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Stereoselective Yang cyclizations of α-amido ketones

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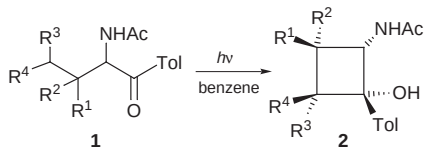
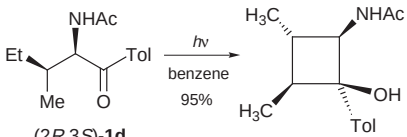
The photocyclization of methyl-substituted α-acetamido butyrophenone derivatives is highly stereoselective and leads to 2-aminocyclobutanols with complete control of three new stereogenic centers.

The term Yang cyclization describes the formation of cyclobutanols from 1-hydroxytetramethylene biradicals which are produced *via* photochemical γ-hydrogen abstraction.[1] In the course of this reaction up to eight diastereoisomers could be formed from one chiral substrate molecule. Three subsequent steps influence the chemo- and stereoselectivity of this reaction: (i) γ-H abstraction, (ii) biradical dynamics and (iii) biradical combination *vs.* cleavage reaction. Triplet excited carbonyls give rise to triplet 1,4-biradicals and, consequently, the lifetime of these intermediates (100–1000 ns)[2] rises due to slow spin inversion processes (ISC). The γ-H abstraction proceeds most likely through a six-membered chair-like transition state.[3] Detailed mechanistic investigations have been performed by Wagner and co-workers which also included stereochemical probing.[4] During our studies on photochemical transformations of enantiomerically pure α-amino acids (N-activation mode)[5] we became interested in using Yang cyclizations as a simple tool for the synthesis of 2-aminocyclobutanols (C-activation mode). As substrates α-acetamido butyrophenone derivatives **1a**–**f** were synthesized from the corresponding amino acids by a three-step reaction protocol.[6] The photochemical behaviour of these compounds was investigated by irradiation with light λ > 320 nm in benzene solutions (Scheme 1). The *tert*-leucine derivative **1a** gave the cyclobutanol **2a** (Φ_C = 0.11 ± 0.02) and the Norrish II fragmentation product **3** (Φ_F = 0.08 ± 0.02).[7] The Yang cyclization product was isolated in 45% yield as a single diastereoisomer. The *tert*-leucine **1a** and the leucine derivative **1b**, respectively, were transformed into cyclobutanols with only one additional stereogenic center and thus solely show the influence of a given stereogenic center on a proximate radical center. In both cases, the *cis*-diastereoisomers were formed with ds > 96%.

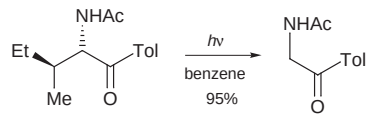


1 **2**

	R^1	R^2	R^3	R^4	C/F
a	Me	Me	H	H	50:50
b	H	H	Me	Me	49:51
c	Me	H	H	H	74:26
e	H	H	Me	H	33:67
f	H	H	Et	H	48:52



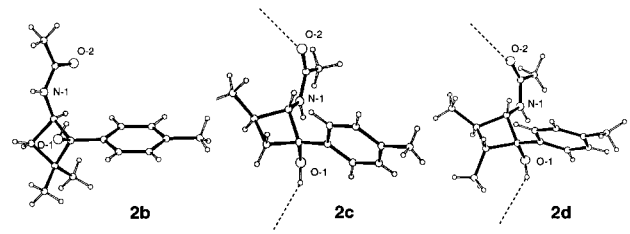
(2*R*,3*S*)-**1d** **2d**



(2*S*,3*S*)-**1d** **3**

Scheme 1 C/F = cyclization/fragmentation ratio.

Characteristic NMR shifts were observed for H-2 (δ 4.2–4.8) and the methyl groups in **2b** which showed strong anisotropic effects ($\Delta\delta$ = 0.45 ppm).[8] Additional proof came from the X-ray structure analysis for **2b** (Fig. 1).† A reasonable explanation for the high 1,2-asymmetric induction might be an intramolecular hydrogen bond at the stage of the triplet 1,4-biradical which has already been described for Yang cyclizations of α-ester-substituted ketones.[9] The valine derivative **1c** cyclized more efficiently (Φ_C = 0.19 ± 0.02) and gave the cyclobutanol **2c** in 74% yield with ds > 96%. The relative configuration was established *via* X-ray structure analysis.† Two explanations for the high 1,3-asymmetric induction are possible: selective γ-H abstraction from one of the diastereotopic methyl groups or non-selective γ-H abstraction followed by selection at the biradical stage (radical combination *vs.* cleavage and/or hydrogen back transfer). Biradical dynamics most likely were responsible for the results obtained with the isoleucine and alloisoleucine derivatives (2*S*,3*S*)-**1d** and (2*R*,3*S*)-**1d**. Whereas the (2*S*,3*S*)-isomer gave exclusively the Norrish II cleavage product **3**, (2*R*,3*S*)-**1d** cyclized efficiently to give the cyclobutanol **2d**. The latter compound again was formed diastereoisomerically pure (*i.e.* ds > 96%) with complete control of the three newly formed stereogenic centers. X-Ray structure analysis completed the configuration analysis.†

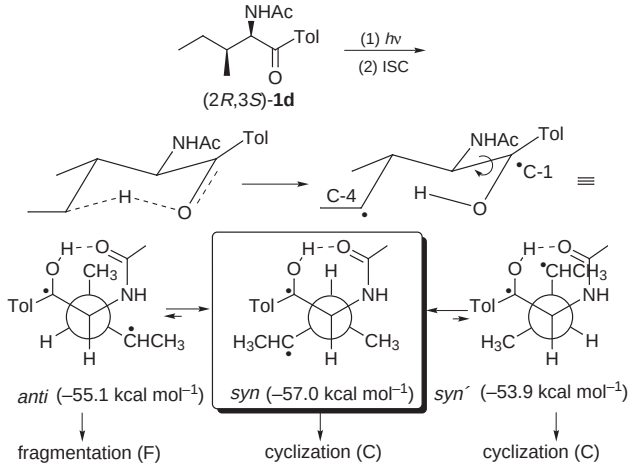


2b **2c** **2d**

Fig. 1 Crystal structures of the cyclobutanols **2b**, **2c** and **2d**.

Finally, the unbranched substrates **2e** and **2f** (from norvaline and norleucine, respectively) were investigated. Both substrates preferentially showed fragmentation and, as a minor reaction path, formation of the cyclobutanols **2e**,**f** with excellent diastereoselectivity. Thus, the radical coupling step also proceeds with high *inherent* stereoselectivity in addition to the 1,2-*induced* stereoselectivity.

In the mechanistic scenario (*vide supra*) for the Yang cyclization process *induced* and *inherent* diastereoselectivity are related to two different steps: biradical dynamics and spin inversion coupled with radical-radical combination. This relation is depicted in Scheme 2 for substrate (2*R*,3*S*)-**2d**. After hydrogen abstraction from the more reactive methylene group, equilibration of the triplet 1,4-biradical leads to three possible conformers, *anti*, *syn* and *syn*′. The energies of these species were calculated using the PM3 method. The cyclization path is not available from the *anti*-isomer, however, this structure is less favourable compared with the *syn*-isomer. Hydrogen



Scheme 2 Mechanistic scenario for the photocyclization of (2*R*,3*S*)-**1d**.

bonding stabilizes all three possible conformers and is the major contribution to the high 1,2-asymmetric induction.

The reverse is the case for (2*S*,3*S*)-**2d** and fragmentation dominates the reaction due to the more stable triplet *anti* 1,4-biradical. This theory however, does not take into account the fact that the calculated biradical minima structures are not necessarily identical with the actual ISC-reactive structures. Spin–orbit coupling, the major contribution to triplet/singlet ISC, is higher for *syn*-biradicals[10] and depends on the orientation of the p-orbitals localized at the spin-bearing carbon atoms.[11] An orthogonal orientation of these orbitals prior to C–C bond formation leads to a *trans* arrangement of the methyl at C-4 and the tolyl group at C-1 (inherent diastereoselectivity). Thus, the *induced* and *inherent* stereoselectivity of the Yang cyclization can be correlated with different selection stages of the reaction.

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Notes and references

† *Crystal data* for **2b**: $C_{15}H_{21}NO_2 \cdot 1/2H_2O$ (from MeOH), M = 256.3, monoclinic, a = 12.840(1), b = 18.077(1), c = 12.920(1) Å, β = 90.62(1)°, space group $C2/c$, Mo-Kα, 11448 reflections measured, 1748 reflections with $I > 2\sigma(I)$, R_1 = 0.058, wR_2 = 0.117. For **2c**: $C_{14}H_{19}NO_2$ (from MeOH), M = 233.3, monoclinic, a = 7.459(1), b = 11.63(2), c = 15.652(3) Å, β = 102.67(2)°, space group $P2_1/c$, Mo-Kα, 2478 reflections measured, 1202 reflections with $I > 2\sigma(I)$, R_1 = 0.064 , wR_2 = 0.119. For **2d**: $C_{15}H_{21}NO_2$ (from MeOH), M = 247.33, orthorhombic, a = 7.546(1), b = 11.848(1), c = 15.712(1) Å, space group $P2_12_12_1$, Mo-Kα, 3096 reflections measured, 1942 reflections with $I > 2\sigma(I)$, R_1 = 0.050, wR_2 = 0.099. CCDC 182/1248. See http://www.rsc.org/suppdata/cc/1999/1109/ for crystallographic files in .cif format.

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