Tetrahedron Letters,Vol.30,No.39,pp 5341-5344,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC 3-AZA-COPE REARRANGEMENTS USING $TiCl_4$ CATALYSIS

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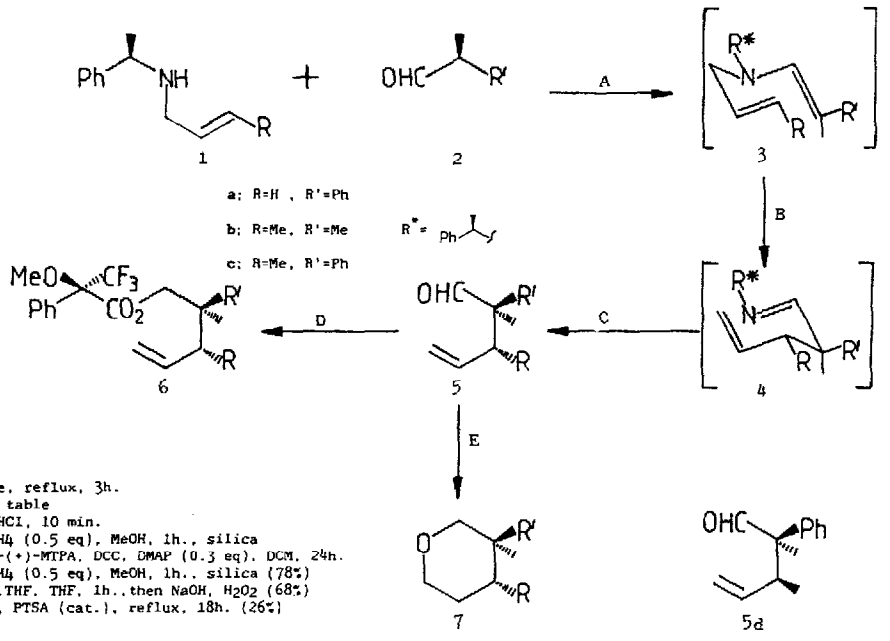
Summary. Under conditions of $TiCl_4$ catalysis, the 3-aza-Cope rearrangement of (R)-N-(1-phenylethyl)-4-aza-2-phenylocta-2,6-diene proceeds with high diastereo- and enantio-selectivity.

We were interested in effecting 1,4- or 1,5-asymmetric induction via the 3-aza-Cope rearrangement using the readily accessible 1-phenylethyl chiral auxiliary; hydrolysis of the rearranged products was expected to yield valuable α-allyl carbonyl compounds containing 1 or 2 chiral centres.

Most of the aza-Cope rearrangements that have found synthetic use have been thermally activated,[1] although there are examples of these rearrangements using Pd(0)[2] or $TiCl_4$[3] catalysis. There are no examples of high asymmetric induction using metal catalysis, but thermal rearrangement of chiral oxazolines is an effective tactic.[4]

Initially we chose to investigate whether significant 1,4-asymmetric induction could be observed in the $TiCl_4$ catalysed 3-aza-Cope rearrangement. In a simple 3-step procedure, the allylamine (1a)[5] was refluxed with 2-phenylpropanal (2a) in toluene, $TiCl_4$ was added to trigger the rearrangement, and the α-allyl aldehyde (5a) was isolated after acidic hydrolysis. Reduction with $NaBH_4$, followed by formation of the Mosher's ester,[6] revealed only minor asymmetric induction (30% e.e.).

Scheme.



Similarly, when allylamine (1b)[7] and 2-methylpropanal (2b) were taken through the same sequence of reactions, only 18% e.e. for (5b) was observed, indicating that low 1,5-asymmetric induction had occurred.

In contrast, high e.e.'s were observed when simultaneous 1,4- and 1,5-asymmetric inductions were attempted. Thus, when (1b) and (2a) were reacted as before, the major diastereoisomer (5c) [predominating over (5d) by a ratio of 6:1] was obtained in 81% optical purity. This e.e. could be increased to 90% by reducing the temperature for the rearrangement to 55°C.

	Amine, aldehyde	Solvent	Temp./°C	Catalyst	%de[8]	%ee[8]	%Yield[9]
1	1a, 2a	PhMe	110	$TiCl_4$	-	30	16
2	1b, 2b	PhMe	110	$TiCl_4$	-	18	48
3	1b, 2a	PhMe	110	$TiCl_4$	72	81 (76)	56
4	1b, 2a	PhMe	55	$TiCl_4$	70	90 (98)	46
5[10]	1b, 2a	PhH	55	$TiCl_4$	40	1 (12)	18
6	1b, 2a	o-$C_6H_4Cl_2$	179	-	50	15 (13)	44

Table. Rearrangement conditions and stereochemical outcome. For entries 3-6, the e.e. refers to the major diastereoisomer (5c), with the e.e. for (5d) in brackets.

The RR/SS stereochemistry of the major diastereoisomer (5c) could be ascertained by conversion of the major product (5c) into the tetrahydropyran (7c) (see Scheme), and analysis by NMR;[11] this is the expected diastereoisomer if the bulkiest substituents occupy equatorial positions in a chair-like transition state. So, of the 4 possible stereoisomeric products, one enantiomer of the RS/SS-α-allyl aldehyde predominates to the extent of greater than 80%; this is particularly noteworthy in view of the limited number of methods available for the preparation of quaternary centres (especially when an α-phenyl group is present)[4] and represents the first example of high asymmetric induction being observed in the $TiCl_4$ catalysed 3-aza-Cope rearrangement.

Thanks are due to Dr G K Barlow, Mrs B Chamberlain, Dr T A Dransfield, and Mr B R Glennie for NMR and mass spectra and to the SERC for a studentship (to MJH).

References and notes.

1. a) E J Jacobsen, J Levin, and L E Overman, J. Am. Chem. Soc., 1988, 110, 4329 and references cited therein. b) M J Kurth, and C J Soares, Tetrahedron Lett., 1987, 28, 1031. c) P-L Wu, M Chu, and F W Fowler, J. Org. Chem. 1988, 53, 963.

2. S-I Murahashi, Y Makabe, and K Kunita, J. Org. Chem. 1988, 53, 4489.

3. R K Hill, and H N Khatri, Tetrahedron Lett., 1978, 19, 4337.

4. M J Kurth, and E G Brown, Synthesis, 1988, 362 and references cited therein.

5. (1a); (R)-(+)-α-methylbenzylamine (4 eq.), NaH (4 eq.), DMF, -50°C, allylbromide (1 eq.), warm to r.t., (69%).

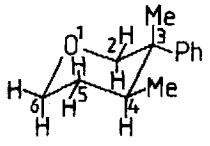
6. a) J A Dale, D L Dull, H S Mosher, J. Org. Chem., 1969, 34, 2543
b) B Neises, W Steglich, Angew. Chem. Int. Ed. Engl., 1978, 17, 522.

7. (1b); (i) (R)-(+)-α-methylbenzylamine, crotonaldehyde, PhMe, reflux, 10 min., (ii) $NaBH_4$/Methanol, 24h., silica, (66% overall).

8. Isomer ratios were determined by $^{19}F\{^1H\}$ NMR, and the integrations were corrected for NOE and any enantioselectivity in ester formation [by comparison with the d.e. from ^1H NMR spectra, and by ^{19}F NMR analysis of racemic (5)]. Absolute stereochemistries of (5)-(7) were not determined.

9. Yields for (5a) and (5b) were over 3 steps, based on allylamines (1a) and (1b) respectively. Yields for (5c) were over 2 steps based on enamine (3c). All reactions were conducted over a standard 24h, and were not optimised. All isolated compounds gave satisfactory ^1H NMR, ^{13}C NMR, IR, and high resolution mass spectra.

10. It is noteworthy that the stereoselectivity is so dependent on the solvent. The Pd(0) catalysed 3-aza-Cope rearrangement of (3a) has been studied by Murahashi et al (J. Org. Chem., 1988, 53, 4489). They observed a 12% e.e. for (5a), when the rearrangement was conducted for 20h in PhH at 80°C using $Pd(PPh_3)_4$ catalysis.

11. 

7c

$\delta_H(CDCl_3)$ 0.68 [3H, d, J 6.7 Hz, $CH_3(4')$], 1.37 [3H, s, $CH_3(3')$], 1.49 [1H, dddd, J 13.6, 4.5, 2.8 and 1.6 Hz, $H(5)_{eq}$], 1.71 (1H, dddd, J 13.6, 12.2, 11.8 and 4.8 Hz, $H(5)_{ax}$], 2.17 [1H, ddq, J 11.8, 4.5 and 6.7 Hz, H(4)], 3.51 [2H, s, $CH_2(2)$], 3.54 [1H, ddd, J 12.2, 11.4 and 2.8 Hz, $H(6)_{ax}$], 4.06 [1H, ddd, J 11.4, 4.8 and 1.6 Hz, $H(6)_{eq}$], 7.18-7.43 (5H, m, Ph]

The large coupling constant (J = 11.8 Hz) for H(4) indicated that this proton was axial. The $H(5)_{ax}$ proton was similarly identified by its large coupling constants. A strong NOE between $H(5)_{ax}$ and $CH_3(3')$ showed that the latter was also axial, thereby defining the stereochemistry as RR/SS.

(Received in UK 8 August 1989)