Aluminium-Catalysed Oxazolidinone Synthesis and their Conversion into Functional Non-Symmetrical Ureas

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Abstract: An efficient and practical aluminium-catalysed approach towards a range of functional oxazolidinones is reported. The method is based on cheap and readily available starting materials including terminal and internal (bicyclic) epoxides and phenyl carbamate. The oxazolidinones serve as highly useful synthons for the high yield preparation of non-symmetrical ureas by nucleophilic ring-opening affording the targeted urea compounds with excellent functional group diversity, high regioselectivity and isolated yields up to >99%.

Keywords: aluminium; homogeneous catalysis; N,O ligands; oxazolidinones; ureas

Introduction

Organic ureas are ubiquitous structures in organic chemistry and their re-emerged application potential in various areas of chemistry has been recently highlighted.[1] Prominent fields where ureas have gained importance include (asymmetric) organocatalysis[2,3] and supramolecular chemistry.[4] Organocatalytic activation of organic substrates by means of hydrogen-bonding patterns that consist of the two urea NH groups has been recognised as a powerful tool to orientate carbonyl fragments in order to increase the efficiency of various organic conversions. Asymmetric ureas have also been developed successfully and applied as enantio-controlling mediators in, for instance, the asymmetric Strecker reaction.[5] In the context of supramolecular applications, *N,N'*-disubstituted urea derivatives have proven to be versatile building blocks for the preparation of hydrogen-bonded supramolecular polymers,[6,7] helical type foldamers[8] and anion transporting molecules.[9]

There exist various synthetic methods towards non-symmetrical ureas although in most cases reactive species such as carbonylimidazolide[10] or (*in situ* prepared) isocyanate reagents[11–13] are required together with air-sensitive/toxic additives[14,15] and/or expensive metal catalysts/ligands.[12] Therefore, we set out to explore a practical synthesis of non-symmetrical ureas from readily available and cheap starting materials combined with a highly modular nature of the reaction partners (see Scheme 1). The approach uses oxazolidinones (cyclic carbamates) as intermediates that allow for nucleophilic ring-opening by suitable amines. Such an approach is not completely without precedence,[16,17] however so far oxazolidinone type intermediates have been rarely used for the preparation of non-symmetrical ureas with wide scope[18–20] and thus a more general methodology based on these precursors derived from readily available, cheap epoxides and phenyl carbamate (Scheme 1) would provide an attractive and simple route towards highly functional ureas.

Jacobsen et al. recently disclosed a method for the formation of chiral amino alcohols through a Co(salen) mediated enantioselective conversion of *meso*-
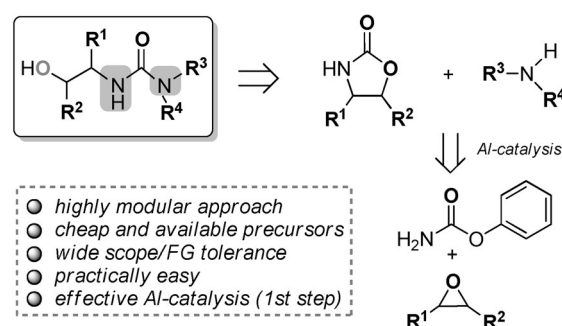
Scheme 1. A modular approach towards non-symmetrical ureas through oxazolidinone intermediates.

cyclic epoxides in the presence of phenyl carbamate as nucleophile.[21] This approach demonstrated the use of phenyl carbamate as a cheap and readily available reagent in the formal transfer of an "amide" unit to an epoxide giving enantioenriched oxazolidinones as intermediates towards the synthesis of chiral amino alcohols. However, the reported method was restricted to a limited number of cyclic epoxides. In order to be able to develop a more general method towards oxazolidinone precursors *en route* to non-symmetrical ureas, we envisioned that our previously reported Lewis acidic Al(aminotriphenolate) catalysts would present an alternative catalyst for oxazolidinone formation (Scheme 1). Recently we showed that both internal as well as terminal epoxides are easily activated towards nucleophilic ring-opening by these catalyst systems to form highly functional cyclic carbonates in the presence of carbon dioxide.[22–24] In this work we will show that these Al catalysts provide easy access to a wide range of oxazolidinone precursors useful for a modular approach towards highly functionalised ureas that are generally obtained in excellent yield and regioselectivity.

Results and Discussion

We first set out to test a small series of Al(aminotriphenolate) complexes **A–C** (Figure 1) in the synthesis of oxazolidinone **1** under various conditions (Table 1) using the coupling of cyclohexene oxide (CHO) and phenyl carbamate as a benchmark reaction. The reaction without the addition of catalyst does not proceed at 50 °C (entry 1), and at 70 °C only low conversion of the phenyl carbamate reagent is noted. In general we found that those reactions that were carried out at this latter temperature (entries 2, 5–8 and 14–15) caused (partial) decomposition of the carbamate reagent and the white precipitates noted could be isolated and assigned to the formation of 1,3,5-triazine-2,4,6(1*H*, 3*H*, 5*H*)-trione, a cyclic structure supported by ^{1}H, ^{15}N, ^{13}C NMR and IR analysis (see the Supporting Information).

Therefore, we decided to optimise further the catalysis conditions at 50 °C using various catalysts, catalyst loadings and amount of the epoxide (CHO). Al catalyst **A** performs much better than **B** (*cf.*, entries 5–8) but its use results in moderate substrate conversion
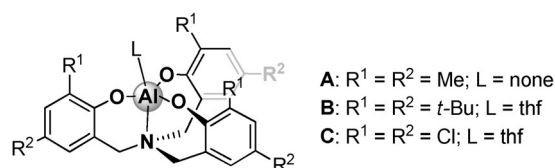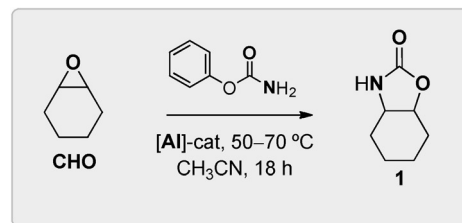
Figure 1. Al catalysts **A–C** used in this work.

A: R[1] = R[2] = Me; L = none
B: R[1] = R[2] = t-Bu; L = thf
C: R[1] = R[2] = Cl; L = thf

Table 1. Screening of catalyst structures **A–C** and reaction conditions in the synthesis of oxazolidinone **1** from cyclohexene oxide and phenyl carbamate.[a]

Entry	Cat.	Amount [mol%]	CHO [mmol]	Temp. [°C]	Conv.[b] [%]
1	–	–	1.0	50	0
2	–	–	1.0	70	17[c]
3	A	2.5	1.0	50	41
4	A	5.0	1.0	50	47
5	A	2.5	1.0	70	94[c]
6	A	5.0	1.0	70	99[c]
7	B	2.5	1.0	70	10[c]
8	B	5.0	1.0	70	15[c]
9	C	2.5	1.0	50	95 (89)[d]
10	C	5.0	1.0	50	99
11	C	2.5	0.5	50	81
12	C	2.5	0.75	50	84
13	C	2.5	2.0	50	99
14	C	1.0	1.0	70	99[c]
15	C	2.5	1.0	70	99 (71)[c,d]

[a] *General conditions:* 0.5 mmol phenylcarbamate, catalyst **A–C** (0–5 mol%), 18 h, CH$_3$CN.
[b] Conversion determined by ^{1}H NMR (CDCl$_3$) based on phenol formation.
[c] White precipitate noted.
[d] Isolated yield of oxazolidinone product in brackets.

levels at 50 °C (entries 3 and 4). Much better activity was noted for the chloride-substituted Al complex **C** for which a loading of 2.5 mol% and an equimolar amount of epoxide (entry 11) already provided 81% conversion. Further increasing the epoxide/carbamate ratio to 2 led to nearly full conversion (95%) with a high isolated yield (89%) for the oxazolidinone product (entry 9). Therefore, the reaction conditions of this latter entry seem to be rather ideal for the synthesis of oxazolidinone **1**.

Once we had discovered the best conditions for the conversion of CHO into product **1** using the most effective Al catalyst (i.e., **C**), we then started to investigate the scope of this process (Scheme 2). In general, this Al-mediated synthesis allows for a wide range of (functional) groups to be present in the epoxide substrate including alkene (**2** and **4**), alkyl halide (**5**), epoxidic (**8**), aryl bromide (**9**), alkyne (**13**) and ether (**10** and **13–15**) groups. Of further note are the syntheses of oxazolidinones **11** and **16** and compounds **1–3** that consist of an (a)cyclic dialkyl-substituted pattern. The alternative formation of acyclic and cyclic 4,5- and
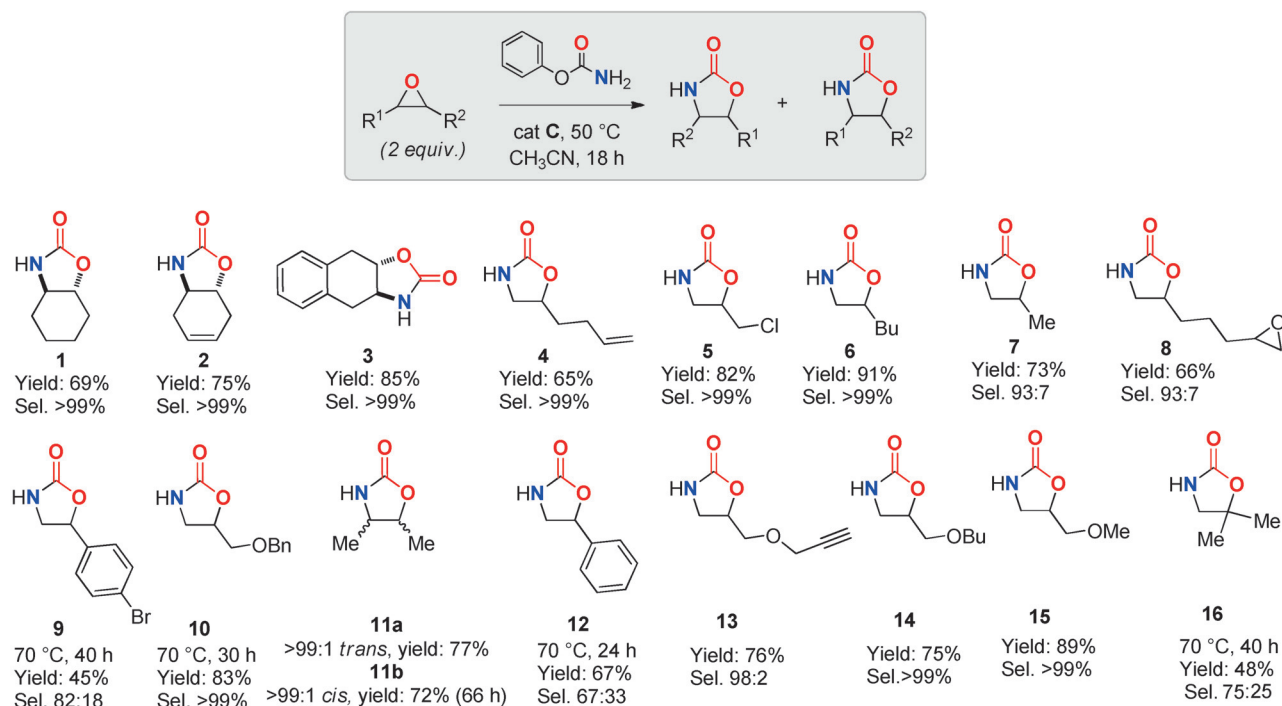
Scheme 2. Synthesis of oxazolidinones **1–16** from various epoxides and phenyl carbamate catalysed by Al-aminotriphenolate complex **C** (2 mol%). Reported here are isolated yields after column purification; selectivities refer to regioisomers formed in the case of terminal epoxide conversion (note: only the *major* isomer is shown).

5,5′-disubstituted oxazolidinone regioisomers from aziridenes/CO$_2$,[25–27] epoxide/isocyanate[28,29] or propargylic amine/CO$_2$[30] substrate combinations typically require harsher reaction conditions, a higher loading of catalyst and/or the use of stoichiometric/expensive additives and more elaborate procedures. The method disclosed here towards oxazolidinones **1–16** is operationally simple and allows for high conversion under attractive reaction conditions (50 °C, 2 mol% of catalyst). The majority of the oxazolidinone compounds could be isolated in good yields (up to 91%) and high regioselectivity for the 5-isomer was noted with some exceptions (*cf.*, the synthesis of **9**, **12** and **16**). Since these reactions occur with inversion of configuration at the carbon centre at the initial stage of the reaction (i.e., nucleophilic attack of the carbamate reagent onto the epoxide-Al complex), those reactions that involve *cis*-configured carbon centres in the oxirane unit give rise to oxazolidinones with a *trans* disposition (*cf.*, syntheses of **1–3** and **11a**). Thus these conversions proceed with formal inversion unlike the reactions between isocyanates and epoxides.[29] This inversion pathway was further substantiated by the synthesis of **11b** (*cis* diastereoisomer of **11a**; *dr* > 99%) that was prepared from the *trans*-epoxide.

The envisioned mechanism involves a nucleophilic attack of the phenyl carbamate on the coordinated epoxide producing a reactive alkoxide which is stabilised by the Al complex (Scheme 3) displaying dual
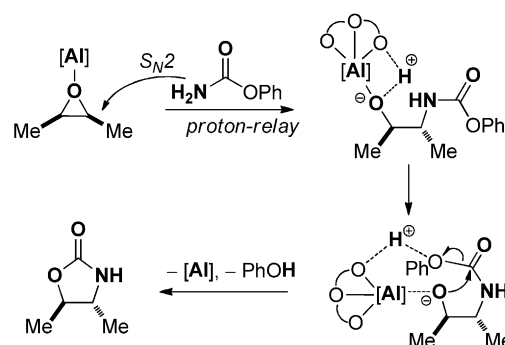
Scheme 3. Proposed mechanism leading to formal inversion in *cis*-2,3-dimethyloxirane.

character: the aminotriphenolate ligand acts here as a proton relay mediator increasing the nucleophilic character of the alkoxide which allows a more efficient ring-closing to occur releasing the final (configurationally inverted) product and a phenoxide as a leaving group.[31] The formation of phenol, as a result of the phenoxide abstracting a proton, is easily recognised in the reaction mixture and thus allows for following the course of the process (see Table 1, Scheme 3).

The oxazolidinones **1–16** serve as useful precursors towards the formation of highly functional, non-symmetrical ureas as shown in Scheme 4. Treatment of the respective oxazolidinone precursor with a suitable
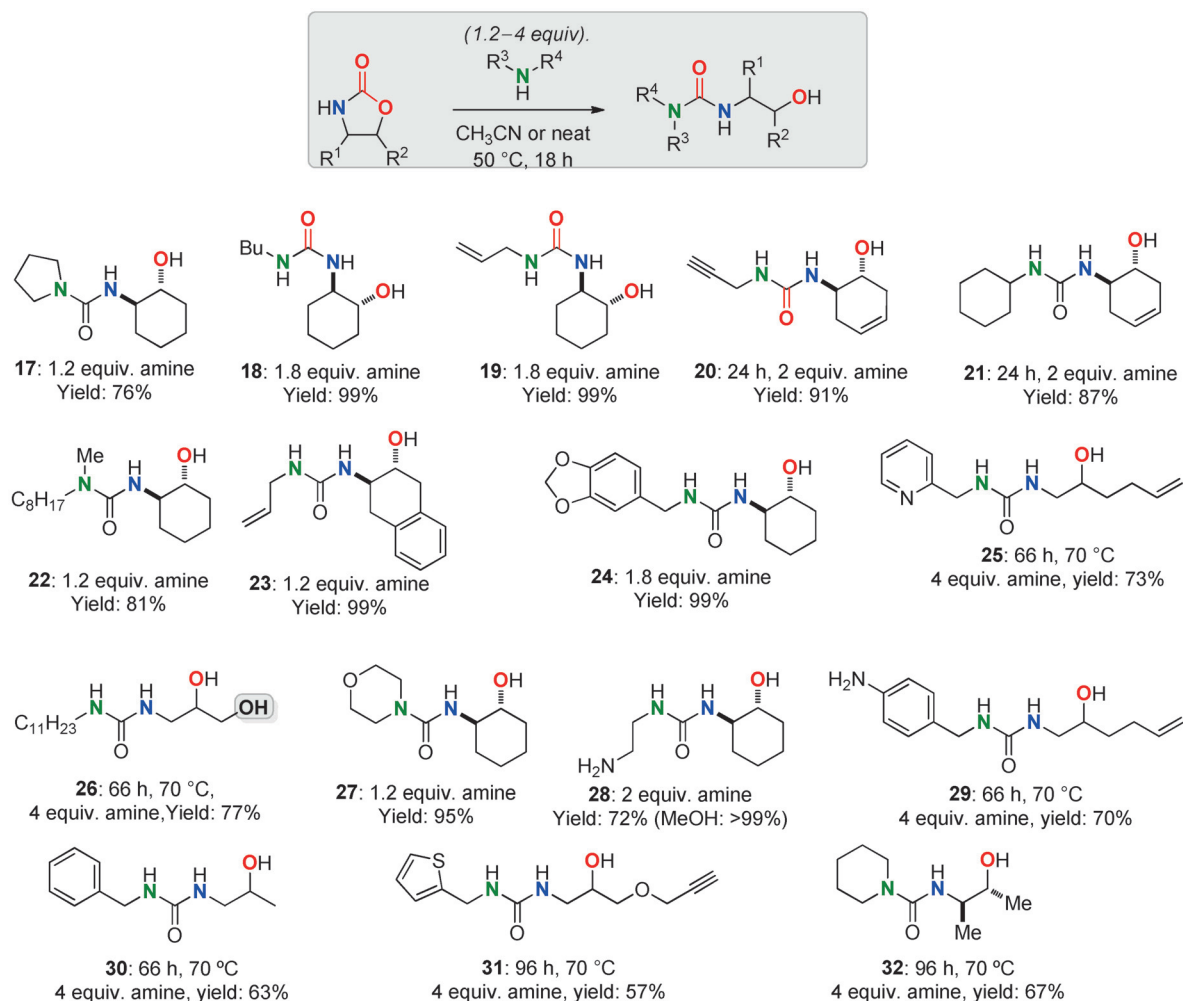
Scheme 4. Synthesis of non-symmetrical ureas **17–32** from oxazolidinone precurcors and primary/secondary amines. Reported yields are isolated ones after column purification/crystallisation.

amine (1.2–4 equiv,) allows for isolation of the urea product in high yield and chemoselectivity. The aminolysis of the oxazolidinone occurs with exclusive preference for scission of the NH−C=O bond. The formation of ureas **17–24**, **27** and **28** from bicyclic oxazolidinones proceeds generally under mild reaction conditions in the presence of a small excess of amine reagent in CH_3CN solvent. This procedure is attractive, practical and proceeds with full conversion of the starting materials. In the case where oxazolidinones derived from terminal epoxides are used as starting materials (i.e., **25**, **26** and **29–32**), the aminolysis reaction required generally higher temperature, longer reaction times and a larger excess of amine reagent (4 equiv.) under solvent-free conditions. In the latter cases, somewhat lower isolated yields are noted (up to 73%).

The scope demonstrated in Scheme 3 illustrates that highly functionalised ureas can be prepared including those incorporating pyrrolidine (**17**), alkene (**19**, **20**, **21**, **23**, **25** and **29**), alkyne (**20** and **31**), hetero-

cyclic (**24**, **25**, **27**, **31** and **32**), alkylamine (**28**) and vicinal diol (**26**) groups. Note that urea **26** is derived from the oxazolidinone **5** which is based on the initial use of epichlorohydrin. The longer reaction time needed to convert **5** into **26** resulted in effective hydrolysis of the alkyl chloride fragment which is in line with the recorded NMR data and mass spectrometric analysis (see the Supporting Information).

Both primary as well as secondary amines (cf., syntheses of **17**, **22**, **27** and **32**) react smoothly with the oxazolidinone precursors further amplifying the potential scope of this urea formation reaction. The molecular structure of urea **27** (Figure 2) was determined by X-ray diffraction. Compound **27** was derived from oxazolidinone **1**. Thus, the relative configuration of the urea and the free alcohol groups (trans) is a further testament for the proposed inversion mechanism as depicted in Scheme 3.

The diversity of functional groups in the presented scope of urea products has potential in post-synthetic modifications as shown in Scheme 5. To demonstrate
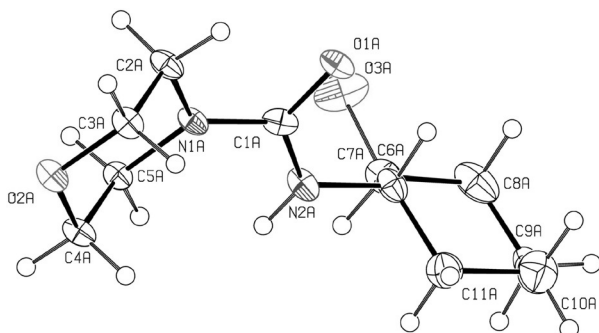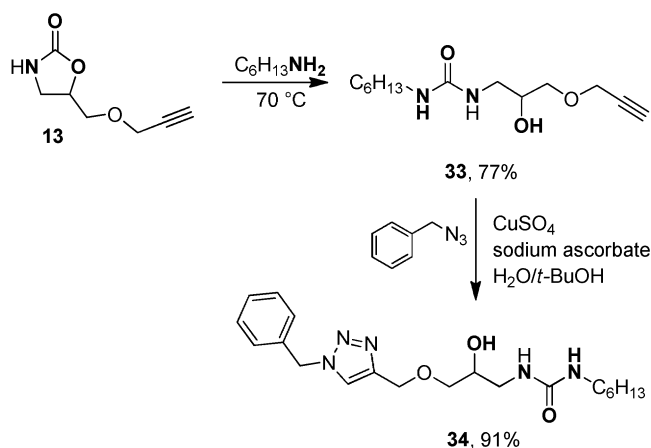
Figure 2. X-ray molecular structure determined for urea **27**. Selected interatomic distances (Å) and angles (°) with esds in parentheses: N(1A)−C(1A)=1.366(5), N(2A)−C(1A)= 1.356(5), C(1A)−O(1A)=1.248(5), N(2A)−C(6A)= 1.449(5); N(1A)−C(1A)−N(2A)=117.8(4), N(1A)−C(1A)− O(1A)=120.4(4), N(2A)−CC(1A)−CO(1A)=121.8(4).

Scheme 5. Synthetic potential of urea **13**.

further use of these scaffolds, urea **13** was subjected to "click" chemistry conditions using benzyl azide as coupling partner: this afforded the triazole **34** smoothly in 91% yield.[32] The use of click reactions to functionalise polymer supports or other macromolecular structures is interesting for catalytic[33] and supramolecular applications[34,35] and therefore this chemistry combined with suitable urea synthons opens up new opportunities in the aforementioned areas.

Conclusions

We here disclose a simple but effective two-step method for the formation of highly functional, nonsymmetrical ureas from easy to prepare oxazolidinones. The cyclic carbamates are derived from cheap and readily available epoxides and phenyl carbamate mediated through Al catalysis. The method is further characterised by its operational simplicity and wide

scope in ureas that can be attained. Further to this, these functional ureas may serve as suitable scaffolds in organic synthesis which can be post-modified using "click" type reactions as demonstrated herein.

Experimental Section

Oxazolidinone Synthesis

Typically, phenyl carbamate (1 mmol), the epoxide (2 mmol), the aluminium catalyst (2 mol%) and acetonitrile (2 mL) were introduced into a glass vial (5 mL) equipped with a stirring bar. The vial was closed and introduced into a silicon oil bath preheated at the desired reaction temperature (50–70 °C) and the mixture was stirred for 18 h. Once the reaction mixture had cooled down to room temperature the product was purified by flash-column chromatography and analysed. Full characterisation data and copies of relevant spectra are provided in the Supporting Information.

Urea Synthesis

Typically, the oxazolidinone (0.5 mmol) was introduced into an HPLC vial equipped with a stirring bar. For the oxazolidinones based on bicyclic scaffolds, the amine reagents were introduced (usually 1.2 equiv. but was increased to 1.8 equiv. when dealing with volatile amines) with addition of acetonitrile (0.2 mL) and heated to the desired temperature (50 °C) for 18 h. Once the reaction mixture had cooled down to room temperature the pure product was isolated by evaporation of the excess of amine. The crude ureas were recrystallised from dichloromethane (ureas **20**, **21**, **23**, **24**, **27** and **28**) or purified by flash column chromatography. The oxazolidinones with monocyclic scaffolds were treated with the respective amine reagent (4 equiv.) under neat conditions and heated to 70 °C for 66 h. The products were then isolated by recrystallisation from dichloromethane (for urea **29**) or purified by flash column chromatography. Full characterisation data and copies of relevant spectra are provided in the Supporting Information.

Crystallographic Studies

The measured crystal was stable under atmospheric conditions; nevertheless it was treated under inert conditions immersed in perfluoro-polyether as protecting oil for manipulation. Data collection: measurements were made on a Bruker-Nonius diffractometer equipped with an APPEX II 4 K CCD area detector, a FR591 rotating anode with Mo Kα radiation, Montel mirrors and a Kryoflex low temperature device ($T=-173$ °C). Full-sphere data collection was used with ω and ϕ scans. Programs used: data collection Apex2 V2011.3 (Bruker-Nonius 2008), data reduction Saint+Version 7.60A (Bruker AXS 2008) and absorption correction SADABS V. 2008-1 (2008). Structure solution: SHELXTL Version 6.10 (Sheldrick, 2000) was used.[36] Structure refinement: SHELXTL-97-UNIX VERSION.

Crystal data for **27**: $C_{11}H_{20}N_2O_3$, $M_r=228.29$, triclinic, *P*-1, $a=6.4520(13)$ Å, $b=9.1250(18)$ Å, $c=20.031(4)$ Å, $\alpha=92.00°$, $\beta=92.90°$, $\gamma=90.06°$, $V=1177.1(4)$ Å^3, $Z=4$, $\rho=1.288$ mg M^{-3}, $\mu=0.094$ mm^{-1}, $\lambda=0.71073$ Å, $T=100(2)$ K,

Acknowledgements

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