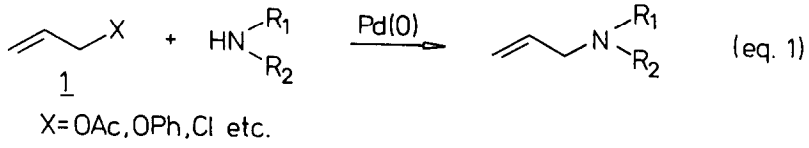
Tetrahedron Letters,Vol.26,No.14,pp 1749-1752,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF PROTECTED ALLYLAMINES VIA PALLADIUM-CATALYZED AMIDE ADDITION TO ALLYLIC SUBSTRATES

Styrbjörn E. Byström, Robert Aslanian, and Jan-E. Bäckvall*
Department of Organic Chemistry, Royal Institute of Technology
S-100 44 Stockholm, Sweden

Summary: Palladium-catalyzed reaction of allylic substrates with sodium p-toluenesulfonamide leads to the N-allylic-p-toluenesulfonamides. The reaction takes place with retention of configuration at the allylic carbon.

Palladium-catalyzed amination of allylic substrates is a convenient method for the preparation of allylic amines (eq. 1).[1-5] Primary and secondary amines react smoothly but



1

X=OAc,OPh,Cl etc.

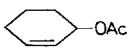
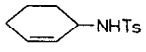
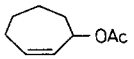
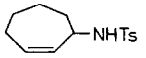
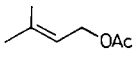
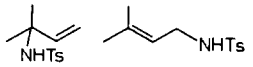
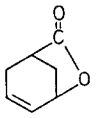
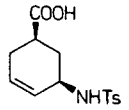
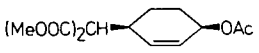
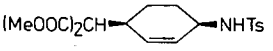
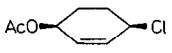
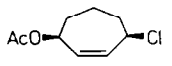
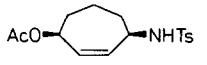
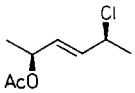
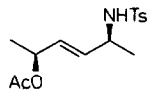
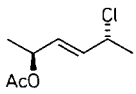
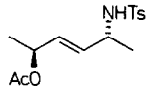
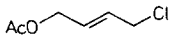
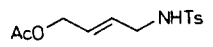
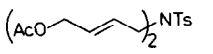
(eq. 1)

unfortunately ammonia cannot be used as the nucleophile. Therefore, primary allylic amines are not available by direct palladium-catalyzed amination of allylic substrates 1 (cf. eq. 1). To overcome this problem Trost and Keinan[5] used 4,4'-dimethoxybenzhydrylamine as a protected ammonia equivalent. Another more convenient route to introduce an ammonia equivalent on substrates 1 (eq. 1) would be to use an amide as the nucleophile. To our knowledge, no successful use of amides as nucleophiles in the palladium-catalyzed reactions of allylic substrates 1 has been reported in the literature. In this communication we report that p-toluenesulfonamide anion can be used as a nucleophile to produce protected primary allylic amines in good yield.

Treatment of the appropriate allylic substrate[6] with sodium p-toluenesulfonamide[7] in the presence of $Pd(PPh_3)_4$ in THF-DMSO (80:20) afforded the desired allylic sulfonamide in good yield (Table 1). The reaction of the allylic chlorides is complete after 3-5 h at room temperature, whereas the reaction of the allylic acetates requires longer reaction time at elevated temperature. This difference in reactivity allows the selective substitution of the chloro group in compounds that have both an allylic chloro group and an allylic acetoxy group (entries 6-10).

The substrates in entries 1-9 gave only the monoalkylated amides. No dialkylated amide (<2%) could be observed in the crude product even with only 1.1 equivalents of sodium p-toluensulfonamide when THF-DMSO (80:20) was used as the solvent.[8] Surprisingly, the chloroacetate in entry 10 gave mainly dialkylation under these reaction conditions. In the latter case it was necessary to add an excess of p-toluensulfonamide to increase the monoalkylation product.

Table 1. Palladium-catalyzed p-toluenesulfonamidation of allylic substrates.[a]

Entry	allylic substrate[b]	time, temp.	allylic sulfonamide[c]	yield (%)[d]
1		22h,[e] 50°C		75
2		21h,[e] 40°C		73
3		20h,[e] 40°C	 2 : 1	70
4		17h, 45°C		77[f,g]
5		5h,[e] 45°C		87[g]
6		5h, 20°C		81[g]
7		3h, 20°C		61[g]
8		4.5h, 20°C		80[h,i]
9		4.5h, 20°C		81[h,i]
10		4h,[j] 20°C		36[i]
				39[i]

a. All reactions were performed in THF-DMSO (80:20) with 5 mol% of $Pd(PPh_3)_4$ as the catalyst, using 1.1 equivalents of NaNHTs and 0.1-0.4 equivalents of $TsNH_2$. b. The allylic substrates were prepared according to reference 6. c. Ts = p-$CH_3C_6H_4SO_2$. d. Isolated yields after column chromatography or recrystallization. e. 5 mol% of 1,2-bis(diphenylphosphino)ethane was added. f. After extraction and recrystallization from chloroform-hexane. The acid was characterized according to reference 13. g. >98% cis. h. >95% of one diastereoisomer. i. Only the E isomer was observed. j. 9 equivalents of $TsNH_2$ were used in this case.

The palladium-catalyzed amidation was stereospecific and proceeded with retention of configuration at carbon (entries 4-9). This is consistent with the commonly accepted mechanism[1-5] involving a (π-allyl)palladium intermediate. Formation of the (π-allyl)palladium intermediate with inversion of configuration[9] followed by a trans external attack by the amide anion would account for the observed stereochemistry. The stereochemical assignment of the 4-substituted cyclohexenyl sulfonamides in entries 5 and 6 was made by ^{1}H NMR spectroscopy.[10,11] For the sulfonamide in entry 6 this assignment was confirmed by an independent synthesis of the trans isomer.[12]

There are a number of methods available[13] for the reductive cleavage of allylic sulfonamides, including electrochemical reduction[14] and sodium naphtalene.[15] In combination with these, the present procedure constitutes a method for the synthesis of primary allylic amines from allylic substrates. Furthermore, the protective group should prove useful for further elaboration of the allylic amine derivatives. For example, the product of entry 4 (Table 1) is an important synthetic intermediate for gabaculine synthesis.[13] In preliminary experiments[16] the monoalkylated sulfonamide of entry 10 was converted to N-tosyl-1-amino-1,3-butadiene by elimination of acetic acid as described previously.[17] Such dienes should be useful in Diels-Alder reactions as synthetic equivalents for 1-amino-1,3-dienes.[18,19]

Acknowledgment. We thank the Swedish Board of Technical Development and the Swedish Natural Science Research Council for financial support.

REFERENCES AND NOTES

1. (a) K.E. Atkins, W.E. Walker, and R.M. Manyik, Tetrahedron Lett., 3821 (1970). (b) K. Takahashi, A. Miyaki, and G. Hata, Bull. Chem. Soc. Jpn., 45, 230 (1972).

2. (a) B.M. Trost and J.P. Genêt, J. Am. Chem. Soc., 98, 8516 (1976). (b) B.M. Trost and E. Keinan, J. Am. Chem. Soc., 100, 7779 (1978).

3. (a) J.E. Bäckvall, R.E. Nordberg, J.E. Nyström, T. Högberg, and B. Ulff, J. Org. Chem., 46, 3479 (1981). (b) J.P. Genêt, M. Balabane, J.E. Bäckvall, and J.E. Nyström, Tetrahedron Lett., 24, 2745 (1983).

4. S.A. Godleski, J.D. Meinhart, and D.J. Miller, Tetrahedron Lett., 22, 2247 (1981).

5. B.M. Trost and E. Keinan, J. Org. Chem., 44, 3451 (1979).

6. The lactone in entry 4 (Table 1) was prepared according to: M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara, and A.Yoshikoshi, J. Org. Chem., 40, 1932 (1975); B.M. Trost, J.M. Timko, J.L. Stanton, J. Chem. Soc. Chem. Comm., 436 (1978). The starting materials in entries 5-10 were prepared according to: J.E. Bäckvall, R.E. Nordberg, and J.E. Nyström, Tetrahedron Lett., 23, 1617 (1982); J.E. Bäckvall, J.E. Nyström, and R.E. Nordberg, J. Am. Chem. Soc., accepted for publication.

7. Sodium p-toluenesulfonamide was prepared as a crystalline storable material by reaction of equimolar amounts of sodium hydride (3.2 g) and p-toluenesulfonamide (22.8 g) in THF (225 mL) under nitrogen for 24 h. This resulted in a white slurry from which the solvent was removed on a rotary evaporator connected to an oil pump and a cooling trap to avoid humidity in the system.

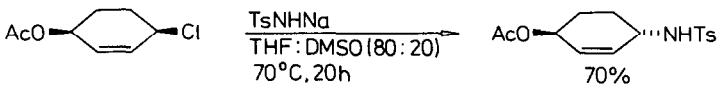
8. The use of only THF as the solvent afforded a considerable amount of dialkylated product due to the low solubility of NaNHTs compared to the sodium salt of the monoalkylated product.

9. Oxidative addition of allylic acetates to Pd(0), producing a (π-allyl)palladium complex, has recently been shown to proceed with inversion: T. Hayashi, T. Hagihara, M. Konishi, and M. Kumada, J. Am. Chem. Soc., 105, 7767 (1983).

10. (a) J.E. Bäckvall and R.E. Nordberg, J. Am. Chem. Soc., 103, 4959 (1981). (b) R.E. Nordberg, Dissertation, Royal Institute of Technology, Stockholm, 1982.

11. J.E. Bäckvall, S.E. Byström, and R.E. Nordberg, J. Org. Chem., 49, 4619 (1984).

12. The trans isomer of the product in entry 6 was prepared by an S_N2 reaction of 1-acetoxy-4-chloro-2-cyclohexene with sodium p-toluenesulfonamide:



The ^1H NMR spectra of the two isomers are given below ($CDCl_3$, 200 MHz):
trans-1-acetoxy-4-(p-toluenesulfonamido)-2-cyclohexene: δ 7.78 (d, 2 H), 7.32 (d, 2 H), 5.76-5.54 (m, 2 H, CH=CH), 5.22 (m, 1 H, CHO), 4.62 (d, 1 H, NH), 3.90 (m, 1 H, CHN), 2.44 (s, 3 H, CH_3), 2.02 (s, 3 H, OAc), 2.05-1.45 (m, 4 H, CH_2CH_2).
cis-1-acetoxy-4-(p-toluenesulfonamido)-2-cyclohexene: δ 7.78 (d, 2 H), 7.32 (d, 2 H), 5.85-5.56 (m, 2 H, CH=CH), 5.12 (m, 1 H, CHO), 4.57 (d, 1 H, NH), 3.82 (m, 1 H, CHN), 2.44 (s, 3 H, CH_3), 2.03 (s, 3 H, OAc), 1.85-1.65 (m, 4 H, CH_2CH_2).

13. S.P. Singer and K.B. Sharpless, J. Org. Chem., 43, 1448 (1978).

14. (a) P.T. Cottrell and C.K. Mann, J. Am. Chem. Soc., 93, 3579 (1971).
(b) V.G. Mairanowski, Angew. Chem. Int. Ed. Engl., 15, 281 (1976).

15. (a) S. Ji, L.B. Gortler, A. Waring, A. Bittisti, S. Bank, W.D. Closson, and P. Wriede, J. Am. Chem. Soc., 89, 5311 (1967). (b) W.D. Closson, S. Ji, and S. Schutenberg, J. Am. Chem. Soc., 92, 650 (1970).

16. R. Aslanian, J.E. Bäckvall, and P. Helquist, unpublished results.

17. B. Åkermark, J.E. Nyström, T. Rein, J.E. Bäckvall, P. Helquist, and R. Aslanian, Tetrahedron Lett., 25, 5719 (1984).

18. (a) W. Oppolzer and W. Fröstl, Helv. Chim. Acta, 58, 590 (1975).
(b) W. Oppolzer, W. Fröstl, and H.P. Weber, ibid., 58, 593 (1975).
(c) W. Oppolzer, Angew. Chem. Int. Ed. Engl., 16, 10 (1977). (d) W. Oppolzer, L. Bieber, and E. Francotte, Tetrahedron Lett., 981 (1979).

19. (a) L.E. Overman, G.F. Taylor, and P.J. Jessup, Tetrahedron Lett., 3089 (1976).
(b) L.E. Overman, R.L. Freerks, C.B. Petty, L.A. Clizbe, R.K. Ono, G.F. Taylor, and P.J. Jessup, J. Am. Chem. Soc., 103, 816 (1981). (c) L.E. Overman, L.A. Clizbe, R.L. Freerks, and C.K. Marlowe, J. Am. Chem. Soc., 103, 2807 (1981).
(d) L.E. Overman, C.B. Petty, T. Ban, and G.T. Huang, J. Am. Chem. Soc., 105, 6335 (1983).

(Received in UK 7 February 1985)