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SYNTHESIS OF CHIRAL TETRAAMINOPHOSPHONIUM CHLORIDES FROM *N*-BOC α-AMINO ACID ESTERS‡

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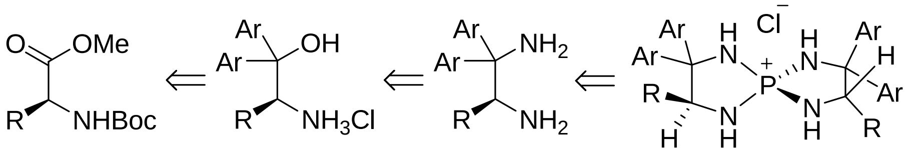
‡Dedication to Professor Ryoji Noyori on the occasion of his 70th birthday

Abstract – Preparation of chiral tetraaminophosphonium chlorides of type **1** starting from *N*-Boc α-amino acid esters is described. Modified conditions for the displacement of the tertiary hydroxy group of the intermediary amino alcohol pave a way for the assembly of **1** with various geminal aromatic groups, particularly those having electron-withdrawing substituents.

We have recently introduced chiral tetraaminophosphonium chlorides of type **1** and have demonstrated the effectiveness of (*M*,*S*)-**1** as a catalytic stereocontroller in the asymmetric direct Henry reaction.[1] Particularly, combined use of (*M*,*S*)-**1f** and a strong base such as potassium *tert*-butoxide in situ generates the corresponding chiral triaminoiminophosphorane,[2] which efficiently catalyzes the highly *anti*- and enantioselective Henry reactions of nitroalkanes with a wide range of aldehydes under mild conditions. A key finding for this success was that the steric and electronic manipulations of the geminal aromatic substituents (Ar) of **1** significantly affected the enantioselectivity. For the preparation of structurally diverse **1** to facilitate the identification of the optimal catalyst, however, we needed to establish a flexible synthetic route to various chiral 1,2-diamines **5**[3] from commercially available *N*-Boc α-amino acid esters.

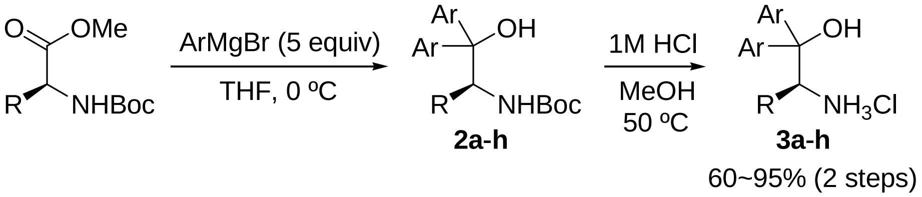


3 **5** (*M*,*S*)-**1**

1a (R = ^{i}Pr, Ar = Ph)
1b (R = ^{i}Pr, Ar = *p*-tolyl)
1c (R = ^{i}Pr, Ar = 3,5-xylyl)
1d (R = ^{i}Pr, Ar = *p*-F-C_6H_4)
1e (R = ^{i}Pr, Ar = *p*-Cl-C_6H_4)
1f (R = ^{i}Pr, Ar = *p*-CF_3-C_6H_4)
1g (R = ^{s}Bu, Ar = Ph)
1h (R = ^{t}Bu, Ar = Ph)

Here, we report the details of our efforts on this important subject, which have been mainly devoted to determining the appropriate conditions for the conversion of amino alcohol hydrochloride **3** to the requisite diamine **5**.

Since we assumed that *P*-spiro aminophosphonium salt **1** could be readily assembled from chiral 1,2-diamine **5** and simple phosphorus source,[4] phosphorus pentachloride (PCl_5), our attention was focused on the synthesis of **5**, and L-valine-derived **5a** was chosen as an initial target. Thus, *N*-Boc L-valine methyl ester was reacted with an excess amount of PhMgBr in THF at 0 ˚C and subsequent treatment of the crude product **2a** with 1M HCl in methanol at 50 ˚C furnished the corresponding amino alcohol hydrochloride **3a** in 82% yield. This procedure allowed us to prepare **3** possessing various geminal aromatic substituents not only from the L-valine derivative but also from other protected α-amino acids such as *N*-Boc L-isoleucine and L-*tert*-leucine methyl esters in good to excellent yields (Scheme 1).

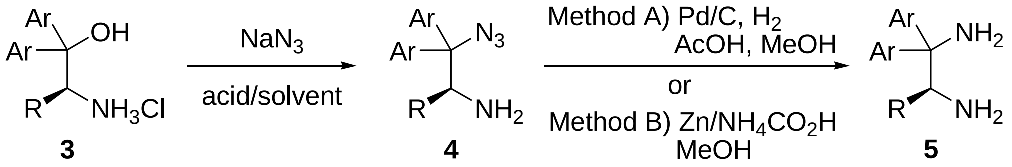


Scheme 1. Preparation of Amino Alcohol Hydrochlorides **3** from *N*-Boc α-Amino Acid Esters

However, we encountered difficulty in the next substitution of the tertiary hydroxy group of **3** with azide (Table 1). Actually, attempted reaction of **3a** with sodium azide (NaN_3) in the presence of sulfuric acid in aqueous methanol and dichloromethane at 0 ˚C to room temperature did not proceed at all (entry 1), and switching the organic solvent to aprotic dioxane brought virtually no improvement (entry 2).[5,6] Although the substitution took place when the acid concentration was increased, the chemical yield of diamine **5a**, obtained after reduction of the azide moiety of **4a** under hydrogen atmosphere with 5% Pd/C and acetic acid in methanol, was less than 30% (entry 3). In marked contrast, use of trifluoroacetic acid as solvent led to the clean formation of **4a**, and thus **5a** was isolated in 89% yield (entry 4).[7] Here, we found that the reduction of **4a** can also be performed with a comparable efficiency by treating with zinc powder and ammonium formate in methanol (entry 5).[8] These conditions were applicable to the conversion of *p*-tolyl- and 3,5-xylyl-substituted **3b** and **3c** into the corresponding diamines **5b** and **5c**, respectively (entries 6-9), but not equally effective for the substrates with aromatic groups bearing electron-withdrawing functionalities (**3d-f**) (entries 10, 12 and 14). Fortunately, this problem was overcome by using trifluoromethanesulfonic acid (TfOH) as co-solvent (entries 11 and 13) and it was particularly the case for the reaction of **3f** that possessed *p*-trifluoromethylphenyl group (entries 15 and 16). It should be added that the preparation of L-isoleucine- and L-*tert*-leucine-derived diamines **5g** and

5h appeared to be feasible in a similar manner as included in Table 1 (entries 17 and 18).

Table 1. Optimization of the Reaction Conditions for the Conversion of Amino Alcohol Hydrochloride **3** to Amino Azide **4** and Subsequent Reduction to Diamine **5**[a,b]

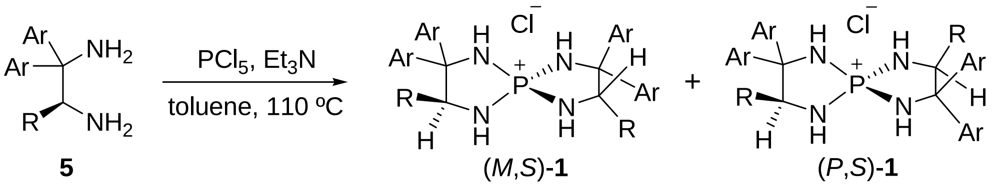


Entry	R	Ar	Acid	Solvent	Acid conc.	Method	Yield[c]
1	^{i}Pr	Ph (**3a**)	H_2SO_4	MeOH *aq.*/CH_2Cl_2[d]	3.6 M	-	NR[e]
2			H_2SO_4	10% dioxane *aq.*	3.8 M	-	NR[e]
3			H_2SO_4	10% dioxane *aq.*	12 M	A	<30%[f]
4			CF_3CO_2H		-	A	89%
5			CF_3CO_2H		-	B	88%
6	^{i}Pr	*p*-tolyl (**3b**)	CF_3CO_2H		-	A	71%
7			CF_3CO_2H		-	B	84%
8	^{i}Pr	3,5-xylyl (**3c**)	CF_3CO_2H		-	A	75%
9			CF_3CO_2H		-	B	83%
10	^{i}Pr	*p*-F-C_6H_4 (**3d**)	CF_3CO_2H		-	A	50%
11			CF_3CO_2H/20% TfOH		-	B	73%
12	^{i}Pr	*p*-Cl-C_6H_4 (**3e**)	CF_3CO_2H		-	A	36%
13			CF_3CO_2H/20% TfOH		-	B	70%
14	^{i}Pr	*p*-CF_3-C_6H_4 (**3f**)	CF_3CO_2H		-	-	NR[e]
15			CF_3CO_2H/20% TfOH		-	A	76%
16			CF_3CO_2H/20% TfOH		-	B	68%
17	^{s}Bu	Ph (**3g**)	CF_3CO_2H		-	A	61%
18	^{t}Bu	Ph (**3h**)	CF_3CO_2H		-	A	60%

[a] **3** was treated with NaN_3 (5 equiv) under the given conditions at 0 ˚C to room temperature for 3 h. [b] For the reduction of **4**, Method A: H_2 balloon with 5% Pd/C and AcOH in MeOH at room temperature; Method B: Zn power (2 equiv) and NH_4CO_2H (2 equiv) in MeOH at room temperature. [c] Isolated yield of diamine **5**. [d] 50% aqueous MeOH/CH_2Cl_2 = 4:5 (v/v). [e] NR = no reaction. [f] NMR yield, not pure form.

With a wide variety of chiral 1,2-diamine **5** in hand, we undertook the tuning of the reaction parameters for the assembly of **1**, which eventually revealed that the treatment of **5** with PCl_5 and Et_3N in toluene at 110 ˚C resulted in the facile formation of the desired **1** as shown in Scheme 2. Although the diastereomeric ratio (*MS*/*PS*) was highly dependent on the structures of the parent amino acid side chain

(R) and the geminal aromatic substituents (Ar) on the diamine subunits, essentially pure (*M*,*S*)-**1** can always be obtained by silica gel column chromatography and recrystallization.



1a: 92% (*MS*/*PS* = 6:1)
1b: 94% (2:1)
1c: 63% (>19:1)
1d: 75% (3:1)
1e: 68% (6:1)
1f: 99% (5:4)
1g: 90% (2:1)
1h: 72% (4:3)

Scheme 2. Assembly of Chiral Tetraaminophosphonium Chloride **1** from **5** and PCl_5

In summary, we have identified the appropriate conditions for the substitution of the tertiary hydroxy group of amino alcohol hydrochloride **3** with azide, thereby leading to the establishment of the reliable synthetic route to structurally variable chiral *P*-spiro tetraaminophosphonium chloride **1**. This study provides a solid basis for further structural modification of **1** to be able to exert sufficient reactivity and selectivity in the targeted asymmetric transformation.

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REFERENCES

1. D. Uraguchi, S. Sakaki, and T. Ooi, *J. Am. Chem. Soc.*, 2007, **129**, 12392.
2. Chiral triaminoiminophosphoranes: (a) J. M. Brunel, O. Legrand, S. Reymond, and G. Buono, *J. Am. Chem. Soc.*, 1999, **121**, 5807. (b) X. Liu, P. Ilankumaran, I. A. Guzei, and J. G. Verkade, *J. Org. Chem.*, 2000, **65**, 701. (c) P. Ilankumaran, G. Zhang, and J. G. Verkade, *Heteroatom Chem.*, 2000, **11**, 251. (d) M. Sauthier, J. Forniés-Cámer, L. Toupet, and R. Réau, *Organometallics*, 2000, **19**, 553. (d) U. Köhn, M. Schulz, A. Schramm, W. Günther, H. Görls, S. Schenk, and E. Anders, *Eur. J. Org. Chem.*, 2006, 4128.
3. Review for chiral 1,2-diamines: D. Lucet, T. Le Gall, and C. Mioskowski, *Angew. Chem. Int. Ed.*, 1998, **37**, 2580.
4. (a) T. B. Cameron, H. N. Hanson, G. F. de la Fuente, and J. E. Huheey, *Phosphorus, Sulfur, Silicon*, 1993, **78**, 37. (b) R. Schwesinger, J. Willaredt, H. Schlemper, M. Keller, D. Schmitt, and H. Fritz, *Chem. Ber.*, 1994, **127**, 2435. (c) P. R. Raithby, C. A. Russell, A. Steiner, and D. S. Wright, *Angew.*

Chem., Int. Ed. Engl., 1997, **36**, 649. (d) J. F. Bickley, M. C. Copsey, J. C. Jeffery, A. P. Leedham, C. A. Russell, D. Stalke, A. Steiner, T. Stey, and S. Zacchini, *Datlton Trans.*, 2004, 989.

5. W. H. Saunders Jr. and J. C. Ware, *J. Am. Chem. Soc.*, 1958, **80**, 3328.
6. (a) S.-J. Wey, K. J. O'Connor, and C. J. Burrows, *Tetrahedron Lett.*, 1993, **34**, 1905. (b) T. Ohkuma, H. Ooka, S. Hashiguchi, T. Ikariya, and R. Noyori, *J. Am. Chem. Soc.*, 1995, **117**, 2675.
7. A. Kalir and D. Balderman, *Org. Synth. Coll. Vol.*, 1990, **7**, 433.
8. G. R. Srinivasa, L. Nalina, K. Abiraj, and D. C. Gowda, *J. Chem. Res. (S)*, 2003, 630.