# Intermolecular hydrogen binding of a chiral host and a prochiral imidazolidinone: enantioselective Norrish–Yang cyclisation in solution

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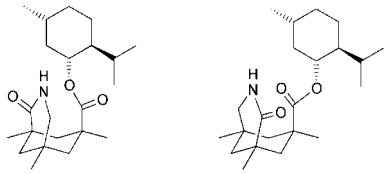
**The Norrish–Yang cyclisation of a prochiral imidazolidinone which was conducted in the presence of a chiral host afforded enantiomerically enriched (up to 26% *ee*) 1,3-diazabicyclo[3.3.0]octanones in good yields (73–86%) with a distinct preference for the *exo*-diastereoisomer (dr = 77/23–90/10).**

The photochemical cyclisation of ketones *via* intramolecular hydrogen abstraction and subsequent ring closure is termed Norrish–Yang cyclisation.[1] It is a valuable C–C-bond forming reaction in the course of which two new stereogenic centres are formed. The facial diastereoselectivity of the reaction has been extensively studied[2,3] and applications of the Norrish–Yang cyclisation to natural product synthesis have been reported.[4] For the photocyclisation of amino acid derivatives a remarkable chirality transfer has been observed.[5] Enantioselective variants of the Norrish–Yang cyclisation have been investigated in the solid phase employing either precursors that crystallize in chiral space groups[6] or inclusion compounds of a prochiral substrate and a chiral host.[7] We have now attempted to achieve an enantioselective Norrish–Yang cyclisation in the liquid phase mediated by a chiral complexing agent[8] and report on the preliminary results of this work. The chiral host compounds **1** and **2** can be readily prepared from trimesic acid (1,3,5-



**1** **2**

benzenetricarboxylic acid) *via* the well-known all-*cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (Kemp's triacid).[9,10] They are diastereomeric due to the chiral menthyl residue and can be separated by flash chromatography.

Lactams are attached to the host **1** or its diastereoisomer **2** *via* the carbonyl group and *via* the NH-group by two hydrogen bonds.[11] The lactam is fixed by the two-point binding in a chiral environment with the result that formerly enantiotopic faces become diastereotopic. As the menthyl residue acts simply as a sterically bulky substituent hosts **1** and **2** are expected to behave as if they were enantiomers. The prochiral imidazolidin-2-one **3** was selected as Norrish–Yang cyclisation substrate. It exhibits a lactam binding site which should allow for an association with the host compounds. The compound was readily prepared from the parent imidazolidin-2-one by monoacetylation,[12] 1,4-addition to phenyl vinyl ketone and deprotection. Upon irradiation (Rayonet RPR 3000 Å or Original Hanau TQ 150/duran filter) the ketone yielded four products which are depicted in Scheme 1.

The results of the preliminary study conducted with the easily accessible hosts **1** and **2** are summarized in Table 1. In general,

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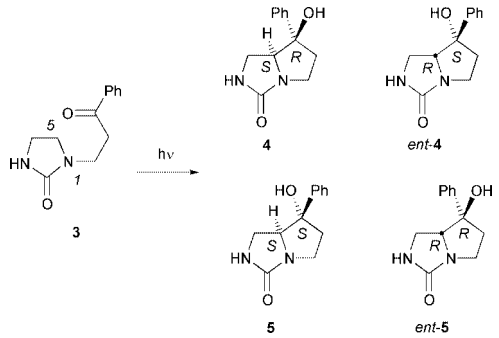

**3** **4** ***ent*-4** **5** ***ent*-5**

**Scheme 1** Possible stereoisomers obtained from the Norrish–Yang cyclisation of imidazolidin-2-one **3**.

the conversion is complete and the yield of photocyclisation products are high (73–86%). The *exo*-isomers **4** and *ent*-**4** are the preferred diastereoisomers formed in toluene solution (entries 2–14)[13] whereas the *endo*-isomers **5** and *ent*-**5** are favored in the polar protic solvent *tert*-BuOH. It is reasonable to assume that *tert*-BuOH increases the size of the substituent OH by coordination[1,2] and leads to a reversal of the steric demand from Ph > OH to OH > Ph. The *exo*/*endo*-selectivity did not change (entries 3/7/11, 4/8/12, *etc*.) upon variation of the temperature. Contrary to that, the enantioselectivity was significantly influenced by this variation. The increase from 5% *ee* at 30 °C (entry 4) to 26% *ee* at −45 °C (entry 12) observed with 2.5 equiv. of host **1** exemplifies the typical temperature dependence which is partially due to an increased association. The increase in enantioselectivity upon increasing the host concentration (entries 3/4, 5/6, 7/8, *etc*.) undermines the crucial

**Table 1** Norrish–Yang cyclisation of imidazolidinone **3** in the presence of hosts **1** and **2**

| Entry | Host | Equiv. | Temp./°C | Yield (%)[a] | *exo*/*endo*[b] | Ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | —[d] | — | 30 | 75 | 38/62 | — |
| 2 | — | — | 30 | 73 | 88/12 | — |
| 3 | **1** | 1 | 30 | 82 | 90/10 | 3 |
| 4 | **1** | 2.5 | 30 | 86 | 88/12 | 5 |
| 5 | **2** | 1 | 30 | 73 | 88/12 | −4 |
| 6 | **2** | 2.5 | 30 | 82 | 89/11 | −7 |
| 7 | **1** | 1 | −10 | 86 | 78/22 | 7 |
| 8 | **1** | 2.5 | −10 | 77 | 77/23 | 16 |
| 9 | **2** | 1 | −10 | 73 | 85/15 | −6 |
| 10 | **2** | 2.5 | −10 | 73 | 80/20 | −15 |
| 11 | **1** | 1 | −45 | 77 | 81/19 | 11 |
| 12 | **1** | 2.5 | −45 | 77 | 79/21 | 26 |
| 13 | **2** | 1 | −45 | 82 | 79/21 | −14 |
| 14 | **2** | 2.5 | −45 | 77 | 84/16 | −25 |

[a] Yield of isolated product after chromatographic purification. [b] The ratio of the two diastereoisomers (**4** + *ent*-**4**)/(**5** + *ent*-**5**) was determined by $^1$H-NMR spectroscopy of the crude product mixture. [c] The ee of the major *exo*-diastereoisomer was determined as (**4** − *ent*-**4**):(**4** + *ent*-**4**) by chiral HPLC (eluent: $H_2O$–MeCN = 95:5 → 90:10; column: Macherey-Nagel EC 200/4 nucleodex beta-OH). [d] *tert*-BuOH was used as the solvent.

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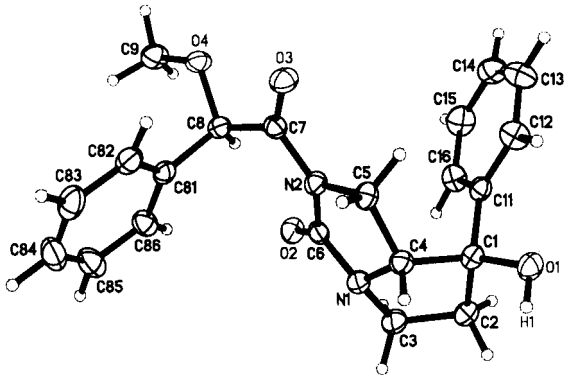


**Fig. 1** A molecule of compound **6** in the crystal.

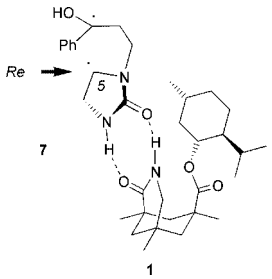


**Fig. 2** The differentiation of enantiotopic sites at the C-5 radical center in the 1,4-biradical intermediate **7** associated to host **1**.

role the association plays in the enantioselective photocyclisation under scrutiny. The earlier assumption that the hosts **1** and **2** should behave as if they were enantiomers was proven experimentally. The opposite enantiomer was formed upon replacement of **1** with **2** (entries 3/5, 4/6, 5/7, etc.) resulting in a negative ee value. The minor diastereoisomers **5** and *ent*-**5** behaved similar to the major diastereoisomers with regard to the ee.

The absolute configuration of the major enantiomer *ent*-**5** obtained from the irradiation of compound **3** in the presence of host **2** was elucidated by single crystal X-ray crystallography. To this end, it was converted into its *N*-acyl derivative **6** by a sequence of *O*-silylation, *N*-acylation with (*R*)-(−)-*O*-methylmandelic acid chloride and desilylation.[14]

If host **2** delivers *ent*-**5** as major enantiomer host **1** delivers **5** with opposite optical rotation as was experimentally confirmed. The C–C-bond formation step which is decisive for the absolute configuration of products occurs from the C-5 *Re*-face of a 1,4-biradical intermediate **7** depicted in Fig. 2. The shielding of the *Si*-face by the menthyl group of host **1** is apparent although it is certainly not optimal. It is an obvious conclusion from this mechanistic picture that the absolute configuration of the major enantiomer **4** is also determined in the complex **7**–**1** (Fig. 2) and that the stereogenic centres within the imidazolidinone ring of diastereoisomers **4** and **5** have identical (*S*)-configuration. This assignment has already been implemented in Scheme 1.

Our preliminary study unequivocally demonstrates that a differentiation between the enantiotopic faces of radical centres are possible upon association to hosts of type **1**. Based on this observation enantioselective radical type cyclization reactions at chiral hosts are conceivable. Further studies are under way which will address this question in detail.

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13 Representative procedure: A solution of the substrate **3** (0.1 mmol, 21.8 mg) and the chiral host **1** (0.25 mmol, 91.0 mg) in 20 ml of toluene was degassed for 30 min by a continuous stream of argon. The mixture was subsequently irradiated in a liquid cooled merry-go-round apparatus at −45 °C until the reaction was complete according to TLC (12 h). After evaporation of the solvent the diastereomeric ratio (dr) was determined from the crude product by integration of appropriate $^1$H-NMR signals. The residue was purified by flash chromatography (eluent: EtOAc–MeOH = 98 : 2). The host **1** ($R_f$ = 0.46; pentane–*tert*-butyl methyl ether = 25 : 75) was recovered and the products **4**/*ent*-**4** ($R_f$ = 0.50; EtOAc–MeOH = 80 : 20) and **5**–*ent*-**5** ($R_f$ = 0.52; EtOAc–MeOH = 80 : 20) were separated. The total yield was 16.8 mg (77%). The collected fractions of compounds **4**–*ent*-**4** were evaporated and the enantiomeric excess was determined by chiral HPLC (Table 1).

14 *Crystal data:* for **6**: chemical formula: $C_{21}H_{22}N_2O_4$, formula weight: 366.44 g mol$^{-1}$, crystal system: orthorhombic, unit cell dimensions: $a$ = 894.6(1); $b$ = 1250.0(1); $c$ = 1635.0(1) pm, volume: 1828.3(3) × $10^{-30}$ m$^3$, temperature: 213 K, space group symbol: $P2_12_12_1$, number of molecules in unit cell: $Z$ = 4, absorption coefficient: 7.6 cm$^{-1}$, reflections collected: 3696, independent reflections: 3399 [$R_{int}$ = 0.0238], $R$ index (all data): $wR_2$ = 0.0925, $R$ index conventional [$I > 2\sigma(I)$]: $R$ = 0.0343. CCDC 156228. See http://www.rsc.org/suppdata/cc/b1/b100300n/ for crystallographic data in .cif or other electronic format.