SEQUENTIAL 1,3-DIPOLAR CYCLOADDITION-PALLADIUM CATALYSED CYCLISATION.

A POWERFUL NEW TACTICAL COMBINATION.

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Abstract A new flexible tactical combination of a 1,3-dipolar cycloaddition of an *in situ* generated azomethine ylide followed by a palladium catalysed cyclisation is described. The two reactions can be carried out as a 1 pot procedure if desired. Four new stereocentres and two new rings are created by this strategy.

The combination of a sequence of individually powerful synthetic methods often has a value in synthesis significantly greater than the sum of the individual reactions. Corey¹ has termed such a sequence a TACTICAL COMBINATION. In recent years we have been developing novel approaches to 1,3-dipoles² and palladium catalysed cyclisation processes.³ Both processes furnish powerful synthetic methodology and we now report their utility as a new tactical combination.⁴

One approach we have developed to the *in situ* generation of azomethine ylides involves the condensation of an aldehyde with a secondary α -amino ester. Facile deprotonation of the intermediate iminium ion furnishes the azomethine ylide.⁵ The palladium catalysed cyclisation utilises an aryl or vinyl halide moiety and this can be located either on the aldehyde substrate or the α -amino ester. Examples of both type are described.

The N-allyl glycine esters (1a) and (1b) were prepared by reaction of ethyl glycinate with the appropriate allyl bromide. Glycine ester (1a) reacts (toluene, 110°C, 24h) with o-bromobenzaldehyde and N-methylmaleimide (NMM) to give a 1:2.3 mixture (88%)⁶ of (2) and (3), which is readily separable by flash chromatography. Isomer (3) cyclised (MeCN, 80°C, 40h) to (4) (52%) using a catalyst system comprising 10mol% Pd(OAc)₂, 20mol% triphenylphosphine, Et₄NCl(1mol) and anhydrous K₂CO₃ (2 mol).⁷

The indole aldehyde (5) reacts with (1b) and NMM in boiling toluene over 15h to give a 1:2 mixture (67%) of (6) and (7). The isomers were separated by flash chromatography and cyclised separately using our standard catalyst system noted above. Isomer (7) cyclised to (8) (85%) more rapidly (MeCN, 80° C, 45 min) than isomer (6) cyclised (MeCN, 80° , 4h) to (9) (66%).













This new tactical combination can be carried out as a one pot procedure if desired. A typical example is provided by the reaction (anisole, 110° C, 20h) of aldehyde (10) with (1a) and NMM, followed by addition of the catalyst system noted above, with KOAc (2 mol) replacing K₂CO₃ as base, raising the reaction temperature to 125°C and continuation of heating for a further 4h. The product (75%) consists of a 9.5:1 mixture of (11) and (12).



The production of isomeric cycloadducts is due to both endo- and exo-cycloaddition of NMM to a stereospecifically formed anti-dipole (13). No adducts arising from the sterically more congested syndipoles (14) or (15) are observed.⁵ Efforts to improve the endo-selectivity of the cycloaddition are underway and extension of this tactical combination to our recently developed palladium catalysed tandem cyclisation-anion capture process⁸ are in hand.

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References

- 1 Corey, E.J.; Cheng, X.-M., "The Logic of Chemical Synthesis", Wiley-Interscience, 1989, p. 31.
- 2 A Grigg, R.; in "Proceedings of the 4th International Kyoto Conference on New Aspects of Organic Chemistry", ed. Yoshida, Z., Shiba, T., and Ohshiro, Y., VCH Verlagsgesellschaft, 1989, 113-134;
 ⁶Grigg, R.; Gunaratne, H.Q.N., and Kemp, J., *Tetrahedron*, 1990, <u>46</u>, 6467-6482 and earlier papers.
- Grigg, R.; Sridharan, V., Stevenson, P., Sukirthalingam, S., and Worakun, T., Tetrahedron, 1990, <u>46</u>, 4003-4018; Grigg, R.; Loganathan, V., Santhakumar, V., Sridharan, V., and Teasdale, A., Tetrahedron Letters, 1991, <u>32</u>, 687-690.

4 N For the combination of the Diels-Alder reaction with subsequent radical cyclisation see: Ghosh, T.; Hart, H., J. Org. Chem, 1988, <u>53</u>, 2396-2398; Clive, D.L.J.; Bergstra, R.T., *ibid*, 1990, <u>55</u>, 1786-1792;

UFinch, J.; Harwood, L.M., Robertson, G., and Sewell, R.C., Tetrahedron Letters, 1989, 2585-2588;

- Finch, H.; Harwood, L.M., Highcock, R., Jackson, B., Prout, K., Robertson, G., and Sewell, R.C., Synlett., 1990, 384-385.
- 5 Grigg, R.; Duffy, L.M., Dorrity, M.J., Malone, J.F., Rajviroongit, S., and Thornton-Pett, M., *Tetrahedron*, 1990, <u>46</u>, 2213-2230.
- 6 The stereochemistries of the products described in this paper are assigned on the basis of n.O.e. data.
- 7 The catalyst system was used for all the palladium catalysed cyclisation reactions described in this paper.
- Grigg, R.; Loganathan, V., Sukirthalingam, S., and Sridharan, V., *Tetrahedron Letters*, 1990, <u>31</u>, 6573 6576; Grigg, R.; Sridharan, V., and Sukirthalingam, S., *ibid*, 1990, <u>31</u>, 1343-1346.

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