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Efficient Synthesis of Quaternary and P-Stereogenic Phosphonium Triflates†

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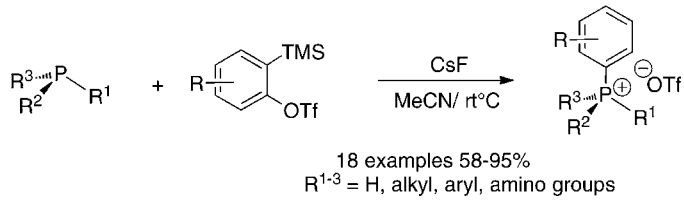
ABSTRACT



An efficient and general method for the preparation of achiral and chiral phosphonium salts is reported. This synthesis is based on the quaternization of phosphines and their derivatives with arynes generated *in situ* from 2-(trimethylsilyl)aryl triflates. This methodology is successfully applied to the synthesis of new valuable P-stereogenic phosphonium triflates.

Recently, organocatalysis has received increasing interest as it offers clean alternative methodologies to organic transformations relying on neither transition metals nor enzymes. In addition, the usefulness of chiral organocatalysts to promote asymmetric reactions has been widely demonstrated.[1−3] Thus, ionic or neutral chiral catalysts (ammonium or phosphonium salts, aminoacids, peptides, amines, phosphines, acids, diols, biphenols, etc.) can be used in many highly enantioselective reactions, notably for C−C bond formations.[1b] Furthermore, the use of chiral organophosphorus compounds as Lewis or Brönsted acid−base promoters is widely responsible for the progress in this area.[2,3] Phosphonium salts can also be used as ionic liquids,[4] organic reagents,[5−8] counterions,[9] or ligands.[10] Nowadays, the chirality of phosphonium salts is exclusively based on the atropoisomery of a binaphtyl backbone or central chirality

† This paper is dedicated to Pr. Octavio Antunes who disappeared with his family in the flight AF447 accident on the 30th of May 2009.

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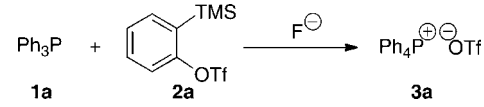
at carbon center.[3] On the other hand, chiral phosphonium salts bearing the chirality at phosphorus have been scarcely reported in asymmetric reactions.[3i] This is due to the few stereoselective methodologies allowing their easy preparation and structural modifications. Over the past decade, asymmetric synthesis of organophosphorus compounds has made much progress due to the use of borane as P(III)-protecting group.[11,12]

In connection with our ongoing work on asymmetric synthesis of P-stereogenic phosphorus compounds,[12] we previously reported the preparation of chiral phosphonium salts[13] and their NMR enantiodifferentiation using BINPHAT or liquid crystal.[14] However, these methods are limited to the quaternization by alkylhalides, whereas the synthesis of P-stereogenic tetraaryl phosphonium salts is still unknown. In the latter case, the quaternization requires harsh conditions or high temperature nickel- or palladium-mediated P−C bond formations,[15] which are inappropriate with the configurational stability of phosphines.[16,17] Recently, new advances in the field of arynes have been described, allowing their preparation under mild conditions based on the fluoride-induced 1,2-elimination of (*o*-trimethylsilyl) aryl triflates **2**.[18] As electrophilic species, arynes are well-known to readily react with various types of nucleophiles.[18−20]

We report here a new strategy for the preparation of chiral and achiral phosphonium salts **3** based on the quaternization of phosphines **1** with arynes generated from (*o*-trimethylsilyl)aryl triflates **2**.

In a pioneering work, Wittig has shown that arynes generated from 1,2-dihaloaryls can be used for the quaternization of phosphine.[20] Preliminary investigations on the reaction of triphenylphosphine with benzyne, generated from 1,2-dibromobenzene, led to tetraphenylphosphonium bromide in 42% yield. The use of (*o*-trimethylsilyl)phenyl triflate **2a** to generate the transient benzyne species in the presence of fluoride anions was then investigated for the quaternization (Table 1). The proposed mechanism for this reaction is based on a first attack of the fluoride anion to the trimethylsilyl group of **2a** affording the benzyne intermediate by β-elimination of the triflate. The trapping of the phosphine then leads to a phosphonium anion that is protonated by acetonitrile, giving **3a** (Scheme 1).[21]

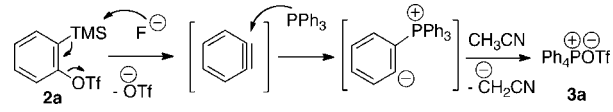
Table 1. Results of the Quaternization of Triphenylphosphine **1a** with (*o*-Trimethylsilyl)phenyltriflate **2a**



entry	fluoride source (equiv)	solvent	t (°C), time (h)	yield (%)[a] **3a**
1	CsF (3.3)[b]	THF	25, 15	18
2	CsF (3.3)[b]	CH_3CN	25, 15	38
3	CsF (6.0)[c]	CH_3CN	25, 15	89
4	CsF (6.0)[c]	$PhCH_2CN$	25, 15	51
5	CsF (6.0)[c]	CH_3CN	60, 15	58
6	LiF (6.0)[c]	CH_3CN	25, 15	0
7	NaF (6.0)[c]	CH_3CN	25, 15	0
8	KF (6.0)[c]	CH_3CN	25, 15	32
9	CuF_2 (6.0)[c]	CH_3CN	25, 15	23
10	TBAF (6.0)[c]	CH_3CN	25, 15	0

[a] Isolated yields after crystallization of the crude. [b] Reaction carried out with 1.1 equiv of **2a**. [c] Reaction carried out with 2.5 equiv of **2a**.

Scheme 1. Proposed Mechanism for the Quaternization



After optimization, CsF (6 equiv) was identified as the best fluoride source to generate benzyne from excess of **2a** (2.5 equiv) at room temperature in acetonitrile. Under these conditions, the corresponding tetraphenyl phosphonium triflate **3a** was isolated in 89% yield (Table 1, entry 3).

These optimized conditions were then applied for the quaternization of various P(III)-phosphorus compounds by benzyne (Table 2). Aryl- or alkylphosphines **1b**−**e** led to the corresponding phenylphosphonium triflates **3b**−**e** in 68−95% isolated yields (Table 2, entries 1−4 and 6). In the

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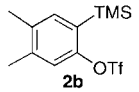
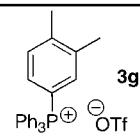
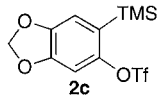
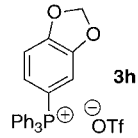
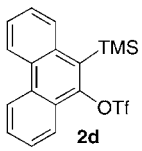
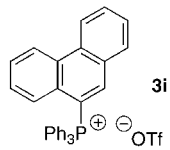
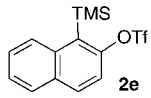
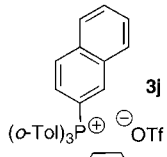
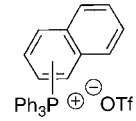
Table 2. Quaternization of Phosphorus Compounds **1b**−**i** and Arsine **4** with Benzyne[a]

	substrate		product		yield (%)
1	$(n\text{-Bu})_3P$	**1b**	$(n\text{-Bu})_3PhP^+\ ^-OTf$	**3b**	90[b]
2	$(t\text{-Bu})_3$	**1c**	$(t\text{-Bu})_3PhP^+\ ^-OTf$	**3c**	95[b]
3	$MePh_2P$	**1d**	$MePh_3P^+\ ^-OTf$	**3d**	68[b]
4	$(o\text{-Tol})_3P$	**1e**	$Ph(o\text{-Tol})_3P^+\ ^-OTf$	**3e**	88[b]
5	Ph_3As	**4**	$Ph_4As^+\ ^-OTf$	**5**	92[c]
6	$(Et_2N)Ph_2P$	**1f**	$(Et_2N)Ph_3P^+\ ^-OTf$	**3f**	60[b]
7	$(PhO)_3P$	**1g**			0
8	$PhPH_2$	**1h**	$Ph_4P^+\ ^-OTf$	**3a**	58[c,d]
9	Ph_2PH	**1i**	$Ph_4P^+\ ^-OTf$	**3a**	98[c,e]

[a] Reaction carried out overnight at room temperature in acetonitrile, using **2a** (2.5 equiv) and CsF (6 equiv). [b] Isolated yields after crystallization. [c] Isolated yields after purification over silica gel. [d] Reaction carried out with 4 equiv of **2a**. [e] Reaction carried out with 3 equiv of **2a**.

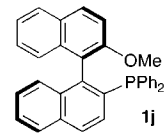
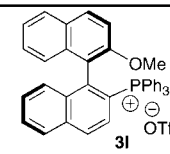
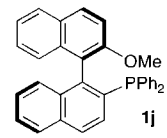
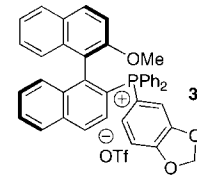
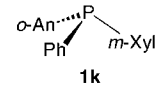
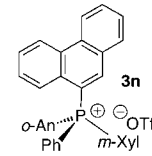
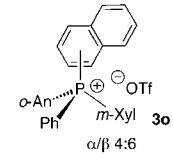
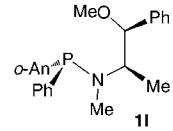
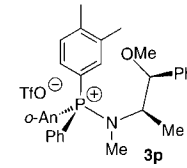
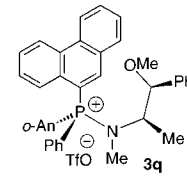
case of arsine **4** the quaternization with benzyne afforded the tetraphenylarsinium triflate **5** in 92% yield (entry 5). Interestingly, the *N*,*N*-diethylamino diphenylphosphine **1f** reacts also under these conditions, affording the corresponding aminophosphonium salt **3f** in 60% yield (entry 6). However, when the triphenylphosphite **1g** was tested, no quaternization was observed, certainly due to the weak nucleophilicity of the phosphorus center (entry 7).

Table 3. Phosphonium Salts **3g**−**k** from Aryne Precursors **2b**−**e**[a]

entry	phosphines	aryne precursor	phosphonium salts	yield[b] (%)
1	Ph_3P **1a**	 **2b**	 **3g**	90
2	Ph_3P **1a**	 **2c**	 **3h**	88
3	Ph_3P **1a**	 **2d**	 **3i**	65
4	$(o\text{-Tol})_3P$ **1e**	 **2e**	 **3j**	58
5	Ph_3P **1a**	**2e**	 **3k** α/β 3:7	56

[a] Reaction carried out overnight in acetonitrile, at room temperature using **2b**−**e** (2.5 equiv) and CsF (6 equiv). [b] Isolated yields (%).

Table 4. Synthesis of Chiral Phosphonium Triflates[a]

entry	substrate	aryne precursor	chiral phosphonium[b] triflates	yield (%)
1	 **1j**	**2a**	 **3l**	83[c]
2	 **1j**	**2c**	 **3m**	90[c]
3	 **1k**	**2d**	 **3n**	80[c]
4	**1k**	**2e**	 **3o** α/β 4:6	63[c,d]
5	 **1l**	**2b**	 **3p**	95[c]
6	**1l**	**2d**	 **3q**	87[e]

[a] Reaction carried out overnight in acetonitrile at room temperature in the presence of **2b**−**e** (2.5 equiv) and CsF (6 equiv). [b] >98% ee or de. [c] Isolated yields after crystallization. [d] Ratio of α,β-**3o** regioisomers determined by ^{31}P NMR. [e] Isolated yields after purification over silica gel.

We also investigated the quaternization of primary **1h** and secondary phosphines **1i** under these conditions. Surprisingly, the tetraphenylphosphonium triflate **3a** was formed as the sole product in good to excellent yield (Table 2, entries 8 and 9). These results suggest subsequent deprotonation of the hydrogenophosphonium salt intermediates, followed by a new quaternization with benzyne leading to the secondary and/or tertiary phosphine, and then to the phosphonium salt **3a**.

The quaternization of the phosphines **1a** and **1e** was investigated with various triflates reagents **2b**−**e** featuring more challenging aromatic backbones (Table 3). These aryne precursors **2b**−**e** were conveniently prepared from the corresponding bromophenols, according to the literature.[22] The phosphonium salts **3g**−**k** were successfully prepared in yields ranging from 56% to 90% (Table 3, entries 1−5).

Interestingly, the quaternization of tris(*o*-tolyl)phosphine **1e** by the aryne derived from **2e** regiospecifically leads to

the β-naphtylphosphonium triflate **3j** in 58% isolated yield (Table 3, entry 4). However, under the same conditions the triphenylphosphine **1a** affords an inseparable mixture of both α- and β-naphthyl triphenylphosphonium triflates **3k** in a 3:7 ratio (entry 5). These results suggest that the regioselectivity of the quaternization with benzyne depends on steric hindrance of the phosphine.[23]

Chiral phosphonium triflates **3l**−**q** were synthesized starting from MOP **1j** and P-stereogenic organophosphorus compounds **1k,l**, previously prepared from the ephedrine methodology[12] (Table 4). The quaternization took place efficiently, and the chiral phosphonium salts **3l**−**q** were obtained in good to excellent yields (63−95%; Table 4, entries 1−6). The stereospecificity of the quaternization was controlled for **3n,o** by ^{31}P NMR analysis in the presence of the chiral anion BINPHAT[14b,c] or by ^{1}H NMR for the **3p,q**. In the case of the reaction with the aryne precursors **2a**−**e**, neither racemization nor epimerization was observed since the products **3l**−**o** and **3p,q** were obtained with >98% ee or de, respectively.

For the phosphonium salt **3o**, the attack of the phosphine **1k** was slightly favored at the β-position of the transient aryne intermediate derived from **2e**, which has already been observed with the triphenylphosphine **1a** (Table 3, entry 5). The regioisomers α,β-**3o** were obtained as an inseparable mixture in 63% overall yield.

In conclusion, we have developed a general and efficient method for the synthesis of quaternary phosphonium salts from P(III)-organophosphorus compounds and arsines. This quaternization was performed overnight under mild conditions in the presence of arynes generated *in situ* from (*o*-trimethylsilyl)aryl triflates. Chiral phosphonium triflates bearing chirality on the phosphorus atom and/or the carbon backbone were readily prepared in enantio- or diastereomerically pure form. Our ongoing efforts seek to apply these original chiral phosphonium salts as chiral counterions or organocatalysts and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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