N,N-Dialkylhydrazones as the Imine Component in the Staudinger-Like [2+2] Cycloaddition to Benzyloxyketene**

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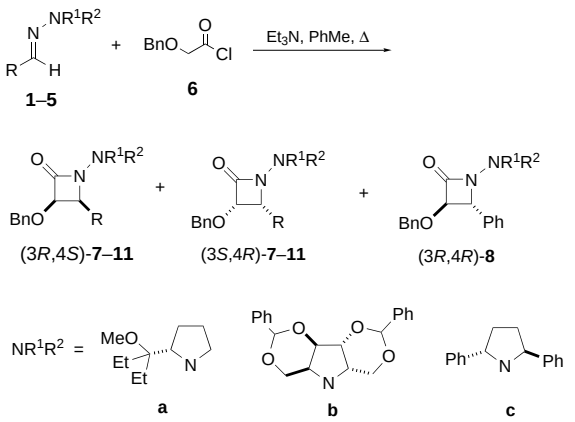
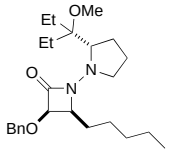
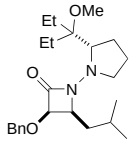
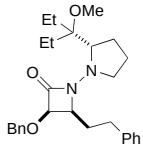
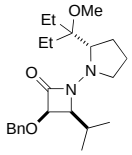
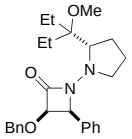
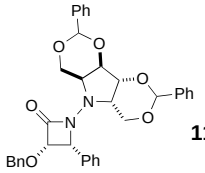
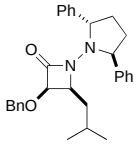
The presence of a β-lactam ring as a key substructure of the most widely used family of antibiotics has stimulated considerable activity focused on the development of stereoselective routes for its synthesis.[1] One of the most popular methods involves the [2+2] cycloaddition of ketenes and imines (the Staudinger reaction),[2] but this straightforward method suffers limitations imposed by the poor stability of some imines, such as methanimines (unstable against polymerization) and those derived from aliphatic aldehydes (easily enolizable and thermally unstable). Previously, we reported the use of formaldehyde *N,N*-dialkylhydrazones as a stable class of monomeric methanimines in the asymmetric Staudinger [2+2] cycloaddition to α-alkoxy- and α-aminoketenes.[3] Stimulated by the promising results obtained in this particular case, we decided to investigate also the behavior of higher aldehyde *N,N*-dialkylhydrazones as a stable class of enolizable imines in the same context.

Considering the lack of general approaches for the enantioselective synthesis of 4-alkyl(aryl)-3-hydroxy-β-lactams and their potential as precursors of bioactive β-amino-α-hydroxy acids,[4] we focused on the [2+2] cycloaddition of chiral aldehyde hydrazones to α-benzyloxyketene (Scheme 1). Studies started with the reaction of proline-derived hydrazones **1a**–**5a** with benzyloxyacetylchloride **6** which leads to the desired cycloadducts **7a**–**11a**, respectively, in excellent yields (84–98%), even for compounds derived from easily enolizable substrates (Table 1, entries 1–4). Under optimized conditions (toluene, Et_3N, 80 °C for primary substrates, 100 °C for secondary or aromatic substrates), moderate to good 3*R*,4*S*/3*S*,4*R* selectivities were found, and only traces of *trans* isomers were detected in some cases. Nevertheless, the collected results were satisfactorily evaluated because the diastereomers could be separated easily in all cases, thus allowing the isolation of the optically pure major *cis* isomers (3*R*,4*S*)-**7a**–(3*R*,4*S*)-**11a** in yields of 70–82%.



Scheme 1. [2+2] Cycloadditions of *N,N*-dialkylhydrazones to benzyloxyketene. **1**: R = *n*-pentyl, **2**: R = *i*Bu, **3**: R = $PhCH_2CH_2$, **4**: R = *i*Pr, **5**: R = Ph. Bn = benzyl.

Table 1. Synthesis of 1-*N,N*-dialkylamino-3-benzyloxyazetidin-2-ones **7a**–**11a**, **11b**, and **8c**.

Entry	Hydrazone	*T* [°C]	Product	Yield [%][a]	3*R*,4*S*: 3*S*,4*R*[b]	*cis*: *trans*[b]
1	**1a**	80	 **7a**	85 (70)	82:18	98:2
2	**2a**	80	 **8a**	84 (73)	87:13	98:2
3	**3a**	80	 **9a**	97 (78)	80:20	>99:1
4	**4a**	100	 **10a**	90 (82)	91:9	>99:1
5	**5a**	100	 **11a**	98 (75)	76:24	>99:1
6	**5b**	100	 **11b**	66	<1:99	>99:1
7	**2c**	80	 **8c**	53	>99:1	90:10

[a] Yield of isolated product. Values in parentheses correspond to the pure (98% *de*) major isomer. [b] Determined by means of ^{13}C and ^{1}H NMR spectroscopy.

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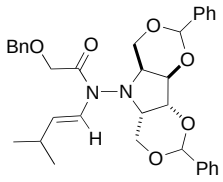
The behavior of D-mannitol-derived hydrazones[3] was studied next. However, the reaction of isobutyraldehyde hydrazone **2b** with **6** afforded only compound **12** under a



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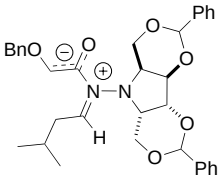

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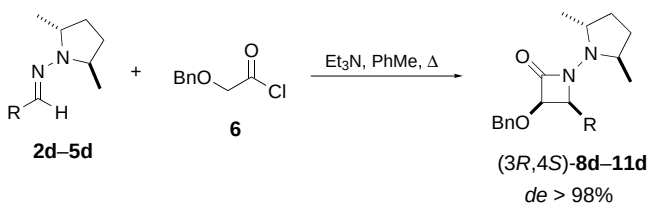
variety of reaction conditions, thus suggesting that an intramolecular H transfer in the zwitterionic intermediate[5] **13** takes place faster than the ring closure to the β-lactam. On the other hand, the non-enolizable hydrazone **5b** reacted with **6** under forcing conditions, to give the desired β-lactam **11b** in a moderate yield (66%), but with excellent stereoselectivity (Table 1, entry 6). From these results, it appears that the mannitol-derived C_2-symmetric auxiliary offers better induction in the cycloaddition process than the proline-derived auxiliary (Table 1, entries 5 and 6), but the lower reactivity of the former prevents a better result. Considering that steric factors would hardly explain the observed differences in behavior, the lack of conformational flexibility in **5b**, associated with the condensed dioxane rings, was seen as a possible reason.

Therefore, a more flexible C_2-symmetric hydrazone such as **2c**, which has (2*S*,5*S*)-diphenylpyrrolidine as the auxiliary, was synthesized[6] and treated with **6**. The desired cycloadduct **8c** was obtained with an excellent (3*R*,4*S*/3*S*,4*R*) selectivity (Table 1, entry 7), thus supporting the validity of the hypothesis mentioned above, but the yield (53%) was disappointing, and the product was contaminated with approximately 10% of the undesired *trans*-3*R*,4*R* diastereomer. The moderate reactivity of this system was attributed to a higher steric hindrance around the C=N bond, but the suitability of C_2-symmetric auxiliaries in this context was confirmed again in view of the exhibited selectivity.

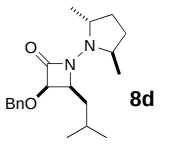
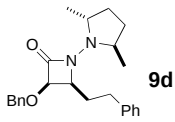
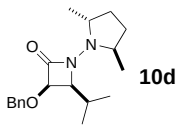
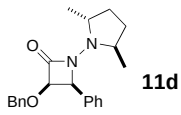
An ultimate attempt to improve the results obtained with hydrazones **1a**–**5a** was therefore based on the strategy outlined above, but with substrates that contain the sterically less demanding (2*R*,5*R*)-dimethylpyrrolidine as the auxiliary. As expected, a higher reactivity was observed in the reactions of **2d**–**5d**[7] with **6**, which proceeded smoothly to give the corresponding cycloadducts **8d**–**11d** in high yields and with excellent 3*R*,4*S*/3*S*,4*R* selectivities (Scheme 2, Table 2). In this



2d–5d + **6** → (3*R*,4*S*)-**8d–11d**, *de* > 98%

Scheme 2. [2+2] Cycloadditions using (2*R*,5*R*)-dimethylpyrrolidine as the auxiliary.

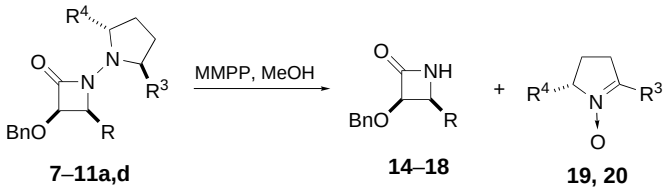
Table 2. Synthesis of 1-*N*,*N*-dialkylamino-3-benzyloxyazetidin-2-ones **8d**–**11d**.

Entry	Hydrazone	T [°C]	Product	Yield[a] [%]	3*R*,4*S*: 3*S*,4*R*[b]	*cis*: *trans*[b]
1	**2d**	60	 **8d**	70	> 99:1	95:5[c]
2	**2d**	80		91	> 99:1	85:15
3	**3d**	rt	 **9d**	67	> 99:1	> 99:1
4	**3d**	60		83	> 99:1	> 99:1
5	**3d**	80		91	> 99:1	91:9
6	**4d**	80	 **10d**	80	> 99:1	> 99:1
7	**5d**	100	 **11d**	96	> 99:1	> 99:1

[a] Yield of isolated product. [b] Determined by means of ^{13}C and ^{1}H NMR spectroscopy. [c] Inseparable mixture. The pure *cis* isomer was obtained after release of the auxiliary (see Table 3).

case, an optimum reaction temperature of 60 °C was applied to the reaction of **6** with aliphatic primary hydrazones **2d** and **3d** (Table 2, entries 1 and 4), since significant amounts of *trans* isomers appeared at 80 °C (Table 2, entries 2 and 5). The high reactivity of **2d**–**5d** allows cycloadditions even at room temperature (Table 2, entry 3), in contrast to all other hydrazones tested. Secondary (**4d**) and aromatic (**5d**) hydrazones reacted smoothly with **6** at optimized temperatures of 80 and 100 °C,[8] to give the corresponding adducts **10d** and **11d** in 80 and 96% yield, respectively (Table 2, entries 6 and 7).

The key N–N bond cleavage, which is required to remove the auxiliaries, failed under standard reductive conditions. Fortunately, the oxidative method previously developed by our group[3] was successfully applied to compounds **7a**–**11a** and **8d**–**11d**, which reacted with magnesium monoperoxyphthalate (MMPP) to afford the deaminated lactams (3*R*,4*S*)-**14**–(3*R*,4*S*)-**18** in high yields (Scheme 3, Table 3). Nitrones **19** and **20** were isolated as by-products from **7a**–**11a** and **8d**–**11d** in moderate (ca. 50%) and good (75–80%) yields,[9] respectively.



7–11a,d → **14–18** + **19, 20**

7–11a, 19: R^3 = CEt_2OMe; R^4 = H
8–11d, 20: R^3 = R^4 = Me

Scheme 3. Oxidative N–N bond cleavage. Release of the auxiliary.

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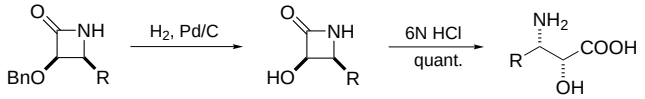
Table 3. Synthesis of 4-alkyl(aryl)-3-benzyloxyazetidin-2-ones **14**–**18**.

Starting Material	*t* [h]	Product	Yield [%][a]	$[\alpha]_D^{22}$[b]
(3*R*,4*S*)-**7a**	3	(3*R*,4*S*)-**14**	78	+28.9
(3*R*,4*S*)-**8a**	2.5	(3*R*,4*S*)-**15**	91	+33.4
(3*R*,4*S*)-**9a**	2	(3*R*,4*S*)-**16**	87	+19.9
(3*R*,4*S*)-**10a**	4	(3*R*,4*S*)-**17**	88	+120.4
(3*R*,4*S*)-**11a**	2	(3*R*,4*S*)-**18**	96	+96.8
(3*R*,4*S*)-**8d**[c]	2	(3*R*,4*S*)-**15**	84[d]	+33.5
(3*R*,4*S*)-**9d**	2	(3*R*,4*S*)-**16**	84	+20.9
(3*R*,4*S*)-**10d**	2	(3*R*,4*S*)-**17**	91	+120.6
(3*R*,4*S*)-**11d**	2	(3*R*,4*S*)-**18**	95	+97.3

[a] Yield of isolated product. [b] $c = 1$, Cl_2CH_2. [c] Starting material was a 9:1 mixture of *cis*:*trans* isomers. [d] Yield of pure *cis* product.

Finally, standard transformations of **18** and **14** afforded β-amino-α-hydroxy acids **24**, a side chain of taxol,[10] and **22**, a component of the renin inhibitor KRI-1230[11] and of the antitumor drug ABT-271,[12] respectively (Scheme 4). These experiments served not only as illustrative examples of the synthetic utility of the method, but also confirmed the absolute configuration assigned to these compounds.[13] The products with the opposite configuration could be also prepared by using the enantiomeric (2*S*,5*S*)-dimethylpyrrolidine[14] as the auxiliary.



14: R = *i*Bu
18: R = Ph

21: R = *i*Bu (85%)
23: R = Ph (72%)

22: R = *i*Bu
24: R = Ph

Scheme 4. Synthesis of β-amino-α-hydroxy acids.

In summary, the Staudinger cycloaddition of chiral *N*,*N*-dialkylhydrazones to benzyloxyketene appears to be a new general approach to the enantioselective synthesis of 4-substituted 3-alkoxyazetidin-2-ones. The (2*R*,5*R*)-dimethylpyrrolidine substituent is the key element in several aspects: 1) it confers the needed stability to the starting substrates, particularly in the aliphatic series; 2) it efficiently controls the stereochemical course of the reaction; and 3) it behaves as an efficient protecting group that can be removed easily from the β-lactam ring.

Experimental Section

7–**11**: Benzyloxyacetyl chloride (**6**, 4 mmol) in toluene (10 mL) was added stepwise (8 portions of 0.5 mmol over 3 h) to a solution of hydrazone **1**–**5** (1 mmol) and Et_3N (8 mmol) in dry toluene (5 mL). The mixture was stirred until completion and purified by chromatography.

14–**18**: $MMPP \cdot 6H_2O$ (0.9 mmol) was added to a solution of **7**–**11** (0.3 mmol) in MeOH (0.75 mL), and the mixture was stirred at room temperature until completion.

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[6] Prepared from known (1*S*,4*S*)-diphenylbutanediol (D. J. Aldous, W. M. Dutton, P. G. Steel, *Tetrahedron: Asymmetry* **2000**, *11*, 2455) by mesylation, reaction with hydrazine, and condensation with isovaleraldehyde (60% overall).
[7] Prepared from known (2*S*,5*S*)-hexanediol (J. K. Lieser, *Synth. Commun.* **1983**, *13a*, 765) by mesylation, reaction with hydrazine, and condensation with aldehyde (50–60% overall).
[8] Higher reaction temperatures, which give higher yields of product, can be applied without the formation of *trans* isomers in these cases.
[9] The isolation of **20** was possible only when MMPP was used in stoichiometric amounts. Excess oxidant results in products of over-oxidation. Details of the scope and mechanism of this deamination procedure will be published elsewhere. The recycling of the auxiliary from **20** is currently being investigated.
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