P_2-Et-Mediated Deprotonation of *ortho*-Halobenzyl Sulfones: Synthetic Applications as Zwitterionic Synthons

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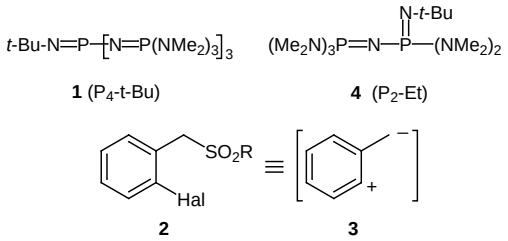
Abstract: α-Sulfonyl benzylic carbanions, derived from *ortho*-halobenzyl sulfones **5** (Hal = Br, I), can be easily generated by the phosphazene base P_2-Et and react with different electrophiles such as alkyl halides, aldehydes and ethyl acrylate. Palladium catalysed cross-coupling reactions performed at the halogen atom, followed by P_2-Et-mediated alkylation-dehydrosulfinylation process using bromoacetates as electrophiles allow the preparation of *ortho*-substituted cinnamates.

Key words: sulfones, phosphazene bases, alkylations, aldol reaction, Heck reaction, cross-coupling

α-Sulfonyl carbanions[1] are usually generated by means of alkyllithium and Grignard reagents, lithium amides and other strong bases as alkali hydrides or alkoxydes under strict anhydrous conditions and low temperatures. Solladié-Cavallo et al. have described[2] the diastereoselective aldol reaction of α-sulfonyl carbanions derived from benzyl sulfones employing phosphazene base P_4-*t*-Bu **1**.[3,4] This base gave better results than *n*-butyllithium or ethylmagnesium bromide in the case of butyraldehyde and chiral isopropylidene glyceraldehyde.[2] Phosphazene base P_4-*t*-Bu has also been employed in the alkylation reaction of episulfones.[5] In general, these cation free Schwesinger bases[3] are strong non-ionic systems, which allow the deprotonation of a wide range of acidic protons ($^{MeCN}pK_a$ = 27–42)[3] to give high reactive naked carbanions.[6] They can be managed under simpler reaction conditions than the above mentioned bases and the high cost of phosphazene bases is partially overcome because recovery from the reaction mixture after acidic treatment can be made.[3,4]

We envisaged that *ortho*-halobenzyl sulfones **2** can be appropriate equivalents of the zwitterionic synthon **3**, useful for the synthesis of interesting disubstituted benzenes through a sequence comprised of electrophilic functionalisation at the benzylic position and palladium cross-coupling reactions of the halogen atom or the reverse sequence. In this way, we have found that phosphazene base P_2-Et **4**,[3,4] a moderate hindered base[7] whose $^{MeCN}pK_a$ is similar to 33, is the most suitable base for the proton abstraction of *ortho*-halobenzyl sulfones **2** and further reaction with different electrophiles[8] under very simple reaction conditions.



Figure

For the preparation of *ortho*-halobenzyl sulfones **5**, 2-halobenzyl bromides[9] were treated with sodium *para*-toluenesulfinate in refluxing methanol to give the bromo derivative **5a** and the *ortho*-iodobenzyl sulfone **5b** in 80% and 85% overall yield, respectively.[10] Initially, the alkylation reaction of sulfones **5** using P_4-*t*-Bu or BEMP,[2,4] as phosphazene bases, failed. However, P_2-Et gave satisfactory results for the alkylation of compounds **5** with alkyl halides at room temperature in dry THF and in absence of an inert atmosphere (Scheme 1, Table, entries 1–5).[11] The Michael addition reaction with ethyl acrylate could be carried out with 10 mol% of P_2-Et to give adducts **6ad** and **6bd**, both in 75% yields (Table, entries 6 and 7).[11] When ethyl bromoacetate was used as electrophile sequential alkylation-β-elimination reaction of *para*-toluenesulfinic acid took place affording ethyl *ortho*-cinnamates **7a** and **7b**, the presence of two equivalents of base being necessary (Table, entries 8 and 9).[11]

For the aldol reactions the temperature was kept at -78 ºC for times depicted in Table, depending on the aldehyde structure, in order to isolate the addition products **8**.[11] Higher temperatures led to retro-aldol reaction and the formation of vinyl sulfones. The relative configuration of the major -or exclusively obtained- diastereomer *anti*-**8** was deduced from the coupling constants between CHS and CHO[12] (Scheme 1, Table, entries 10–14). The *anti*/*syn* ratio increased notably with the bulkiness of the aldehyde and with the size of the halogen of the sulfone (Table, entries 12–14). The *anti*-aldol products are the favoured ones as it was demonstrated previously by Solladié et al.[2] obtaining the best diastereoselection (89:11 *dr*) using *t*-butyl benzyl sulfone /P_4-*t*-Bu and isopropylideneglyceraldehyde. They justified it by the interaction between the extra α-oxygen atom of the aldehyde moiety and the conjugated acid of the phosphazene base (P_4-*t*-BuH^+). In our reaction, according to the achieved results, the iodine atom in **5b** caused higher diastereoselection to-

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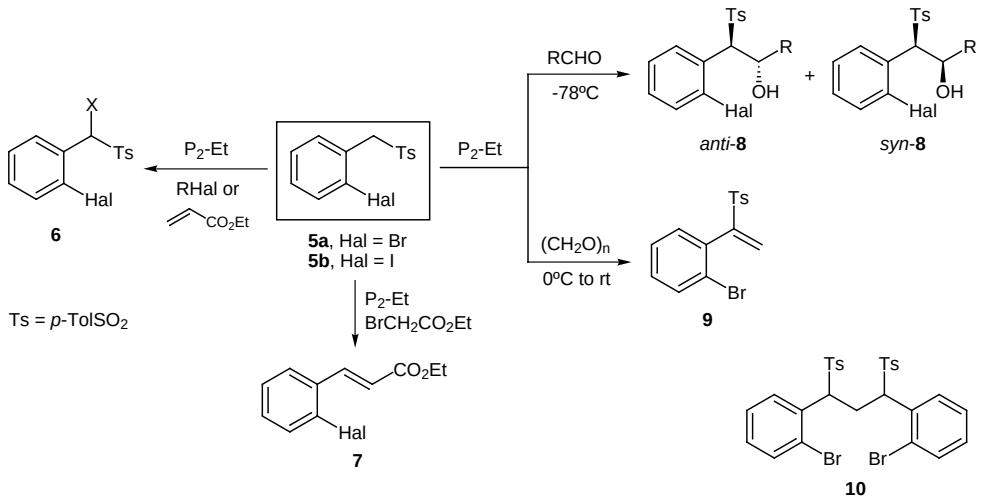
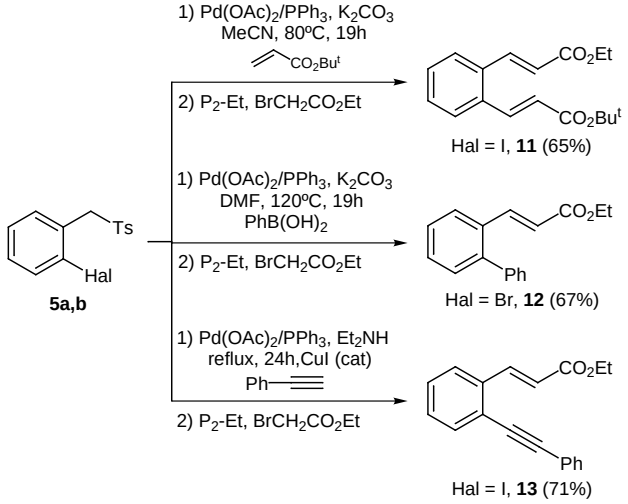


Scheme 1

wards the *anti* isomer. Probably, the main reason is the difference in energy in the opened transition states, such as it was confirmed by preliminary search employing *ab initio* calculations.[13] The analogous condensation reaction was performed with paraformaldehyde and **5a** obtaining an equimolar mixture of vinyl sulfone **9a** and the Michael addition product **10a** as mixture of diastereomers.[14] This very reactive alkenyl sulfone had to be generated in the presence of an excess of paraformaldehyde avoiding large amounts of α-sulfonyl carbanion in the reaction mixture. So, adding the sulfone **5a** or **5b** very slowly (2 h, via syringe pump) to a suspension of paraformaldehyde (10 equiv) and P_2-Et (1 equiv) at 0 ºC, vinyl sulfone **9a** and **9b**[11] were exclusively obtained in 54% and 70% yield, respectively (Scheme 1, Table, entries 15 and 16). The chemoselectivity and basicity of phosphazene base P_2-Et represented a very interesting alternative to strong bases operating at very low temperatures and under strict anhydrous conditions. For instance, when the aldol reaction was carried out using *n*-butyllithium as base in the case of **5a** no reaction was observed and **5b** gave a complex mixture of products.

A combination of Heck reaction/cross-coupling-alkylation-β-elimination sequence[15] was used for preparing cinnamic esters derivatives **11**–**13**. The synthesis of diene **11** was accomplished, in 65% yield, by Heck reaction[16] with ethyl acrylate under Jeffery's PTC conditions[17] (using potassium carbonate as base, 10 mol% of tetra-*n*-butylammonium bromide, in refluxing acetonitrile for 19 h), followed by the mentioned alkylation-elimination protocol with *t*-butyl bromoacetate (Scheme 2). The not easy preparation of 1,2-disubstituted benzenes, bearing two different α,β-unsaturated carbonyl compounds or related derivatives, make this methodology an elegant way to access them.[18,19] Compounds of the type **11** have been employed in electrocyclic reactions,[18c,19a,c] in the synthesis of cispentacin derivatives,[18b] 1,3-dihydroisobenzofuranes[18a] and annulenes,[19b] in the preparation of dopamine β-hydroxylase inhibitors[20] and drugs for treatment of obesity and diabetes.[21] Biaryl acrylate **12** was obtained, in 67% yield, employing the Suzuki-Miyaura cross-coupling reaction[22,23] of **5a** with phenylboronic acid and potassium carbonate in DMF at 120 ºC for 19 h followed by P_2-Et-mediated alkylation-elimination with ethyl bromoacetate. Enyne **13** was isolated in 71% yield through a Sonogashira[24] reaction of **5b** with phenylacetylene in the presence of catalytic amounts of CuI under refluxing diethylamine for 24 h and further synthesis of the acrylic ester moiety (Scheme 2).



Scheme 2

As summary, we have found that *ortho*-halobenzyl sulfones are appropriate zwitterionic synthons for the preparation of *ortho*-disubstituted benzenes by sequential cross-coupling reaction at the halogen atom and P_2-Et-mediated alkylation at the benzylic position. Further applications of these sulfones are underway.

Table P_2-Et Mediated Alkylation and Aldol Reaction of *ortho*-Halobenzyl Sulfones **5a** and **5b**[a]

Entry	Sulfone **5**	Electrophile	T (°C)	Time (h)	Product[b]	X or R	Yield (%)[c]
1	**5a**	EtI	25	16	**6aa**	Et	70
2	**5b**	EtI	25	16	**6ba**	Et	78
3	**5a**	CH_2=$CHCH_2Br$	25	16	**6ab**	CH_2=$CHCH_2$	80
4	**5b**	CH_2=$CHCH_2Br$	25	16	**6bb**	CH_2=$CHCH_2$	65
5	**5a**	HC≡CCH_2Br	25	16	**6ac**	HC≡CCH_2	90
6	**5a**	CH_2=$CHCO_2Et$	25	12	**6ad**	$CH_2CH_2CO_2Et$	75
7	**5b**	CH_2=$CHCO_2Et$	25	12	**6bd**	$CH_2CH_2CO_2Et$	75
8	**5a**	$BrCH_2CO_2Et$	25	19	**7a**	—	70
9	**5b**	$BrCH_2CO_2Et$	25	19	**7b**	—	66
10	**5a**	*n*-PrCHO	–78	0.5	**8aa**	*n*-Pr[d]	75
11	**5b**	*n*-PrCHO	–78	0.5	**8ba**	*n*-Pr[d]	90
12	**5a**	*t*-BuCHO	–78	0.5	**8ab**	*t*-Bu[e]	55
13	**5a**	*n*-$C_6H_{13}CHO$	–78	19	**8ac**	*n*-C_6H_{13}[f]	86
14	**5b**	*n*-$C_6H_{13}CHO$	–78	19	**8bc**	*n*-C_6H_{13}[e]	70
15	**5a**	$(CH_2O)_n$	0[g]	2	**9**[a]	—	54
16	**5b**	$(CH_2O)_n$	0[g]	2	**9b**	—	70

[a] For experimental procedures see ref. 11.
[b] All products gave satisfactory physical and spectroscopic data.
[c] Isolated yield after column chromatography (silica gel).
[d] Obtained as a 7:1 *anti*:*syn* mixture.
[e] Obtained as a 1:0 *anti*:*syn* mixture.
[f] Obtained as a 3:1 *anti*:*syn* mixture.
[g] Slow addition of the sulfone **5** (see text).

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To a solution of the benzyl sulfone **5** (0.2 mmol) and P_2-Et (79 μL, 0.24 mmol for compounds **6aa**–**6ac**, **6ba** and **6bb**;

237 μL, 0.72 mmol for compound **7**; 7 μL, 0.02 mmol for compounds **6ad** and **6bd**) in dry THF (3 mL), at 0 °C, the corresponding electrophile (0.24 mmol) was added. After stirring at this temperature, for reaction times depicted in Table, an aqueous 2 M solution of hydrochloric acid (2 mL) was poured into the flask. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed successively with aqueous 2 M HCl (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated under vacuo. The crude products were purified by flash chromatography (silica gel) using mixtures of *n*-hexane/ethyl acetate as eluent, obtaining products **6** or **7** in yields showed in Table.

A typical procedure for compounds **8** follows:

To a solution of the benzyl sulfone **5** (0.2 mmol) and P_2-Et (79 μL, 0.24 mmol)in dry THF (3 mL), at -78 °C, under an inert atmosphere (N_2) was added the corresponding aldehyde (0.24 mmol). After stirring at this temperature, for reaction times depicted in Table, an aqueous 2 M solution of hydrochloric acid (2 mL) was poured into the flask. The aqueous phase was extracted with EtOAc (3 × 10 mL) and the combined organic layers were washed successively with aqueous 2 M HCl (2 × 10 mL) and brine (10 mL), dried (Na_2SO_4) and evaporated under vacuo. The crude products were purified by flash chromatography (silica gel) using mixtures of *n*-hexane/ethyl acetate as eluent, obtaining aldols **8** in yields showed in Table.

A typical procedure for compounds **9** follows:

To a solution of paraformaldehyde (34 mg, 1.08 mmol) and benzyl sulfone **5** (0.2 mmol) in dry THF (10 mL), at 0 ºC, was slowly added (2 h) a solution of P_2-Et (145 μL, 0.43 mmol) in dry THF (5 mL). The resulting mixture was stirred at room temperature overnight and an aqueous 2 M HCl solution (2 mL) was added. The mixture was treated as described previously affording, after purification by flash chromatography (silica gel), compound **9a** or **9b** in 54% and 70% yield, respectively (see Table).

9a: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3 H, CH_3Ar), 5.93, 6.82 (2 × s, 2 H, CH_2=C), 7.19–7.31 (m, 4 H, Ar*H*) and 7.42–7.52 (m, 4 H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.6 (C*H*$_3$Ar), 124.4 (Ar*C*Br), 127.6, 128.7, 129.1, 130.4, 131.0, 134.7, 136.7, 139.7, 140.1, 144.7 and 148.9 (Ar*C* and CH_2=C). IR (neat): 3101, 1596, 1316, 1303, 1149, 800 cm^{-1}. MS (EI, 70 eV) *m/z*: 338, 336 (M^+, 3%), 259 (11), 258 (80), 257 (96), 199 (54), 197 (49), 184 (39), 182 (78), 181 (100), 140 (27), 103 (31), 102 (44)and 101 (45).

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