 334.0452; found: 334.0456.

Acknowledgements

We gratefully acknowledge the financial support of the Russian Foundation for Basic Research (Grant No. 14-03-00187) and Saint Petersburg State University (Grants No. 12.38.78.2012, No. 12.38.239.2014). This research used resources of the resource center 'Computer Center', 'Research resource center for Magnetic Resonance', 'Center for Chemical Analysis and Material Research', and 'Research resource Centre for X-ray Diffraction Studies' of Saint Petersburg State University.

Supplementary data

^1H, ^{13}C NMR spectra of all new compounds and Cartesian coordinates of optimized structures can be found. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2014.03.101. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363–3401; (b) Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Korneev, S. M.; Yufit, D. S. *Org. Biomol. Chem.* **2013**, *11*, 5535–5545; (c) Alves, M. J.; Teixeira Costa, F. In *Heterocyclic Targets in Advanced Organic Synthesis*; do Carmo Carreiras, M., Marco-Contelles, J., Eds.; 2011; p 145 Research Signpost: Trivandrum, India; (d) Padwa, A. *Adv. Heterocycl. Chem.* **2010**, *99*, 1–31; (e) Lemos, A. *Molecules* **2009**, *14*, 4098–4119; (f) Pinho e Melo, T. M. V. D.; Rocha-Gonsalves, A. M. d'A. *Curr. Org. Synth.* **2004**, *1*, 275–292; (g) Palacios, F.; Ochoa de Retana, A. M.; Martínez de Marigorta, E.; de los Santos, J. M. *Eur. J. Org. Chem.* **2001**, 2401–2414.
2. (a) Novikov, M. S.; Smetanin, I. A.; Khlebnikov, A. F.; Rostovskii, N. V.; Yufit, D. S. *Tetrahedron Lett.* **2012**, *53*, 5777–5780; (b) Khlebnikov, A. F.; Novikov, M. S.; Amer, A. A.; Kostikov, R. R.; Magull, J. *Russ. J. Org. Chem.* **2006**, *42*, 533–544.
3. (a) Khlebnikov, A. F.; Novikov, M. S.; Amer, A. A. *Tetrahedron Lett.* **2004**, *45*, 6003–6006; (b) Khlebnikov, A. F.; Novikov, M. S.; Amer, A. A.; Kostikov, R. R.; Magull, J.; Vidovic, D. *Russ. J. Org. Chem.* **2006**, *42*, 515–526.
4. (a) Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Khlebnikov, V. A.; Korneev, S. M. *Tetrahedron* **2013**, *69*, 4292–4301; (b) Khlebnikov, V. A.; Novikov, M. S.; Khlebnikov, A. F.; Rostovskii, N. V. *Tetrahedron Lett.* **2009**, *50*, 6509–6511.
5. Zavyalov, K. V.; Novikov, M. S.; Khlebnikov, A. F.; Yufit, D. S. *Tetrahedron* **2013**, *69*, 4546–4551.
6. Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.-S. *Tetrahedron* **1996**, *52*, 3095–3106.
7. Francois-Endelmond, C.; Carlin, T.; Thuery, P.; Loreau, O.; Taran, F. *Org. Lett.* **2010**, *12*, 40–42.
8. Barluenga, J.; Tomas, M.; Ballesteros, A.; Kong, J.-S.; Garcia-Granda, S.; Aguirre, A. *J. Chem. Soc., Chem. Commun.* **1993**, 217–218.
9. Schmidt, R. R.; Schwille, D.; Wolf, H. *Chem. Ber.* **1970**, *103*, 2760–2767.
10. (a) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602–8603; (b) Manning, J. R.; Davies, H. M. L. *Tetrahedron* **2008**, *64*, 6901–6908.
11. Kashima, C.; Tsuda, Y.; Imada, S.; Nishio, T. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1866–1869.
12. (a) Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682–4691; (b) Singh, B.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199–1206; (c) Maeda, M.; Kojima, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 239–247; (d) Zen, S.; Harada, K. *Chem. Lett.* **1982**, 1711–1714; (e) Brahma, S.; Ray, J. K. *J. Heterocycl. Chem.* **2008**, *45*, 311–317; (f) Bàtori, S.; Döpp, D.; Messmer, A. *Tetrahedron* **1994**, *50*, 4699–4708; (g) Brahma, S.; Ray, J. K. *Tetrahedron Lett.* **2005**, *46*, 6575–6578.
13. (a) Wasserman, H. H.; Ennis, D. S.; Vu, C. B.; Schulte, G.; Munk, M. E.; Madison, M.; Velusamy, K. V. *Heterocycles* **1993**, *35*, 975–995; (b) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 3521–3529.
14. (a) Momose, T.; Tanaka, T.; Yokota, T. *Heterocycles* **1977**, *6*, 1827–1832; (b) Campaigne, E.; Shutske, G. M. *J. Heterocycl. Chem.* **1974**, *11*, 929–936.
15. Hill, L.; Hunter, G. A.; Imam, S. H.; McNab, H.; O'Neill, W. J. *Synthesis* **2009**, 2531–2534.
16. (a) Chong, R.; Clezy, P. S. *Aust. J. Chem.* **1967**, *20*, 935–950; (b) Momose, T.; Tanaka, T.; Yokota, T.; Nagamoto, N.; Yamada, K. *Chem. Pharm. Bull.* **1978**, *26*, 2224–2232.
17. (a) Gordon, H. J.; Martin, J. C.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2129–2132; (b) Briehl, H.; Lukosch, A.; Wentrup, C. *J. Org. Chem.* **1984**, *49*, 2772–2779; (c) Gordon, H. J.; Martin, J. C.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1983**, 957–958.
18. (a) Schiess, P.; Radimerski, P. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 288–289; (b) Smit, A.; Kok, J. G. J.; Geluk, H. W. *J. Chem. Soc., Chem. Commun.* **1975**, 513–514.
19. Paton, R. S.; Steinhardt, S. E.; Vanderwal, C. D.; Houk, K. N. *J. Am. Chem. Soc.* **2011**, *133*, 3895–3905.
20. Sakaguchi, T.; Okuno, Y.; Tsutsumi, Y.; Tsuchikawa, H.; Katsumura, S. *Org. Lett.* **2011**, *13*, 4292–4295.
21. Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 6908–6918.
22. Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89–121.
23. Mancebo-Aracil, J.; Muñoz-Guillena, M. J.; Such-Basáñez, I.; Sansano-Gil, J. M. *ChemPlusChem* **2012**, *77*, 770–777.
24. (a) Bazureau, J. P.; Hamelin, J.; Lerestif, J. M. *Tetrahedron Lett.* **1993**, *34*, 4639–4642; (b) Bazureau, J. P.; Fraga-Dubreuil, J. *Tetrahedron Lett.* **2001**, *42*, 6097–6100.
25. (a) Crovetto, L.; Rios, R. *Synlett* **2008**, 1840–1844; (b) Chen, X.-H.; Gong, L.-Z.; Wang, C.; Zhou, S.-M. *Chem. Commun.* **2010**, 1275–1277.
26. Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2643–2646.
27. Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797–3800.
28. Shi, G.; Xu, Y. *J. Org. Chem.* **1990**, *55*, 3383–3386.
29. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D. .; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision C.01*; Gaussian: Wallingford, CT, 2010.