Enantiopure imidazolinium-dithiocarboxylates as highly selective novel organocatalysts†

Oksana Sereda, Amélie Blanrue and René Wilhelm*

Received (in Cambridge, UK) 14th October 2008, Accepted 4th December 2008
First published as an Advance Article on the web 24th December 2008
DOI: 10.1039/b817991c

Asymmetric imidazolinium-dithiocarboxylates have been found for the first time to be highly selective catalysts; in the present case, the novel organocatalysts were able to catalyze the Staudinger reaction in up to 96% ee and 99% yield.

Imidazolinium-dithiocarboxylate[1,2] inner salts belong to the extraordinary class of carbene complexes of nonmetals.[1a] They can be formally prepared by the addition of an imidazolinium carbene to CS_2. These zwitterions are known to be stable[1,2] contrary to their CO_2 analogues.[1a,3] The CS_2 group is tilted almost perpendicularly relative to the imidazolinium ring and may be regarded as a Lewis base center (Scheme 1).

Recently, we reported the application of symmetric imidazolinium-dithiocarboxylates as catalysts for the TMSCN addition on aldehydes.[4] Due to our interest in the Staudinger reaction[5] we were wondering if the CS_2 unit of an imidazolinium-dithiocarboxylate would be a sufficient Lewis base catalyst and the positive center of the imidazolinium ring could stabilize a transition state of the intermediate. Hence, we would like to present the application of enantiopure imidazolinium-dithiocarboxylates for the first time as highly selective novel asymmetric organocatalysts[6] in the Staudinger reaction[7] for the preparation of β-lactams. Highly selective catalytic systems for the Staudinger reaction were developed by Lectka *et al.*[7a,d,f,g] using cinchona alkaloid derivatives and Fu *et al.*[7b,c] using a planar chiral ferrocene-DMAP analogue as catalyst. Recently, the groups of Ye and Smith could apply chiral carbenes in an asymmetric Staudinger reaction with either Boc protected imines with up to 99% ee and yields between 53 and 78% or tosyl protected imines in yields of up to 96% with up to 75% ee.[7g,h]

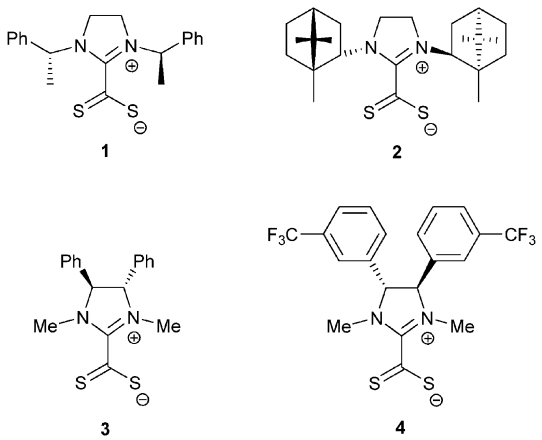
First, enantiopure imidazolinium-dithiocarboxylates depicted above were prepared. The new zwitterion **3** was prepared from its corresponding diamine[8] according to a literature procedure[2h] in 68% yield. The zwitterions **1**, **2** and **4** were synthesised from their corresponding imidazolinium salts[9] *via* two routes. Zwitterions **1** and **2** were prepared by the addition of 1 equiv. KO*t*Bu to the imidazolinium salts in order to generate the carbene in 30 min, followed by the addition of 5 equiv. of CS_2 in 43 and 74% yield, respectively. Zwitterion **4** was obtained by mixing the corresponding imidazolinium salt with 5 equiv. of CS_2 followed by the addition of 1.5 equiv. KHMDS in 54% yield after 15 min.

Institute of Organic Chemistry, Clausthal University of Technology, Leibnizstr. 6, 38678 Clausthal-Zellerfeld, Germany. E-mail: rene.wilhelm@tu-clausthal.de; Fax: +49 (0)5323 722834; Tel: +49 (0)5323 723886

† Electronic supplementary information (ESI) available: Full experimental procedures and data. see DOI: 10.1039/b817991c

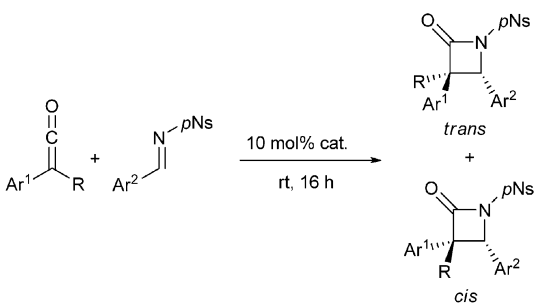
Scheme 1 Imidazolinium-dithiocarboxylates.

The [2+2] cycloaddition of ethylphenylketene[7c] and *N*-tosylbenzaldimine[10] was tested with zwitterion **1** in CH_2Cl_2 at rt for 16 h. However, it was not possible to isolate the desired product.



Assuming that the tosyl group is not activating the imine enough for our system, next the *para*-nosyl group[11] (4-nitrobenzenesulfonyl-), an excellent base and acid stable protecting group, which can be easily removed, was chosen. Under the given conditions with *N-para*-nosylbenzaldimine[12] the desired product was obtained in 98% yield with a *trans–cis* ratio of 62 : 38 related to the position of the two phenyl groups but with low ee (Scheme 2, Table 1, entry 1).

With the much hindered catalyst **2** no conversion was observed. Next, toluene was used as a solvent. The imine and zwitterion were not completely but sufficiently dissolved

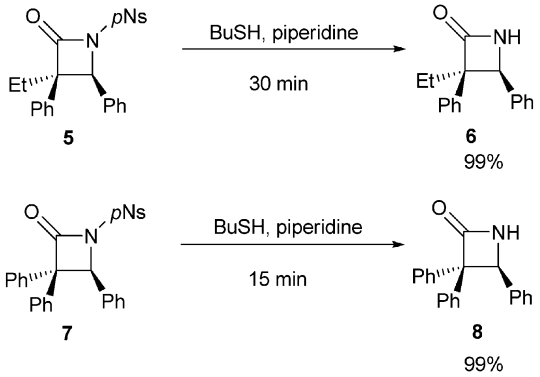


Scheme 2 Staudinger reaction.

Table 1 Staudinger reaction with 1.5 equiv. ketene (Ar^1 = Ph, R = Et) and imine (Ar^2 = Ph) with 10 mol% zwitterion under various conditions in a 0.1 M solution for 16 h

Entry	Catalyst	Solvent	Yield (*trans* : *cis*)[a]	ee (*trans* : *cis*)[b]
1	**1**	CH_2Cl_2	98% (62 : 38)	6% : 4%
2	**2**	CH_2Cl_2	—	—
3	**3**	CH_2Cl_2	99% (81 : 19)	11% : 22%
4	**3**	Toluene	99% (22 : 78)	80% : 74%
5	**4**	Toluene	98% (15 : 85)	65% : 87%[c]

[a] Assignment of diastereomers *via* H-NMR CH_2 signal (*m* for *trans* and *q* for *cis*) in analogy to ref. 13. [b] Absolute configurations *trans*/*cis*: **1** (3*S*,4*S*)/(3*R*,4*S*); **3** (3*S*,4*S*)/(3*R*,4*S*); **4** (3*R*,4*R*)/(3*S*,4*R*). [c] ee could be increased to 99% through simply washing three times with 10% *i*PrOH–hexane.



Scheme 3 Deprotection of β-lactams.

to have an effective catalyst loading of 4 mol% in order to have no influence on the reaction time. However, the diastereomeric ratio shifted in favour of the *cis* diastereomer and more importantly, the obtained ee increased and gave with zwitterion **3** up to 74% ee for the major diastereomer (Table 1, entry 4). The reverse of the diastereoselectivity switching from a polar to an unpolar solvent may be explained by possible equilibriums involving ionic intermediates before the ring closing step leading in a polar solvent to the *trans* product. Zwitterion **4**, with its slightly bulkier groups in the backbone of the imidazolinium ring and its complete solubility in toluene, was prepared, which increased the ee of the *cis*-diastereomer to 87% (Table 1, entry 5). In addition, it was possible to increase the ee of this 87% ee sample to 99% ee by simply washing it three times with 10% *i*PrOH–hexane with a yield of 90%. Obviously, the racemate has a better solubility in the solvent mixture than the pure enantiomer.

With the optimized conditions, several imines and ketenes were investigated with catalyst **4** as shown in Table 2.‡ In all cases very good enantioselectivities were obtained for the *cis* isomers with up to 96%, while the *trans* isomers gave constantly lower ee with up to 83%.

Due to the difficulty of acquiring an X-ray structure in order to determine the absolute configuration of the products, the opportunity arose to show the excellent behaviour of the *p*Ns protecting group for deprotection.[11a] Therefore, samples of *cis*-**5** and **7** were prepared with *ent*-**4** and washed once with a 10% *i*PrOH–hexane mixture to give the compounds in 91 and 85% ee, respectively. However, when the standard conditions for the deprotection of a *p*Ns group were used with either $HSCH_2CO_2H$ or PhSH as nucleophiles under basic conditions, the only product obtained was due to the substitution of the nitro group with the nucleophiles. That this reaction can occur, although just as a minor side reaction, is known.[11b]

Table 2 Staudinger reaction with 1.5 equiv. ketene and imine with 10 mol% **4** in a 0.1 M solution of toluene for 16 h

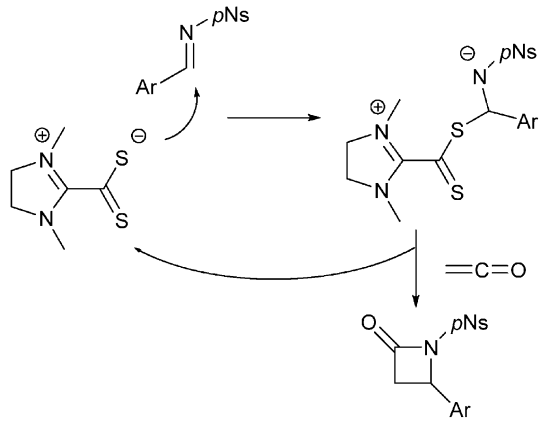
Entry	Ketene (Ar^1, R)	Imine (Ar^2)	Yield (*trans* : *cis*)	ee (*trans* : *cis*)
1	Ph, Et	2-Naphthyl	99% (14 : 86)	62% : 92%
2	Ph, Et	4-Cl-C_6H_4	98% (25 : 75)	48% : 90%
3	Ph, Et	4-CF_3-C_6H_4	96% (13 : 87)	83% : 95%
4	Ph, Et	4-NC-C_6H_4	99% (24 : 76)	74% : 93%
5	Ph, Et	4-F-C_6H_4	99% (18 : 82)	64% : 96%
6	Ph, Et	2-Thiophenyl	99% (25 : 75)	65% : 84%
7	Ph, Et	1-Naphthyl	96% (11 : 89)	70% : 83%
8	Ph, Me	4-F-C_6H_4	99% (25 : 75)	56% : 86%
9	Ph, Ph	4-F-C_6H_4	96%	76%
10[a]	Ph, Ph	Ph	96%	67%

[a] Reaction performed with *ent*-**4**.

After extensive studies it was possible to find a new procedure. As shown in Scheme 3 the protection group could be removed under mild conditions with butanethiol as solvent and piperidine to give the unprotected lactams *cis*-**6** and **8** in nearly quantitative yield. The use of butanethiol as solvent instead of DMF was essential.[11c] A possible ring opening of the lactams was not observed.[11d] The deprotected lactams were protected either with a Boc or tosyl group in order to give the literature known Boc protected lactam from *cis*-**6**[7g] and the tosyl protected lactam from **8**.[7h] By comparing the optical rotation it was possible to assign the absolute configuration. The determined ee revealed that no racemisation took place.

In order to compare the zwitterions with carbenes in the presented reaction system, a reaction was carried out with 10 mol% of the precursor salt of **3** and 9 mol% DBU in toluene with ethylphenylketene[7c] and *N*-*para*-nosylbenzaldimine.[12] After 16 h, the two diastereomers were obtained in 44% yield with a *trans*–*cis* ratio of 40 : 60. Both diastereomers were racemic. Taking into account that the base used to generate the carbene could have an influence on the outcome of the reaction, several other bases like *n*-BuLi, KO*t*Bu and KHMDS were tested. The highest ee was obtained with 10 mol% of the precursor salt of *ent*-**4** and 8 mol% KHMDS. The product was obtained in a *trans*–*cis* ratio of 40 : 60 with the *trans* product as racemate and the *cis* isomer **5** with 20% ee. These experiments should exclude the unprecedented although for many applications desirable possibility that small amounts of carbenes are generated from the zwitterions under the reaction conditions and are therefore coherent with literature.[1a]

In order to determine the possible reaction mechanism, a reaction was carried out in an NMR tube and followed over time by NMR. It was not possible to observe any shift changes of the zwitterion **3**, ketene and imine and it was only possible to observe the appearance of the product.



Scheme 4 Possible mechanism.

Therefore, the following two Lewis base catalysed sequences[7b,g,h] could be possible in the present case. Either the zwitterion is activating the ketene, which is reacting further with the imine, or it is activating the very electron deficient imine, which is reacting further with the ketene. In Scheme 4, the latter possibility is depicted.

In conclusion we have shown that the utilization of enantiopure imidazolinium-dithiocarboxylates as novel organocatalysts in the Staudinger reaction with *p*Ns protected imines can give the product in high yield and high enantiomeric excess. In addition, a procedure has been found to deprotect *p*Ns protected β-lactams in short times and high yields. Currently, the mechanism of the reaction is being further investigated.

This work was supported by the DFG in the framework of the priority research program "Organocatalysis" SPP 1179. Financial support by Fonds der Chemischen Industrie is gratefully acknowledged. In addition, Dr Dräger from the University of Hannover is acknowledged for HRMS measurements.

Notes and references

‡ *General experimental procedure for the Staudinger reaction.* An imine[12] (0.1 mmol), a ketene[7c] (0.25 mmol) and a zwitterion (10 mol%) were dissolved in dry toluene (1 ml) and left to stir for 16 h. After total conversion, the reaction mixture was applied to column chromatography on silica gel, and products were eluted with 1 : 8 diethyl ether–petrol ether mixture to give the desired compounds as white solids (yields: 96–99%). *General experimental procedure for the preparation of zwitterions.* A salt and 5 equiv. CS_2 were dissolved in THF. 1.5 equiv. KHMDS were added, and the reaction was quenched with NH_4Cl solution after 15 to 30 min. The aqueous solution was extracted with CH_2Cl_2, the solvent was removed, and the crude product was purified on silica gel.

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