Excellent stereocontrol in intramolecular Buchner cyclisations and subsequent cycloadditions; stereospecific construction of polycyclic systems

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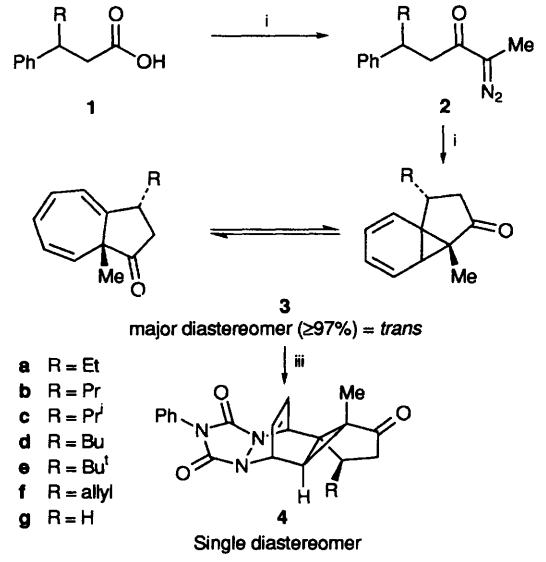
Highly diastereoselective rhodium(II) acetate-catalysed intramolecular addition of α-diazo ketones to aromatic rings to form the azulenones 3 has been achieved; the norcaradiene form of 3 undergoes efficient stereospecific cycloaddition with phenyltriazolinedione, in either a stepwise or a tandem process, leading to the pentacyclic systems 4 as a single diastereomer in each case.

The intramolecular Buchner reaction, involving the rhodium-catalysed decomposition of an α-diazocarbonyl compound[1] and addition of the resulting carbenoid to an aromatic system, has attracted considerable attention in recent years, from both a synthetic and a mechanistic point of view.[2,3] The proposed mechanism for the cyclisation involves initial cyclopropanation of the aromatic ring to form a norcaradiene derivative which is in dynamic equilibrium with the cycloheptatriene. Here we report very efficient internal asymmetric induction in the intramolecular cyclisation to form azulenone derivatives; highly efficient diastereocontrol is achieved due to the presence of an alkyl substituent β to the diazocarbonyl group.

A series of 3-phenylpropanoic acids **1a–f** bearing alkyl substituents at the 3-position were transformed under standard conditions to the diazo ketones **2a–f** as shown in Scheme 1†. The previously reported derivative without any substituent at the 3-position, 2-diazo-5-phenylpentan-3-one **2g**,[2] was also studied for comparison with the novel 3-alkyl substituted compounds.



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$ or $SOCl_2$, then excess $MeCHN_2$ (5–10 equiv.), Et_2O, −20 °C (**2a**, 71%; **2b**, 76%; **2c**, 85%; **2d**, 78%; **2e** 85%; **2f**, 76%; **2g**, 77%); ii, $Rh_2(OAc)_4$, CH_2Cl_2, heat (**3a**, 79%; **3b**, 73%; **3c**, 74%; **3d**, 70%; **3e**, 72%; **3f**, 46% (**5** was also isolated 44%); **3g**, 59%; iii, PTAD, CH_2Cl_2, 0 °C (**4a**, 95%; **4b**, 98%; **4c**, 98%; **4d**, 98%; **4e**, 97%; **4f**, 98%; **4g**, 94%; yields of **4** from **2** directly in tandem process: **4a**, 66%; **4b**, 70%; **4c**, 74%; **4d**, 71%; **4e**, 75%; **4g**, 54%)

Rhodium(II) acetate-catalysed decomposition of the α-diazo ketones **2** resulted in efficient carbenoid addition to the benzene ring as shown in Scheme 1. Interestingly, the presence of the β-alkyl substituent in **2a–e** facilitates the cyclisation, resulting in increased efficiency in the formation of the products of Buchner cyclisation compared to the unsubstituted diazo ketone **2g**, presumably by favouring the conformation required for the cycloaddition process. The azulenones **3** produced are clearly shown by NMR spectroscopy to exist as a rapidly equilibrating mixture of the norcaradiene and cycloheptatriene forms. Most importantly, the cyclisation is highly diastereoselective.‡ In many cases only the *trans* diastereomer of the product **3** could be detected by ^1H NMR spectroscopy of the crude reaction product; even in those cases where the minor *cis* diastereomer was detected, only 2–3% was present in the crude product mixture. The diastereomers of the azulenones **3** can be separated chromatographically; the yields reported in Scheme 1 are for the pure *trans* diastereomers.

While the precise mechanism of the rhodium-catalysed carbenoid addition is unknown, the observed stereocontrol of the intramolecular cycloaddition can be rationalised as illustrated in Fig. 1. Approach of the carbenoid to the aromatic ring *via* conformation A is preferred over conformation B, in which the alkyl substituent experiences $A^{1,3}$ strain.

In the case of the allyl-substituted diazo ketone **2f**, excellent diastereoselection was obtained in both the intramolecular cyclisation to give the azulenone **3f** and the competing intramolecular cyclopropanation to form **5**. Chemoselectivity was low, resulting in formation of essentially equal amounts of the products of the two pathways.[5] Only a single diastereomer of each of the products, the azulenone **3f** and the cyclopropane derivative **5**, could be detected.†

The norcaradiene form of each of the azulenones **3a–g** (**3a–f** *trans* diastereomers only) was trapped efficiently with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) in CH_2Cl_2 solution at 0 °C, resulting in formation of the cycloadducts **4a–g** in good yield (94–98%) as shown in Scheme 1.[3b,6]† While reaction of

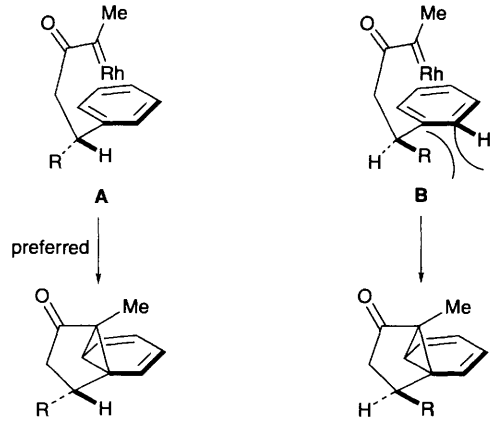


Fig. 1 Diastereoselection in the rhodium-catalysed intramolecular cyclisation

PTAD with most of the azulenones (**3a**, **b**, **d**, **f** and **g**) was complete within 10 min; reaction of the azulenone derivative bearing the bulky Bu^t substituent **3e** was noticeably slower, requiring 30–35 min for complete reaction under the same conditions, with **3c** (R = Pr^i) displaying intermediate reactivity, requiring approximately 20 min. This influence of the nature of the substituent R on the rate of the cycloaddition indicates that approach of the dienophile is hindered by the bulky Pr^i or Bu^t groups. Most importantly, only a single diastereomer of the cycloadducts **4** could be detected, indicating that the cycloaddition to **3** is stereospecific.

The butyl-substituted cycloadduct **4d** crystallises in the centrosymmetric $R\bar{3}$ system with equal numbers of the molecule and its enantiomer in the unit cell. Our X-ray analysis unequivocally establishes the structure and stereochemistry, as shown in Fig. 2 and Scheme 1.§ Molecular dimensions are in accord with accepted values. The structure determined for the cycloadduct **4d** established not only the stereochemistry of the cycloaddition of **3d** with PTAD but also confirmed the stereochemistry of the rhodium(II) acetate-catalysed diazo ketone cyclisation to form **3d** as the *trans* diastereomer. The stereochemistry of each of the remaining cycloadducts **4** was assigned by analogy to **4d**. Approach of the dienophile to the norcaradiene takes place from the less hindered face only (opposite to the bridgehead methyl substituent), as illustrated in Fig. 3, producing the cycloadducts **4** stereospecifically.

Transition metal-catalysed cyclisations are ideally suited for use in tandem or cascade processes due to the mild reaction conditions and selectivity usually associated with such reactions.[7]¶ As the transformation of the α-diazo ketones **2** to the complex pentacyclic systems **4** involved two reactions occurring under mild conditions, it proved possible to conduct these transformations sequentially in one pot without isolation of the azulenones **3**.‖ This rapid (from **2** to **4** in *ca.* 90 min) and efficient tandem cyclisation–cycloaddition results in an enormous increase in complexity (one relatively easily-controlled stereogenic centre in **2** to a total of six asymmetric carbon atoms in **4** with excellent stereoselectivity) in a single reaction flask.

This very simple stereospecific synthesis of the polycycles **4** has considerable synthetic potential. The rigid pentacyclic framework is envisaged to allow further stereospecific transformations to lead to carbocyclic intermediates for use in synthesis. Use of alternative dienophiles, especially carbon based systems, is also under investigation. Also, the precursor acids **1** for diazo ketones **2** are accessible in high enantiomeric purities.

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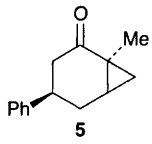

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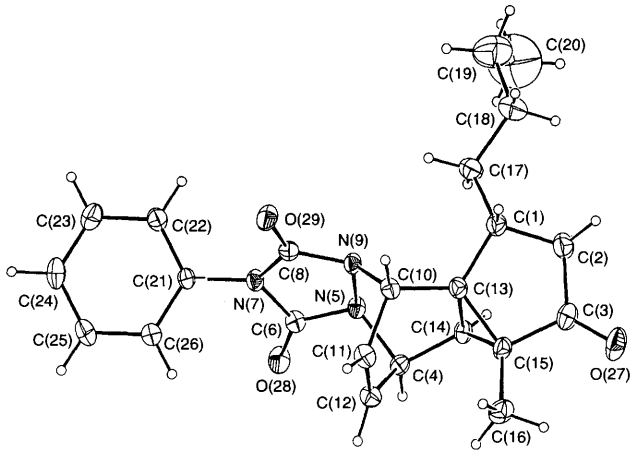

Fig. 2 A view of **4d** with our numbering scheme showing the structure and stereochemistry. Anisotropic dispacement ellipsoids are drawn at the 30% probability level.

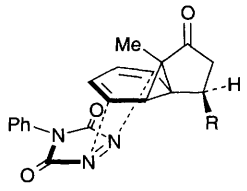

Fig. 3 Stereochemistry of PTAD cycloaddition

Footnotes

† All new compounds gave satisfactory spectroscopic and analytical data.

‡ While Saba [ref. 3(*b*)] investigated Buchner cyclisation of 2-diazo-4-methyl-5-phenylpentan-3-one, in which formation of two diastereomers is possible, the diastereoselectivity of the rhodium catalysed-cyclisation was not reported. In a copper-catalysed intramolecular aromatic cycloaddition, Ledon and co-workers [ref. 4] reported the formation of a mixture of diastereomers.

§ *Crystal data* for **4d**. $C_{23}H_{25}N_3O_3$, M = 391.46, trigonal, space group $R\bar{3}$, $a = b$ = 37.480(3), c = 7.4192(10) Å, V = 9025.7(17) Å^3, Z = 18, $F(000)$ = 3744, D_c = 1.296 g cm^{-3}, μ = 0.087 mm^{-1}; 5786 reflections in the range $2 < \theta < 25°$ were collected with graphite monochromated Mo radiation; of these, 3511 were unique (R_{int} = 0.016) and 1465 had $I > 2\sigma(I)$. The structure was solved using SHELXS-86[8a] and refined with all non-H atoms allowed anisotropic vibration, with NRCVAX[8b] and SHELXL-93[8c] using F^2 and all data. H atoms allowed for as riding atoms; the methyl H atoms on C16 were very well resolved. Final R_{obs}, R_w and *gof* values are 0.055, 0.153 and 0.95 respectively.

Atomic coordinates, bond lengths and angles and thermal parameters, have been deposited at the Cambridge Crystallograpic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/264.

¶ The synthetically powerful combination of transition metal-catalysed cyclisation followed by cycloaddition has been elegantly demonstrated by Padwa and co-workers,[7] where the initial cyclisation involves rhodium-catalysed decomposition of diazocarbonyl compounds to form ylides which subsequently undergo cycloaddition reactions.

‖ Each of the diazo ketones **2a–f** was firstly treated with rhodium(II) acetate in refluxing CH_2Cl_2; the resulting solution of the azulenones **3a–3f** was cooled to 0 °C prior to addition of PTAD to give cycloadducts **4**. Yields for the tandem transformation of **2** to **4** are given in Scheme 1.

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