Asymmetric Synthesis of *trans*-3-Amino-4-alkylazetidin-2-ones from Chiral *N,N*-Dialkylhydrazones

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ABSTRACT
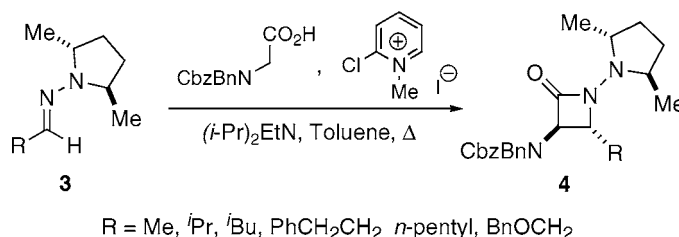
Enantiopure *N,N*-dialkylhydrazones 3 smoothly react with *N*-benzyloxycarbonyl-*N*-benzyl glycine as an aminoketene precursor to afford *trans*-3-amino-4-alkylazetidin-2-ones 4 as single diastereomers. As an exception, hydrazone 3f (R = OBn) affords *cis*-(3R,4R)-4f under modified conditions. N–N Bond cleavage of cycloadducts 4 afforded free azetidinones 5 in high yields.

The discovery of monocyclic β-lactam antibiotics,[1] named and classified as monobactams, and the introduction of drugs such as aztreonam and carumonam (Figure 1) have stimulated considerable activity focused on the development of stereoselective routes for the key 3-aminoazetidin-2-one substructure.[2] One of the most powerful methods for the preparation of these compounds is the [2 + 2] cycloaddition reaction of ketenes to imines (the Staudinger reaction), but the method is in general limited by the poor stability of some imines, in particular, the easily tautomerizable imines derived from aliphatic aldehydes. On the basis of our previous experience with *N,N*-dialkylhydrazones,[3] we recently started a project

based on exploiting the higher stability of these compounds relative to *N*-alkyl(aryl) imines in the Staudinger reaction. It was discovered that formaldehyde derivatives behave as a stable class of monomeric methanimines in their reaction with functionalized (alkoxy and amino) ketenes[4] and that the stability of aliphatic *N,N*-dialkylhydrazones is key for a
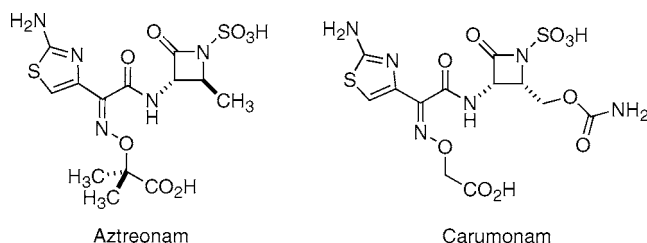

Figure 1. Clinically used monobactams.

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(1) (a) Imada, A.; Kitano, K.; Kintaka, K.; Muroi, M.; Asai, M. *Nature* **1981**, *289*, 590. (b) Sykes, R. B.; Cimarusti, C. M.; Bonner, D. P.; Bush, K.; Floyd, D. M.; Georgopadakou, N. H.; Koster, W. H.; Liu, W. C.; Parker, W. L.; Principe, P. A.; Rathnum. M. L.; Slusarchick, W. A.; Trejo W. H.; Wells, T. S. *Nature* **1981**, *291*, 489.

(2) Review: Ternansky, R. J.; Morin, J. M., Jr. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; p 257.

straightforward synthesis of 3-alkoxy-4-alkyl(aryl)-azetidin-2-ones and of the corresponding isoserines[5] (Scheme 1).
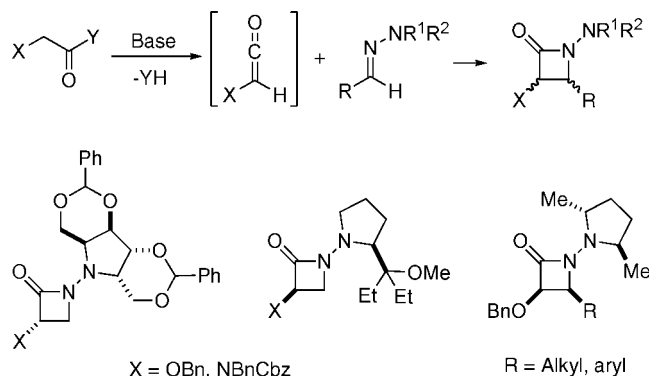
We wish to report herein our results in the Staudinger-like [2 + 2] cycloaddition of chiral, aliphatic *N,N*-dialkyl-hydrazones **3** to α-aminoketenes **2** for the synthesis of 3-amino-4-alkylazetidin-2-ones **4** and derivatives therefrom.

We chose as reagents hydrazones **3a−f**,[6] containing C_2-symmetric (2*R*,5*R*)-2,5-dimethylpyrrolidine as the auxiliary, bearing in mind the excellent stereocontrol and high reactivity observed in their cycloadditions to benzyloxyketene.[5] On the basis of our previous experience with 4-unsubstituted derivatives,[4] we decided to use *N*-benzyloxycarbonyl-*N*-benzyl-glycine **1** as the source of aminoketene **2** and 2-chloro-*N*-methyl pyridinium iodide as activating agent (Scheme 2).

Scheme 2. Synthesis of 3-Amino-4-alkylazetidin-2-ones **4**
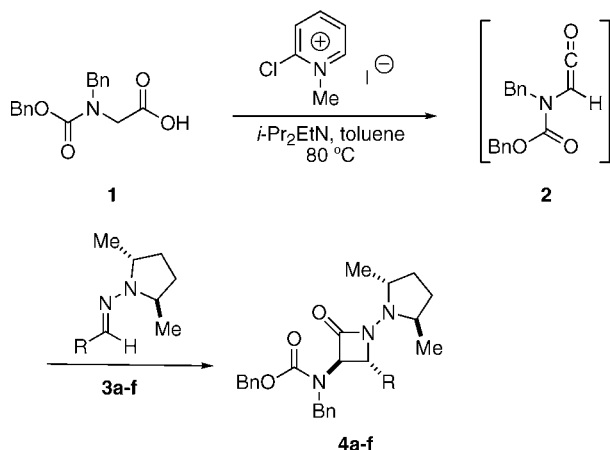
Experiments carried out under the conditions (Et$_3$N, toluene, Δ) previously optimized for formaldehyde derivatives,[4] however, afforded cycloadducts **4a−f** in low yields (25−

50%). On the other hand, the analysis of the reaction mixtures indicated the formation of a single stereoisomer.

Fortunately, a screening of different reaction conditions revealed the key importance of the base used for the generation of the ketene. Thus, replacement of Et$_3$N by the more hindered (*i*-Pr)$_2$EtN resulted in a significant improvement of the results, leading to the isolation of the corresponding products **4a−f** in moderate-to-good yields (Table 1).

Table 1. Synthesis of 3-Amino-4-alkylazetidin-2-ones **4a−f**

entry	educt	R	T (h)	product	yield (%)[a]	*trans*:*cis*[b]
1	**3a**	Me	6	**4a**	74	>99:1
2	**3b**	*i*-Pr	53	**4b**	66	>99:1
3	**3c**	*i*-Bu	26	**4c**	72	>99:1
4	**3d**	PhCH$_2$CH$_2$	20	**4d**	70	>99:1
5	**3e**	*n*-C$_5$H$_{11}$	10	**4e**	58	92:8
6	**3f**	BnOCH$_2$	38	**4f**	66	54:46[c]

[a] Yield of isolated product. Reactions were performed at 1 mmol scale in toluene at 80 °C. [b] Determined by ^{1}H and ^{13}C NMR analysis of the crude reaction mixtures. The (3*R*,4*R*)/(3*S*/4*S*) diasteromeric ratio was >99:1 in all cases. [c] Separable by column chromatography.

Surprisingly, most reactions afforded products **4** as single *trans* (3*R*,4*R*)-isomers,[7] in sharp contrast with the reported *cis*-selective cycloaddition with benzyloxyketene.[5] This different behavior was interpreted as result of the more demanding steric interactions at the conrotatory ring-closing step. A possible *cis* → *trans* base-catalyzed isomerization was experimentally ruled out,[8] thereby confirming that kinetically controlled products are obtained. According to the commonly accepted mechanism for the Staudinger reaction, the analysis of the results collected in Table 1 and comparison with those observed for the cycloaddition to benzyloxyketene (*cis* (3*R*,4*S*)-products) suggests a uniform path (*outward* approach of the ketene) for the formation of the zwitterionic intermediate, which in the absence of severe steric interactions may directly suffer ring closing to afford *cis* products. Alternatively, it may also undergo a C=N bond isomerization prior to ring closing, this last process presumably being favored if the barrier for the conrotatory ring closure to *cis* products is relatively high as a result of steric interactions, as apparently happens between the bulky *N*-benzyloxycarbonyl-*N*-benzylamino group and the hydrazone alkyl group R (Scheme 3).

(4) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2893.

(5) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 831.

(6) Prepared from commercially available (*S,S*)-2,5-hexanediol (alternativelly available from 2,5-hexanedione: Lieser, J. K. *Synth. Commun.* **1983**, *13a*, 765) by dimesylation followed by reaction with hydrazine monohydrate and condensation with aldehydes.

(7) The relative *trans* stereochemistry was assigned after comparison of the $^2J_{H3,H4}$ coupling constants (2.2−2.5 Hz) with the reported typical values [J_{cis} = 4−6 Hz; J_{trans} = 0−3 Hz]: Kagan, H. B.; Basselier, J. J.; Luche, J. L. *Tetrahedron Lett.* **1964**, 941.

(8) Pure *cis*-**4f** was heated at 80 °C under the reaction conditions (6 equiv of **1**, 12 equiv of (*i*-Pr)$_2$EtN, and 6.5 equiv of 2-chloro-*N*-methyl pyridinium iodide). After 24 h no traces of *trans*-**4f** were observed.

(3) (a) Fernández, R.; Lassaletta, J. M. *Synlett* **2000**, 1228. (b) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Lassaletta, J. M. *J. Org. Chem.* **2001**, *66*, 5201. (c) Vázquez, J.; Prieto, A.; Fernández, R.; Enders, D.; Lassaletta, J. M. *Chem. Commun.* **2002**, 498.

Scheme 3. Steric Effects in Conrotatory Ring Closing from Zwitterionic Intermediates
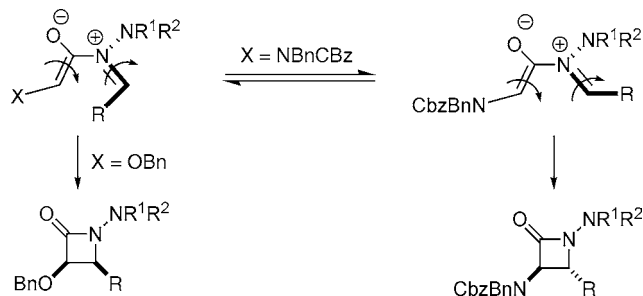
Nevertheless, the initially unexpected *trans* selectivity can be considered as an added value from the synthetic point of view, as the above results complement the only existing method available for the stereocontrolled ketene-aliphatic imine cycloaddition leading to *cis* derivatives.[9]

As a remarkable exception, the reaction of α-benzyloxy-acetaldehyde hydrazone **3f** with **2** under the same conditions afforded product **4f** as a 54:46 *trans/cis* mixture. To improve this particular result, the effect of the reaction temperature in the product distribution was analyzed. Experiments conducted at 100 and 120 °C (Table 2) afforded much lower

Table 2. Effect of Reaction Temperature in the Product Distribution of **4f**

entry	T (°C)	t (h)	yield (%)[a]	*trans*:*cis*[b]
1	rt	96	81	<1:99
2	40	29	95	<1:99
3	60	35	79	37:63
4	80	38	66	54:46
5	100	21	17	69:31
6	120	13	14	97:3

[a] Combined yield of separated *cis* and *trans* adducts after column chromatography. [b] Determined by ^{13}C and ^{1}H NMR spectroscopy in the crude reaction mixture.

yields of product (entries 5 and 6), but the observed *trans/cis* ratios were markedly higher. However, the relatively high reactivity of hydrazone **3f** allowed the reactions to be carried out at lower temperatures, leading to much higher yields of product and increasing dramatically the *cis*:*trans* ratio. An optimum reaction temperature of 40 °C resulted in the formation of pure *cis* (3R,4R)-**4f** in an excellent 95% yield while maintaining a reasonable reaction rate (entry 2).

(9) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432.

The recently reported methodology for the oxidative deamination of hydrazides[10] was applied for the N−N bond cleavage of compounds **4a**−**f**. Treatment of these cycloadducts with methanolic magnesium monoperoxyphthalate (MMPP) afforded enantiomerically pure free β-lactams **5a**−**f** in high yields (72−90%) (Table 3).

Table 3. Oxidative Cleavage of N−N Bonds

educt 4	R	product 5	yield (%)[a]
(3R,4R)-**4a**	Me	(3R,4R)-**5a**	90
(3R,4R)-**4b**	i-Pr	(3R,4R)-**5b**	72
(3R,4R)-**4c**	i-Bu	(3R,4R)-**5c**	85
(3R,4R)-**4d**	PhCH$_2$CH$_2$	(3R,4R)-**5d**	73
(3R,4R)-**4e**	n-C$_5$H$_{11}$	(3R,4R)-**5e**	74
(3R,4R)-**4f**[b]	BnOCH$_2$	(3R,4R)-**5f**	74

[a] Yield of isolated product. [b] The cleavage reaction was performed using the enantiomerically pure *cis*-(3R,4R)-**4f** adduct.

Products **5** are direct precursors for the synthesis of several bioactive compounds, including α,β-diamino acids and monobactams. As illustrative examples, compounds **5a** and **5f** were transformed into free 3-aminoazetidinones **6** and **8** (Scheme 4), enantiomers of the key components of the

Scheme 4
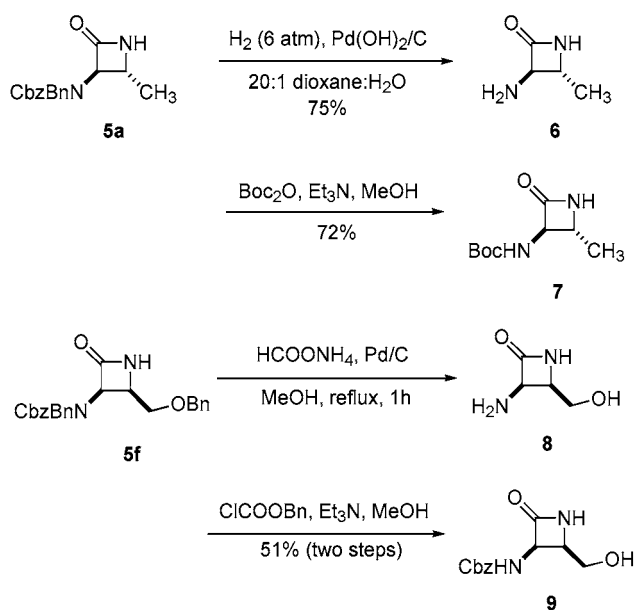
antibiotics aztreonam and carumonam, respectively. The availability of both enantiomers of the used auxiliary[11] allows

the obtention of the products with the desired absolute configuration. It is worth mentioning also that acetaldehyde and benzyloxyacetaldehyde derivatives **3a** and **3f**, used for the above syntheses, are particularly prone to enolization, a fact that highlights the stabilizing effect of the *N*-dialkyl-amino group in hydrazones.

Finally, we used chemical correlation to confirm the absolute stereochemistry assigned to these compounds. Standard protection of compound **6** afforded the known *N*-Boc-derivative **7**. The absolute configuration of (3*R*,4*R*)-**7** was determined by comparison of its optical rotation with literature data.[12] The absolute stereochemistry of the *cis* adduct (3*R*,4*R*)-**5f** was also assigned after chemical correla-tion. Thus, transfer hydrogenation of **5f** by $HCOONH_4$ and Pd/C afforded deprotected (3*R*,4*R*)-**8**, and this material was transformed into known *N*-Cbz derivative (3*R*,4*R*)-**9**.[13]

Summarizing, the unexpected *trans* selectivity and high inductions achieved in the Staudinger-like cycloaddition of *N,N*-dialkylhydrazones **3** to α-aminoketene **2** are key for the development of a short route to bioactive α-amino-*β*-lactams.

Supporting Information Available: Experimental pro-cedures and spectral and analytical data for all new com-pounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Fernández, R.; Ferrete, A.; Llera, J. M.; Magriz, A.; Martín-Zamora, E.; Díez, E.; Lassaletta, J. M. *Chem. Eur. J.* **2004**, *10*, 737.

(11) Ikeda, H.; Sato, E.; Sugai, T.; Ohta, H. *Tetrahedron* **1996**, *52*, 8113.

(12) Compound **7** had $[\alpha]^{22}_D$ +59.0 (*c* 1.9, CH_3OH). Literature data of (3*S*,4*S*)-**7**: $[\alpha]_D$ −64.2 (*c* 0.85, CH_3OH); Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 9.

(13) Compound **9** had $[\alpha]^{22}_D$ −7.4 (*c* 1, $CHCl_3$). Literature data of (3*S*,4*S*)-**9**: $[\alpha]_D$ +8.6 (*c* 0.9, $CHCl_3$); Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3783.