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Nitro-activated Double Bonds in Pd(0)-catalysed [3 + 2]-cycloaddition Reactions

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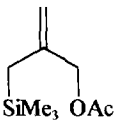
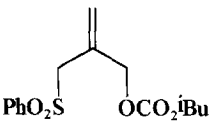
Abstract: Nitro-activation allowed successful Pd(0)-mediated [3 + 2]-cycloaddition reactions of some glycals and aromatic compounds.

The use of Pd(0)-catalysed [3 + 2]-cycloaddition reactions to effect tandem carbon-carbon bond formation has been amply described elsewhere.[1] In certain cases, a strongly electron-withdrawing group is required to successfully activate a double bond towards this type of cycloaddition. Herein we report our findings with respect to nitro-activation of some electron-rich glycals, some simple nitro-compounds, and some aromatic materials.

Following our success with sulphonyl-activated 2,3- and 3,4-unsaturated carbohydrates,[1c] we wished to extend the scope of this reaction to include 1,2-unsaturated carbohydrate derivatives (glycals). In our hands, 2-sulphonylglycals failed to react with the trimethylenemethyl 1,3-dipole (generated *in situ* under Pd(0) catalysis) corresponding to acetate **1** or carbonate **2** under a variety of reaction conditions. It seemed from these findings that the sulphonyl group was insufficiently electron-withdrawing to convert the electron-rich glycals into good Michael acceptors.

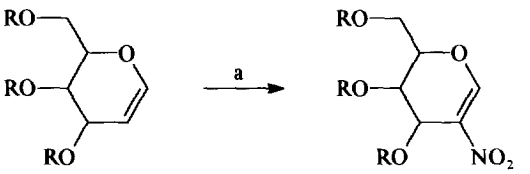


1



2

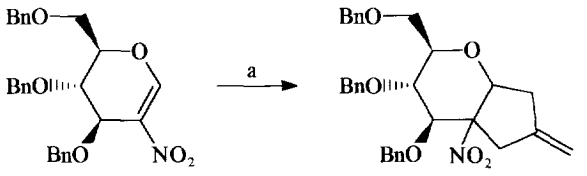
Previous work[2] in our laboratory has shown that 2-nitroglycals are in fact excellent Michael-acceptors, which led to the current investigation. 2-Nitroglycals are readily available by treatment of the particular glycal with *in situ* prepared acetyl nitrate (Scheme 1).



a) Ac_2O, HNO_3

Scheme 1

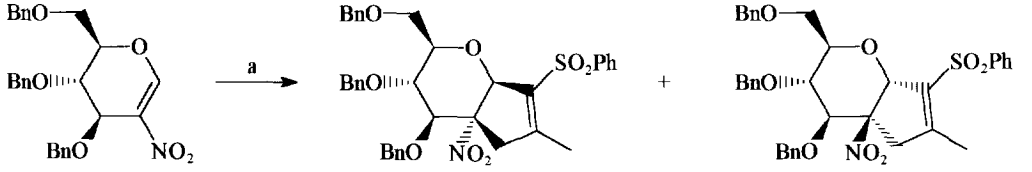
Treatment of glycal **3** with acetate **1** in the presence of an *in situ* prepared Pd(0) catalyst[3] afforded the desired bicycle **4** as an inseparable mixture of isomers (Scheme 2). However, reaction of glycal **3** with carbonate **2** in THF under reflux[4] afforded bicycles **5** and **6** (Scheme 3) in an approximately 1.6:1 ratio.[5] These products (**5** and **6**) presumably arise *via* double bond isomerisation (Scheme 4).



3 4 (isomers)

a) Pd(0), 1

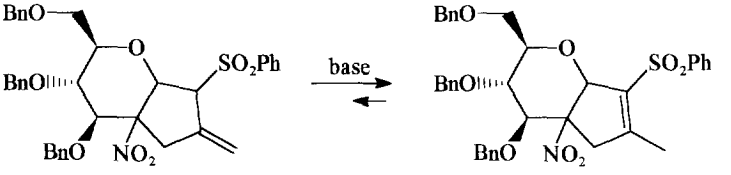
Scheme 2



3 5 6

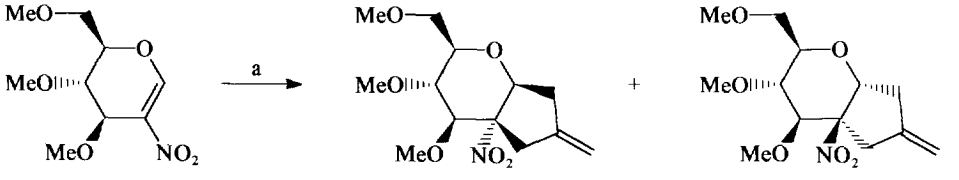
a) Pd(0), 2

Scheme 3



Scheme 4

In an effort to reduce steric hindrance during cycloaddition, methyl ether **7** was prepared.[6] Treatment of **7** with carbonate **2** in the presence of the Pd(0) catalyst failed to effect a significant degree of cycloaddition. The use of acetate **1**, however, led to a 2.4:1 ratio (Scheme 5) of products **8** and **9** (in a combined yield of 69%, compared to 49% of **5** and **6**).

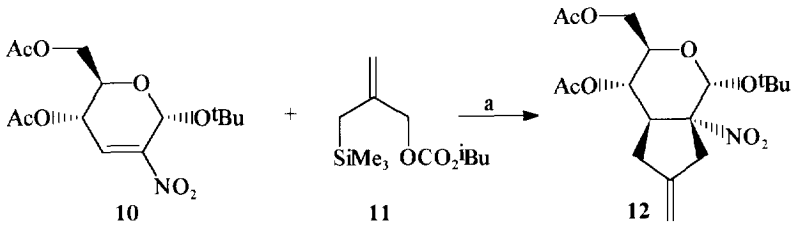


7 8 9

a) Pd(0), 1

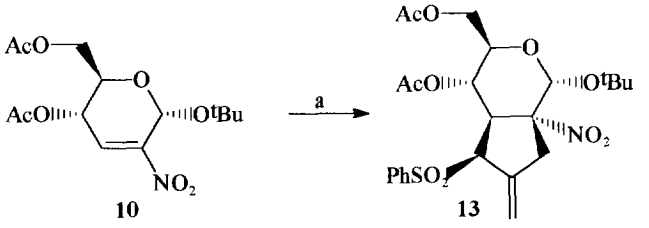
Scheme 5

We believed that a move away from the electron-rich glycals to the less electron-rich pseudoglycal **10** may very well enhance stereoselectivity in these reactions. A secondary advantage of this move was that milder reaction conditions (reactions were carried out as per ref. 6 at room temperature) could be employed. Treatment of **10** with **1** failed to afford any bicyclic product under a variety of reaction conditions. A move to the more reactive carbonate **11** allowed the preparation of bicycle **12** under mild conditions (Scheme 6). Similarly, reaction of **10** with carbonate **2** singularly afforded chiral bicycle **13** in good yield, without double bond isomerisation (Scheme 7).



a) Pd(0), ambient temperature

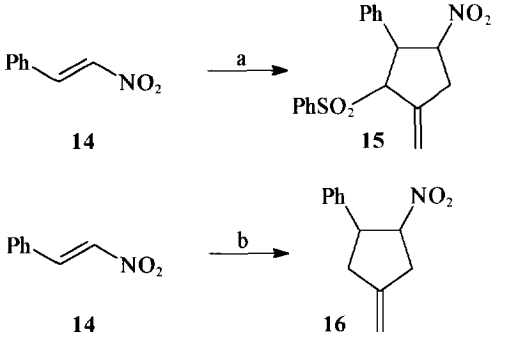
Scheme 6



a) Pd(0), **2**

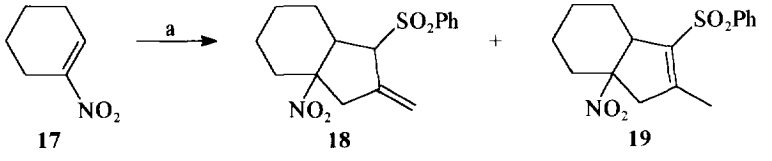
Scheme 7

This [3 + 2]-cycloaddition reaction was extended to other compounds, which included nitrostyrene **14**. This compound reacted with both carbonates **2** and **11**, affording the respective cycloadducts **15** and **16** (Scheme 8). Reaction of 1-nitro-1-cyclohexene **17** with **2** afforded the expected bicycle **18**, along with some of the isomer **19** (Scheme 9).



a) Pd(0), **2** b) Pd(0), **11**

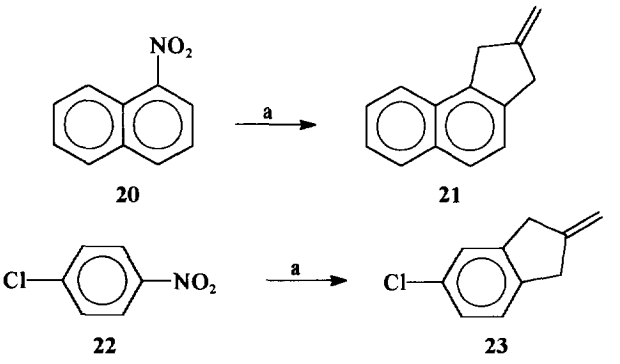
Scheme 8



a) Pd(0), **2**

Scheme 9

Additionally, acetate **1** could be made to react with nitroaromatics **20** and **22** (Scheme 10), the products (87% and 22%, respectively) arising by the elimination of HNO_2.



a) Pd(0), 1

Scheme 10

These results clearly display the efficacy of the nitro-group as a double bond activator. The use of this group allows Pd(0)-catalysed [3 + 2]-cycloadditions on numerous compounds of varying structure, including electron-rich glycals, and aromatic materials.

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REFERENCES AND NOTES

1) a) Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1981**, *103*, 5972; b) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5183; c) Holzapfel, C.W.; van der Merwe, T.L. *Tetrahedron Lett.* **this issue**.

2) a) Marais, C.F. M.Sc. dissertation, Rand Afrikaans University 1981; b) Herbst, M. M.Sc. dissertation, Rand Afrikaans University 1993.

3) The catalyst was prepared by treatment of $Pd(OAc)_2$ (3 mg, 0.013 mmol) with tri-isopropylphosphite (20 µl, 0.077 mmol), followed by stirring at ambient temperature for 30 min.

4) General procedure for cycloaddition reactions (*e.g.* reaction of 7 with 1): to 0.034 mmol Pd(0) catalyst[3] were added methyl ether 7 [80 mg, 0.343 mmol in THF (2 ml)] and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (88 µl, 0.446 mmol). The reaction mixture was placed in a preheated (90°C) oil bath, and was heated under reflux for five hours. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (EtOAc/hexane: 1/4) to afford bicycles 8 and 9.

5) All product provided satisfactory analytical data. For example, for product 13: 77%; mp.: 147-150°C; IR: ν_{max} 1750 (C=O), 1541 (NO_2), 1377 and 1183 (S=O) cm^{-1}; NMR (performed in $CDCl_3$ on a Varian VXR 200 spectrometer): ^1H δ 1.12 (9H, s), 2.03 (3H, s), 2.14 (3H, s), 3.22 (2H, m), 4.12-4.30 (4H, m), 4.40 (1H, m), 4.77 (1H, m), 5.08 (1H, t, J = 9.6 Hz), 5.09 (1H, m), 5.29 (1H, s), 7.56 (3H, m), 7.90 (2H, m); ^{13}C δ 20.7, 21.3, 27.9, 41.2, 45.4, 63.2, 65.9, 67.0, 67.2, 77.5, 91.0, 95.1, 115.8, 128.1, 129.4, 134.0, 135.3, 140.4, 170.4; m/z: 452 (M^+-C_4H_9O, 24%), 384 (M^+-SO_2Ph, 13%), 363 (452-NO_2 and C_2H_3O, 21%), 303 (363-C_2H_4O, 23%).

6) Van der Merwe, T.L. Ph. D. thesis, Rand Afrikaans University 1994.

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