COMMUNICATION

Rhodium-catalysed decomposition of δ,ε-unsaturated β,β-difluoro-α-diazo esters, the direct formation of bicyclo[2.1.0]pentane ring systems *via* intramolecular cyclopropanation

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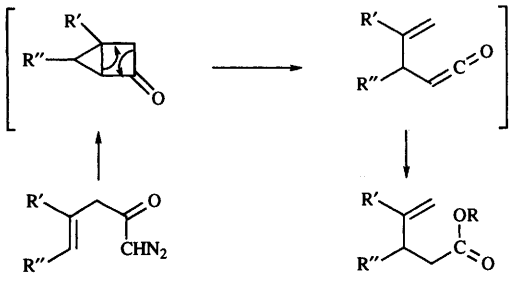
Several δ,ε-unsaturated β,β-difluoro-α-diazo esters, prepared from the corresponding α-keto esters, undergo rhodium-catalysed intramolecular cyclopropanation reaction leading to the unprecedented formation of bicyclo-[2.1.0]pentane ring systems.

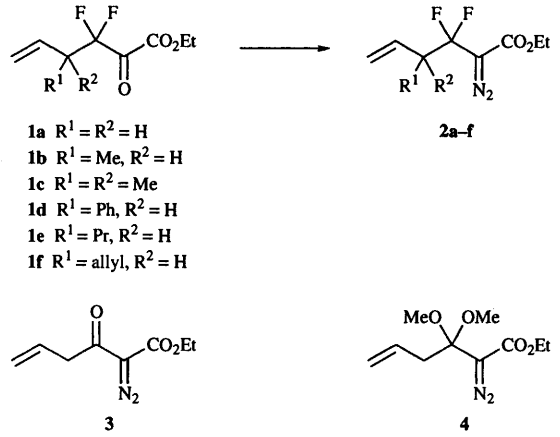
Since the first report in 1961 of catalytic intramolecular cyclisation with an unsaturated diazo ketone,[1] intramolecular cyclopropanation reactions have been extensively studied and have found widespread application to the synthesis of theoretically interesting compounds as well as the syntheses of natural products.[2] However, in all these examples, the formation of bicyclo[3.1.0]hexane or bicyclo[4.1.0]heptane ring systems is virtually the exclusive outcome of catalytic intramolecular cyclopropanation. Only very recently has an extension beyond bicyclo[4.1.0]heptane ring systems been found to be possible with rhodium catalysis.[3] On the other hand, formation of the lower homologue bicyclo[2.1.0]pentane ring systems by intramolecular cyclopropanation has not been demonstrated directly. Diazo compounds that are designed to undergo intramolecular formation of bicyclo[2.1.0]pentan-2-ones proceed through a so-called vinylogous Wolff rearrangement to ketene intermediates that react with alcohols to form pent-4-enoate esters (Scheme 1).[4] We now report the preparation of unsaturated diazo compounds containing a difluoromethylene unit and their rhodium-catalysed cyclopropanation reactions as the first example of direct production of bicyclo[2.1.0]pentane ring compounds.



Scheme 1 Vinylogous Wolff rearrangement

Recently, we have obtained several δ,ε-unsaturated β,β-difluoro-α-keto esters **1** *via* the Claisen rearrangement of allyl enol ethers derived from ethyl trifluoropyruvate.[5] When these keto esters reacted with tosylhydrazine in the presence of an acid catalyst, the corresponding hydrazones were formed in good yield. On treatment with an organic base such as ethyldiisopropylamine, these hydrazones were readily transformed to diazo compounds **2**, which possessed a novel structural feature in that the carbon α to the diazo group was substituted by two fluorine atoms (Scheme 2).

It should be noted that the difluoromethylene unit in compounds **2** appeared to be rendered unstable by the adjacent



1a $R^1 = R^2 = H$
1b $R^1 = Me$, $R^2 = H$
1c $R^1 = R^2 = Me$
1d $R^1 = Ph$, $R^2 = H$
1e $R^1 = Pr$, $R^2 = H$
1f $R^1 = allyl$, $R^2 = H$

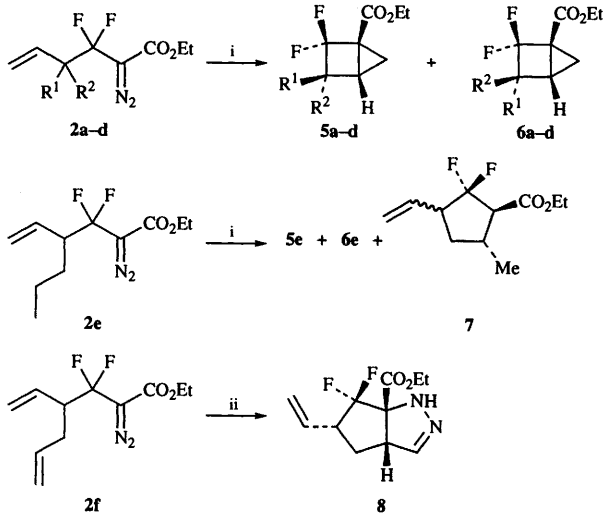
2a–f

3 **4**

Scheme 2 *Reagents and conditions*: i, $NH_2NHSO_2C_6H_4Me$-*p*, HCl (cat.)–EtOH; ii, Pr^i_2NEt (1.0 equiv.), CH_2Cl_2, 55–72% overall yield

diazo group so that defluorination occurred slowly in the presence of moisture or methanol to give, for example, the keto compound **3** and dimethyl acetal **4** from diazo compound **2a**. However, when kept away from protic solvents, compounds **2** have good thermal stability.

With a double bond γ,δ to the diazo group, compounds **2** appeared to be a suitable model to assess the feasibility of intramolecular cyclopropanation for the formation of highly strained bicyclo[2.1.0]pentane ring systems. When compounds **2a–d** were subjected to rhodium-catalysed decomposition in CH_2Cl_2, smooth evolution of nitrogen was observed. ^{19}F NMR analysis of the reaction mixture indicated that the reaction was clean and complete, and the product isolated was identified as a bicyclo[2.1.0]pentane derivative (Scheme 3 and Table 1). With



2a–d **5a–d** **6a–d**

2e **7**

2f **8**

Scheme 3 *Reagents and conditions*: i, 2 mol% of $Rh(OAc)_2$, CH_2Cl_2, reflux; ii, 25 °C, 6 h, 77%

Table 1 Intramolecular cyclopropanation of diazo compounds **2**[a]

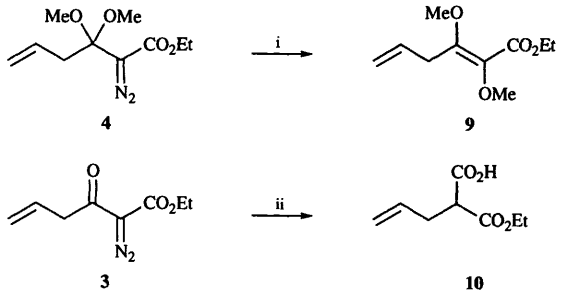
2	Yield[b] (%), 5 + 6	Diastereoisomeric ratio, 5:6
a	77	—
b	82	30:70
c	88	—
d	85	20:80
e	55	25:75

[a] All reactions were performed in refluxing CH_2Cl_2 using 2 mol% of $Rh(OAc)_2$ as the catalyst. [b] Yield of isolated product.

compound **2e**, the C–H insertion reaction was found to be competitive with the cyclopropanation process, so that both the bicyclic compounds **5e** and **6e** and the insertion product **7** were produced in a ratio of 3:1 (Scheme 3). Competition between bicyclo[3.1.0]hexane and bicyclo[2.1.0]pentane ring formation was probed using diazo compound **2f**. Unfortunately, the latter spontaneously underwent an intramolecular 1,3-dipolar cycloaddition to give compound **8** (Scheme 3).

The identity of all products was established by spectroscopic (^1H NMR, ^{19}F NMR, mass, IR) and elemental analysis. For products consisting of diastereoisomers, the relative stereochemistry and the ratio of the two isomers were determined by H–H NOESY experiments and ^1H or ^{19}F NMR signal integration, respectively.

Interestingly, when we tried to perform the intramolecular cyclopropanation with diazo compound **4**, only product **9**, resulting from 1,2-shift of the methoxy group, was formed (Scheme 4). On the other hand, the decomposition of diazo compound **3** under the same catalytic conditions led to the formation of product **10** *via* the expected vinylogous Wolff rearrangement (Scheme 4). A difluoromethylene moiety α to the diazo group thus seemed to be essential for successful observation of a bicyclo[2.1.0]pentane ring product formed by intramolecular cyclopropanation.



Scheme 4 *Reagents and conditions*: i, 2 mol% of $Rh(OAc)_2$, CH_2Cl_2, reflux, 5 h, 70% yield; ii, 2 mol% of $Rh(OAc)_2$, CH_2Cl_2, reflux, 30 min, 75% yield

In conclusion, by using α-difluorinated diazo compounds **2**, we have demonstrated for the first time that intramolecular carbenoid addition to a carbon–carbon double bond is a viable process for the direct formation of the bicyclo[2.1.0]pentane ring system.

† *J* Values in Hz.

Experimental

Ethyl 2,2-difluoro-3-phenylbicyclo[2.1.0]pentane-1-carboxylate 5d and 6d

Typical procedure. A solution of the diazo compound **2d** (0.56 g, 2.0 mmol) and rhodium acetate (8.8 mg, 0.02 mmol) in CH_2Cl_2 (5.0 ml) was heated at reflux for 3 h. The reaction mixture was then concentrated and the residue was chromatographed on silica gel eluting with hexane–ethyl acetate (8:2) to give compounds **5d** and **6d** (0.43 g, 85%) in a ratio of 20:80; **5d**: δ_H(300 MHz, $CDCl_3$) 7.25 (m, 5 H), 4.26 (m, 2 H), 4.07 (dm, *J* 23.5,† 1 H), 2.94 (dm, *J* 14.8, 1 H), 1.93 (m, 1 H), 1.61 (m, 1 H), 1.32 (t, *J* 7.2, 3 H); δ_F(60 MHz, $CDCl_3$) 16.5 (dd, *J* 204.0 and 14.8, 1 F), 22.0 (dd, *J* 204.0 and 23.5, 1 F); **6d**: δ_H(300 MHz, $CDCl_3$) 7.20 (m, 5 H), 4.25 (m, 2 H), 3.20 (t, *J* 5.0, 1 H), 2.78 (dm, *J* 22.2, 1 H), 1.93 (m, 1 H), 1.80 (m, 1 H), 1.31 (t, *J* 7.2, 1 H); δ_F(60 MHz, $CDCl_3$) 10.5 (dd, *J* 204.0 and 22.2, 1 F), 37.8 (dd, *J* 204.0 and 8.1, 1 F); *m/z* 253 ($M^+ + 1$, 31%), 232 (73), 207 (40), 177 (50), 159 (100) (Found: C, 66.73; H, 5.65. $C_{14}H_{14}F_2O_2$ requires C, 66.66; H, 5.59%).

Ethyl 2,2-difluoro-5-methyl-3-vinylcyclopentane-1-carboxylate 7

δ_H(300 MHz, $CDCl_3$) 5.90 (m, 1 H), 5.13 (m, 2 H), 4.20 (q, *J* 7.2, 2 H), 3.21 (m, 1 H), 2.92 (m, 1 H), 2.49 (m, 1 H), 2.08 (m, 1 H), 1.82 (m, 1 H), 1.30 (t, *J* 7.2, 3 H), 1.08 (d, *J* 7.1, 3 H); δ_F(60 MHz, $CDCl_3$) 8.2 (dm, *J* 252.0, 1 F), 31.0 (dm, *J* 252.0, 1 F); *m/z* 219 ($M^+ + 1$, 100%), 199 (31), 173 (52), 125 (55) (Found: C, 60.15; H, 7.41. $C_{11}H_{16}O_2F_2$ requires C, 60.54; H, 7.39%).

Ethyl 8,8-difluoro-7-vinyl-2,3-diazabicyclo[3.3.0]oct-3-ene-1-carboxylate 8

δ_H(300 MHz, $CDCl_3$) 6.68 (s, 1 H), 5.80 (m, 1 H), 5.22 (m, 2 H), 4.31 (m, 2 H), 3.98 (dd, *J* 11.9 and 7.55, 1 H), 3.19 (m, 1 H), 2.40 (m, 1 H), 1.74 (m, 1 H), 1.32 (t, *J* 7.2, 3 H); δ_F(60 MHz, $CDCl_3$) 11.5 (dd, *J* 258 and 21, 1 F), 28.9 (dd, *J* 258 and 7.0, 1 F) (Found: C, 53.86; H, 5.90; N, 11.20. $C_{11}H_{14}O_2F_2N_2$ requires C, 54.09; H, 5.78; N, 11.46%).

Acknowledgements

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