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Synthetic Applications of *o*- and *p*-Halobenzyl Sulfones as Zwitterionic Synthons: Preparation of *Ortho*-Substituted Cinnamates and Biarylacetic Acids

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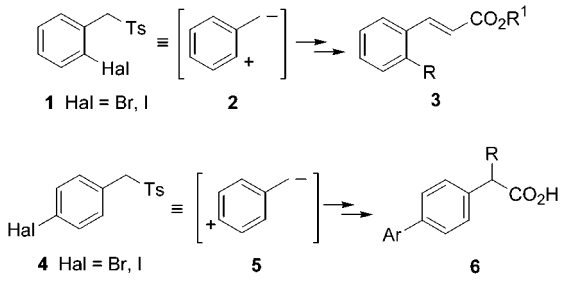
The synthetic applications of *o*-halobenzyl and *p*-halobenzyl sulfones as precursors of 1,3- and 1,5-zwitterionic synthons, respectively, are described. Their α-sulfonyl carbanions, generated by means of the phosphazene base P_2-Et or BuLi or K_2CO_3 under PTC conditions, reacted with different electrophiles such as alkyl halides, aldehydes, and electrophilic olefins. Palladium-catalyzed cross-coupling processes such as Heck, Suzuki, and Sonogashira reactions can be efficiently performed at the halogen atom. These two sequential functionalization processes are applied to the synthesis of *ortho*-substituted cinnamates and pharmaceuticals belonging to the family of *p*-biarylacetic acids such as 4-biphenylacetic acid, namoxyrate, xenyhexenic acid, and biphenylpropionic acid.

Introduction

The sulfonyl group has been extensively applied in organic synthesis as key intermediate in numerous total synthesis.[1] This atomic array directs the desired functionalization, by stabilizing α-radicals,[2,3] by acting as cationic synthons,[3,4] or by generation of its α-anion.[5] We envisaged that *o*- and *p*-halobenzyl sulfones **1** and **4** can be appropriate precursors of 1,3- and 1,5-zwitterionic synthons **2**[6] and **5**, respectively, which are useful for the synthesis of 1,2- and 1,4-disubstituted benzenes. The benzylic position could be converted to a carbanionic center stabilized by the sulfonyl group, and the halogen atom can be used as leaving group in cross-coupling reactions. This reactivity could be applied to the synthesis of important *ortho*-substituted cinnamates **3**[7] and 4-biarylacetic acids **6** (Chart 1). 1,2-Disubstituted benzenes bearing two equivalents or two different acrylic or styryl groups are important compounds from the synthetic and biological point of view.[8,9] For example, compounds **3** were used in electrocyclic reactions,[8d,9a,c] in the synthesis of cispentacin derivatives,[8c,e,d] 1,3-dihydroisobenzofuranes,[8b] and annulenes,[9b] in the preparation of dopamine *β*-hydroxylase inhibitors[10] and drugs for treatment of obesity and diabetes.[11] Regarding 4-biarylacetic acids and their derivatives, they are known for their potent nonsteroidal analgesic, antipyretic, and antiinflammatory activity[12] for

CHART 1



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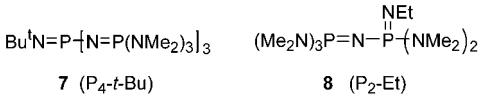
inhibiting the phosphodiesterase type IV[13] and also for increasing the inhibition on the binding $GABA_A$ receptor in animal brain tissue.[14] They were employed as components of pharmaceutical formulations for treatment of oxidative stress and endothelial disfunction[14] and for designing colon-specific drug delivery systems.[15] Several derivatives of these compounds, substituted at the *para* position, were applied in the study of thermotropic liquid crystals.[16] In general, all of them have very important antiinflammatory properties inhibiting the human s-PLA_2 phospholipases.[17] Due to the industrial and pharmaceutical interest aroused by these substances, numerous general methods for the synthesis of the biarylacetic acids[18] are patented. To date, these compounds were synthesized mainly by Willgerodt−Kindler rearrangement,[18a] by homologation[18b] of the corresponding biaryl ketones, by the Suzuki−Miyaura cross-coupling reaction catalyzed by Pd/C,[18a] by combination of known procedures,[18c,d,19] and via photostimulated reactions of phenylacetic acid dianions with aryl halides.[20] The development of new methodologies, allowing the introduction of different aryl substituents and also a variety of alkyl groups at the α-position of the acetic acid moiety, are desirable. Here, we report the experimental results achieved using benzylic sulfones **1** and **4** focused on preparing these very interesting 1,2-disubstituted benzenes, cinnamic esters derivatives, and 4-biarylacetic acids.

Results and Discussion

1. Reactivity of the *o*-Halobenzyl Sulfones 1. Considering the α-sulfonyl carbanions derived from benzylic sulfones are mainly generated using very strong metalated bases under strict anhydrous conditions and at very low temperatures. For example, these conditions were employed in an integrated chemical process[21] and

CHART 2



7 (P_4-*t*-Bu) **8** (P_2-Et)

in the synthesis of biologically active compounds starting from 3-oxo-1,3-dihydroisobenzofuran-1-yl phenyl sulfone.[1,22] By contrast, there is one example in the literature where indoles were prepared from benzylsulfonyl amidates employing a weak base (NaOH).[23] Alternatively, benzyl sulfones were deprotonated by phosphazene base P_4-*t*-Bu **7**[24,25] (Chart 2) in the diasteroselective aldol reaction with aldehydes.[26] Better results in this field were achieved with base **7** in comparison with other bases as *n*-butyllithium or ethylmagnesium bromide when the reaction was attempted with butyraldehyde and chiral isopropylidene glyceraldehyde.[26] Phosphazene base P_4-*t*-Bu was also used in the alkylation reaction of episulfones with benzyl bromide and benzaldehyde obtaining alkenes by loss of SO_2.[27] In general, these metal-free Schwesinger's bases are strong nonionic species, generating highly reactive naked carbanions.[28] They require neither anhydrous solvent nor inert atmosphere, and their relatively high costs are partially overcome by their recovery, after acidic treatment of the reaction mixture.[24,25]

For the functionalization of *o*-halobenzyl sulfones **1**, different bases were assayed, depending on the type of electrophile as well as the halogen atom at the *ortho*-position. For the alkylation reactions of *o*-bromosulfone **1a** with alkyl halides, BuLi at −78 °C in dry THF, NaH in dry DMF, and P_2-Et **8** in THF at room temperature (the addition was carried out at 0 °C) can be used (Scheme 1, Table 1). The best results were obtained with P_2-Et in THF (Table 1, entries 11−14). In the case of the iodosulfone **1b** the alkylation process only succeeds with P_2-Et as base; in the case of BuLi or NaH a complex mixture of products was obtained, presumably originating from side reactions due to the lithium−iodide ex-

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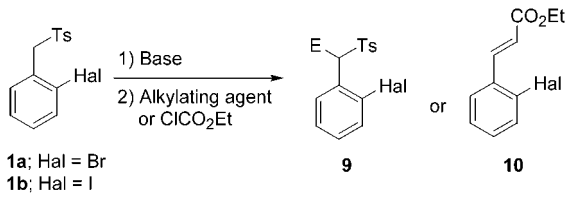
TABLE 1. Alkylation and Carboxylation of *o*-Halosulfones 1

entry	1	base (equiv)	electrophile	*T* (°C)[a]	*t* (h)	9/10	E	yield (%)[b]
1	**1a**	BuLi (1.2)	MeI	−78 to rt	24	**9a**	Me	80
2	**1a**	BuLi (1.2)	methyl oxirane	−78 to rt	12	**9b**	$CH_2CH(Me)OH$	61[c]
3	**1a**	BuLi (1.2)	CH_2=$CHCH_2Br$	−78 to rt	24	**9c**	CH_2=$CHCH_2$	78
4	**1a**	BuLi (1.2)	$BrCH_2CO_2Et$	−78 to rt	24	**9d**[d]	CH_2CO_2Et	54[e]
5	**1a**	BuLi (1.2)[f]	$ClCO_2Et$	−78 to rt	17	**9e**	CO_2Et	41
6	**1a**	BuLi (1.2)[g]	$ClCO_2Et$	−78 to rt	17	**9e**	CO_2Et	45
7	**1a**	BuLi (1.5)[h]	$ClCO_2Et$	−78 to rt	12	**9e**	CO_2Et	60
8	**1a**	NaH (1.2)	MeI	0 to rt	24	**9a**	Me	67
9	**1a**	NaH (1.2)	CH_2=$CHCH_2Br$	0 to rt	5	**9c**	CH_2=$CHCH_2$	88
10	**1a**	NaH (1.2)	$(Me)_2C$=$CHCH_2Br$	0 to rt	48	**9f**	$(Me)_2C$=$CHCH_2$	70
11	**1a**	P_2-Et (1.2)	EtI	0 to rt	24	**9g**	Et	71
12	**1a**	P_2-Et (1.2)	CH_2=$CHCH_2Br$	0 to rt	12	**9c**	CH_2=$CHCH_2$	92
13	**1a**	P_2-Et (1.2)	CH=$CHCH_2Br$	0 to rt	12	**9h**	CH=$CHCH_2$	90
14	**1a**	P_2-Et (3.0)	$BrCH_2CO_2Et$	0 to rt	24	**10a**[d]	−	63
15	**1b**	P_2-Et (1.2)	EtI	0 to rt	24	**9i**	Et	68
16	**1b**	P_2-Et (1.2)	CH_2=$CHCH_2Cl$	0 to rt	24	**9j**	CH_2=$CHCH_2$	58
17	**1b**	P_2-Et (1.2)	CH_2=$CHCH_2Br$	0 to rt	12	**9j**	CH_2=$CHCH_2$	85
18	**1b**	P_2-Et (1.2)	CH=$CHCH_2Br$	0 to rt	24	**9k**	CH=$CHCH_2$	85
19	**1b**	P_2-Et (1.2)	*n*-BuBr	0 to rt	24	**9l**	*n*-Bu	58
20	**1b**	P_2-Et (3.0)	$BrCH_2CO_2Et$	0 to rt	24	**10b**[i]	−	66
21	**1b**	P_2-Et (1.2)	$PhCH_2Br$	0 to rt	12	**9m**	$PhCH_2$	78

[a] The base was added, and the temperature was allowed to rise to room temperature in 2 h from −78 °C and in 15 min from 0 °C. [b] Isolated yield after flash chromatography. [c] Isolated as a 1:1 mixture of diastereomers. [d] See ref 29. [e] A 14% of unsaturated ester **10a** was also isolated. [f] 1.2 equiv of DMPU were added. [g] 1.2 equiv of TMEDA were added. [h] 1.5 equiv of HMPA were added. [i] See ref 30.

SCHEME 1

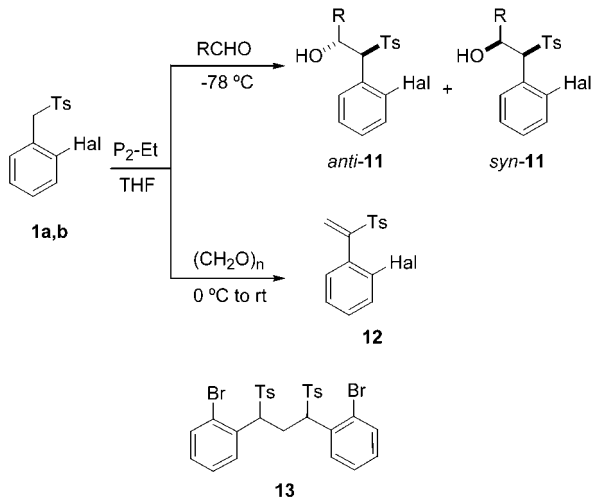


change. Alternatively, phosphazene base P_2-Et **8** (Chart 2) was the most suitable Schwesinger's base for this process, starting from brominated or iodinated benzyl sulfones **1a**,**b**. Working with this base was very advantageous because yields were higher than with metalated bases (Table 1, entries 3, 9, and 12). Neither strict anhydrous conditions nor an inert atmosphere were required, and also nonactivated electrophiles reacted at room temperature (Table 1, entries 11−21).

When the alkylation reaction was performed with ethyl bromoacetate, compounds **10** were exclusively obtained after a subsequent *β*-elimination reaction. The resulting cinnamic ester derivatives **10** were isolated in good yield using P_2-Et as base (Table 1, entries 14 and 20). Other electrophiles such as propylene oxide and ethyl chloroformate did not react in the presence of this nonionic base. However, methyloxirane gave an equimolar mixture of diastereomers when the reaction was carried out with sulfone **1a** using *n*-butyllithium (1.2 equiv). Similarly, the α-carboxylation of **1a** was accomplished in good yields with *n*-butyllithium in the presence of HMPA (Table 1, entries 5−7).

Phosphazene base P_2-Et was the selected base for running the aldol-type reactions at −78 °C in the presence of aliphatic aldehydes[31] for the preparation of

SCHEME 2



compounds **11** (Scheme 2 and Table 2). Higher temperatures led to retro-aldol products and significant amounts of vinyl sulfones, which could not be isolated as pure compounds. The relative configuration of the major, or exclusively generated, diastereomer corresponded to the *anti*-compound **11**, whose relative configuration was deduced from the coupling constants between CHS and CHOH groups in comparison with the reported in the literature.[32] The *anti*/*syn* ratios increased notably with the bulkiness of the aldehyde as well as the size of the halogen atom (Table 2, entries 1−6).

These *anti* aldol products are the favored ones as it was demonstrated previously by Solladié-Cavallo et al.[26] They justified the diastereoselection by the existing

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TABLE 2. Aldol-Type Reaction of *o*-Halosulfones 1 Using P_2-Et as Base

entry	sulfone	aldehyde	*t* (h)	product	*anti*:*syn*[a]	yield (%)[b]
1	**1a**	PrCHO	0.5	**11a**	7:1	61
2	**1a**	Bu^{t}CHO	0.5	**11b**	1:0	56
3	**1a**	$CH_3(CH_2)_5CHO$	19	**11c**	3:1	87
4	**1b**	PrCHO	0.5	**11d**	7:1	52
5	**1b**	Bu^{t}CHO	0.5	**11e**	1:0	30
6	**1b**	$CH_3(CH_2)_5CHO$	19	**11f**	1:0	52
7	**1a**	$(CH_2O)_n$[c]	2	**12a**	–	54
8	**1b**	$(CH_2O)_n$[c]	2	**12b**	–	70

[a] Determined by ^{1}H NMR and analyzing the coupling constant values (see text). [b] Isolated yield after flash chromatography. [c] Slow inverse addition of sulfone **1** via syringe pump was needed (see text).

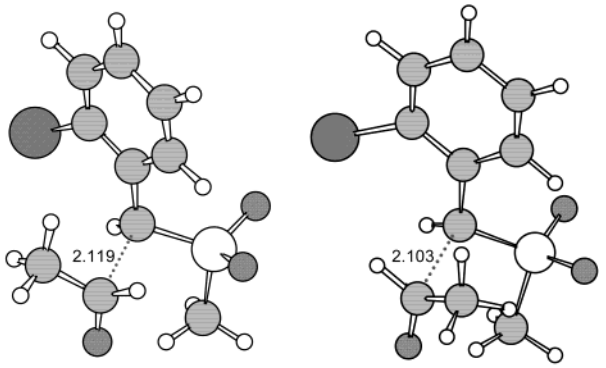
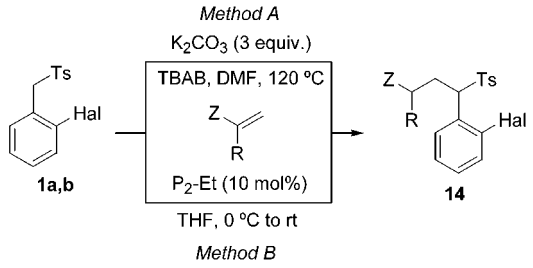


FIGURE 1.

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, an extensive search for transition structures was carried out employing ab initio calculations[33] at the HF/3-21G level of theory, for the reaction in gas phase between acetaldehyde and the α-anion of a simplified brominated methyl sulfone due to computational limitations. Two low-energy transition structures A and B (Figure 1) with minimized electronic interactions could be located driving to *syn* and *anti* stereoisomers, respectively. Other located possible transition structures had higher energies by no less than 7 kcal mol^{-1}.[34,35] The *anti*-forming structure B was favored by 0.9 kcal mol^{-1} compared to structure A, probably as a consequence of a better overlapp of the π-system of the aromatic ring with the molecular orbital based upon the α-carbon, which partially bonds the carbonyl compound. This aromatic ring is almost orthogonal to the new forming bond (84°), whereas a higher deviation exists in structure A (102°) due to the repulsion between the methyl and bromine groups. This deviation would be increased if the reaction is performed with a more sterically hindered aldehyde or if the bromine is substituted by a bulkier iodine atom, therefore favoring the *anti*-driving transition state.

SCHEME 3



When this aldol reaction was performed with paraformaldehyde and sulfone **1a** under the same reaction conditions at 0 °C, an equimolar mixture of vinyl sulfone **12a**, and the Michael addition product **13** as a 5:1 mixture of diastereomers, was obtained. Reactive sulfones **12a** and **12b** were isolated, in 54% and 70%, respectively, by adding sulfone **1a** or **1b** very slowly (2 h via syringe pump) to a suspension of paraformaldehyde (10 equiv) and P_2-Et (1 equiv) at 0 °C (Scheme 2, Table 2, entries 7 and 8).

The α-sulfonyl carbanions, generated from compounds **1** through two different methods, reacted with electrophilic alkenes, giving the corresponding 1,4-addition products **14** (Scheme 3, Table 3). Under phase transfer catalysis (PTC), using potassium carbonate and tetrabutylammonium bromide (TBAB) in DMF at 120 °C (method A), *o*-iodosulfone **1b** afforded better yields of compounds **14** than the corresponding sulfone **1a** (Table 3, entries 1, 2 and 3–9). This reaction could be run under milder conditions employing method B (Table 3, entries 10–18) which needed substoichiometric amounts of P_2-Et (10 mol %) and room temperature to proceed. The yields achieved with this last method were higher than that obtained using method A.

A general study of the reactivity of *o*-halosulfones **1** at the halogen atom was performed. Several attempts to promote the halogen–metal exchange from sulfones **1** with *n*-BuLi or Grignard reagents[6] were unsuccessful. However, cross-coupling reactions catalyzed by palladium(0) complexes could be carried out (Scheme 4, Table 4) using in all cases a catalyst comprised by palladium acetate (5 mol %) and triphenylphosphine (10 mol %). Thus, the Suzuki–Miyaura cross-coupling reaction[36,37] was accomplished with phenylboronic acid and potassium carbonate in DMF at 120 °C for 19 h. Com-

(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. D.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Peterson, G. A. Ayala, Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ciolowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martín, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johson, B.; Chen, W.; Wong, M. W.; Andrés, J. L.; González, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 98, Revision A.9, Gaussian, Inc., Pittsburgh, PA, 1998.

(34) Structures were fully characterized by frequency calculations showing only one negative value corresponding to the motion of the new formed C–C bond. Single point calculations were performed for these two optimized structures at the B3LYP level of theory using the HF/6-31G* basis set: Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(35) The ZPE's were obtained at HF/3-21G and scaled by a factor of 0.94 and distances are expressed in angstroms: Scott, A. P.; Radom, L. *J. Chem. Phys.* **1996**, *100*, 16502–16513.

(36) For recent reviews, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (b) Suzuki, A. In *Metal Catalyzed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH.: Weinheim, 1998; chp. 2, pp 49–97.

TABLE 3. Michael-type Addition of *o*-Halosulfones 1

entry	1	alkene	method[a]	*T* (h)	14	R	Z	yield (%)[b]
1	**1a**	CH_2=$CHCO_2Et$	A	19	**14a**	H	CO_2Et	20
2	**1a**	CH_2=$CHCONH_2$	A	24	**14b**	H	$CONH_2$	50
3	**1b**	CH_2=CHCN	A	24	**14c**	H	CN	84
4	**1b**	CH_2=$CHCONH_2$	A	24	**14d**	H	$CONH_2$	70
5	**1b**	CH_2=C(Me)CN	A	24	**14e**[c]	Me	CN	63
6	**1b**	CH_2=C(Me)$CONH_2$	A	24	**14f**[c]	Me	$CONH_2$	58
7	**1b**	CH_2=C(NHAc)CO_2Me	A	24	**14g**	NHAc	CO_2Me	38
8	**1b**	CH_2=$CHPO_3Et_2$	A	24	**14h**	H	PO_3Et_2	20
9	**1b**	CH_2=CHTs	A	24	**14i**	H	Ts	82
10	**1a**	CH_2=$CHCO_2Et$	B	24	**14a**	H	CO_2Et	55
11	**1a**	CH_2=$CHCONH_2$	B	19	**14b**	H	$CONH_2$	71
12	**1a**	CH_2=C(Me)CN	B	19	**14j**	Me	CN	92
13	**1a**	CH_2=CHTs	B	19	**14k**	H	Ts	90
14	**1b**	CH_2=$CHCO_2Et$	B	12	**14l**	H	CO_2Et	72
15	**1b**	CH_2=$CHCONH_2$	B	12	**14d**	H	$CONH_2$	80
16	**1b**	CH_2=C(Me)CN	B	12	**14e**[c]	Me	CN	70
17	**1b**	CH_2=C(Me)$CONH_2$	B	12	**14f**[c]	Me	$CONH_2$	60
18	**1b**	CH_2=CHTs	B	12	**14i**	H	Ts	90

[a] Method A: K_2CO_3 (3 equiv), DMF, 120 °C, TBAB (2 mol %). Method B: P_2-Et (10 mol %), THF, 0 °C to room temperature. [b] Isolated pure compounds after flash chromatography (silica gel). [c] Obtained as a 1:1 mixture of diastereomers.

SCHEME 4

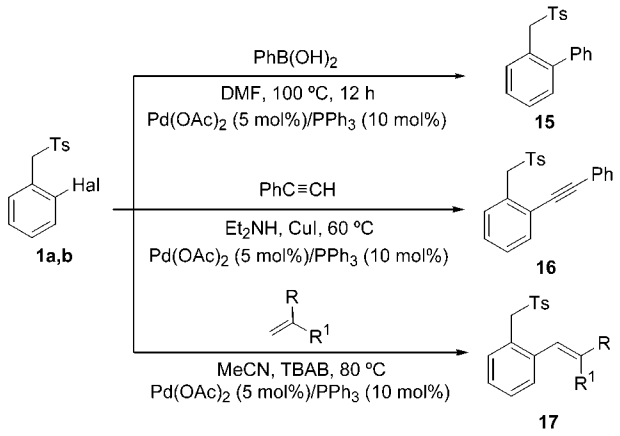
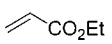
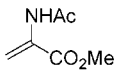


TABLE 4. Heck Reaction of Sulfone 1b with Alkenes

entry	alkene	T (h)	No.	R	R^1	yield (%)[b]
1		17	**17a**[b]	Ph	H	60
2		19	**17b**[b]	CO_2Et	H	80
3		12	**17c**[c]	CO_2Me	NHAc	40
4		19	**17d**	—	—	20

[a] Isolated yield after flash chromatography. [b] Only (*E*)-isomer was detected by ^{1}H NMR. [c] As a 6:1 mixture of (*Z*):(*E*) determined by NOESY experiments.

pound **15** was obtained from **1a** and **1b** in 65 and 73% yield, respectively (Scheme 4). The very known higher reactivity of aryl iodides was once more demonstrated in the Sonogashira cross-coupling reaction.[38] While **1b** afforded product **16** in 45% yield, under refluxing diethylamine and in the presence of substoichiometric amounts of CuI and phenylacetylene, the bromo derivative **1a** was unreactive even when the reaction mixture was heated at 100 °C using pyrrolidine as solvent (Scheme 4). A similar behavior of **1a** was observed in the Heck arylation reaction.[39] Sulfone **1b** generated products **17** after treatment, under Jeffery's PTC conditions,[40] with the corresponding alkene in refluxing acetonitrile. For monosubstituted alkenes, the (*E*)-isomer was exclusively obtained in good yield (Table 4, entries 1 and 2). When the didehydroalanine derivative was used as electrophilic olefin, a 6:1 mixture of (*Z*):(*E*) isomers was generated according to the C−H coupling constants between olefinic proton and carbonylic carbon (5 Hz) in proton-coupled ^{13}C NMR.[41] The low yield achieved with cyclohexenone was caused by the side reactions involving the intermediate palladium(II) enolate.[39]

For the synthesis of *ortho*-substituted cinnamic ester derivatives, a combination of cross-coupling and an α-alkylation−*β*-elimination sequence was performed (Scheme 5). The inverted sequence was discarded because a significant intermolecular Heck reaction onto *o*-halocinnamic ester occurred. Thus, the synthesis of nonsymmetrical dienes **3a** was accomplished in 65% yield by a Heck reaction under Jeffery's PTC conditions, followed by the alkylation−elimination sequence promoted by P_2-Et using *tert*-butyl bromoacetate. Biaryl acrylate **3b** and enyne **3c** were obtained, in 67% and 71% overall yields, employing the Suzuki-Miyaura cross-coupling reaction and the Sonogashira reaction, respectively, followed by alkylation with ethyl bromoacetate (Scheme 5).

(37) In the case of *o*-iodobenzyl chloride Cu-thiophene-2-carboxylate (CuTC)-mediated coupling of boronic acids under nonbasic/room-temperature conditions has been reported as alternative to the traditional Suzuki−Miyaura conditions: Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149−2152.

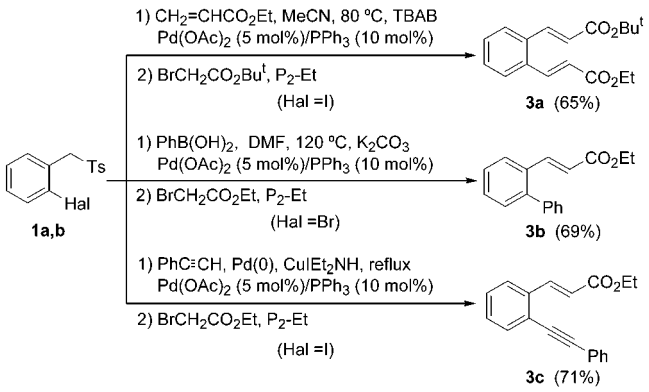
(38) Sonogashira, K. In *Metal Catalyzed Cross Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; chp. 5, pp 203−229.

(39) For a recent review, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

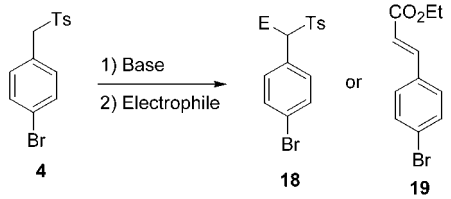
(40) For recent publications regarding the efficiency of tetraalkylammonium salts in Heck reaction, see: (a) Jeffery, T. *Tetrahedron Lett.* **1999**, *40*, 1673−1676. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113−10130, and references therein.

(41) Abellán, T.; Mancheño, B.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 6627−6640, and references therein.

SCHEME 5



SCHEME 6



2. Reactivity of *p*-Bromobenzyl Sulfone 4. *p*-Bromobenzyl sulfone **4** was prepared in 78% yield from the corresponding *p*-bromobenzyl bromide and sodium *p*-toluenesulfinate. Initially, we studied the reactivity of its α-sulfonyl carbanion, generated from inexpensive **4**, according to the results previously described for *o*-halobenzyl sulfones. α-Alkylation reactions were performed by using P_2-Et **8** as base obtaining products **18a**,**b** (Scheme 6, Table 5, entries 1 and 2). As well, a *β*-elimination reaction of *p*-toluenesulfinic acid occurred upon treatment of this anion with ethyl bromoacetate generating exclusively the *E*-isomer **19**[42] in good yield (Scheme 6, Table 5, entry 3). The aldol reaction took place at −78 °C using aliphatic aldehydes with high diastereoselectivity for pivalaldehyde but yield was very low (Table 5, entry 5). By other side, the *anti*:*syn* ratio, achieved in the aldol reaction with butanal, was the opposite to the corresponding ratio isolated for *o*-halobenzyl sulfones (Table 5, entry 4). The role of the halogen atom seems to be crucial according to these results and that obtained for *o*-halobenzyl sulfones **1**. Michael-type addition reactions also worked in the presence of substoichiometric amounts of P_2-Et (10 mol %), affording good yields of compounds **18e** and **18f** (Table 5, entries 6 and 7). Equally, the carboxylation reaction could be exclusively carried out, in 62% yield, employing BuLi in the presence of HMPA, and ethyl chloroformate as electrophile (Table 5, entry 8).

For the preparation of the biaryl sulfone **20**, precursor of 4-biarylacetic acids, the Suzuki−Miyaura cross-coupling reaction was first performed with sulfone **4** by using the oxime carbapalladacycle **21**[8a,43] (0.5 mol %) as catalyst in the presence of potassium carbonate in DMF at 120 °C for 12 h. In a second step, the carboxylation at the α-position with ethyl chloroformate was carried out with *n*-butyllithium as base. The overall yield of the sulfone **20** was 54% (Scheme 7). However, when this first step was performed using $Pd(OAc)_2$ (2.5 mol %) and PPh_3 (5 mol %), the overall yield of product **20** was slightly lower (50%). The reverse sequence was rejected because it gave a lower overall yield (31% from sulfone **4**). This poor yield was caused by a significant decarboxylation[44] of the intermediate α-sulfonylated *p*-bromophenylacetic ester after column chromatography (silica gel or aluminum oxide).

The second functionalization at the benzylic position of compound **20**, directed by the sulfonyl group, could be accomplished by two methods. On the basis of the preceding results, the phosphazene base P_2-Et **8** in THF was employed, giving good yields of the corresponding alkylated sulfones **22** (Method A, Scheme 8, Table 6). The base P_2-Et could be recovered from the reaction mixture after acidic workup and recrystallization as its tetrafluoroborate salt,[24] the same alkylation reaction at the highly acidic α-position, under inexpensive and mild phase-transfer catalysis (PTC) conditions, was assayed. With potassium carbonate as base and TBAB in acetonitrile at room-temperature, products **22** were obtained but in lower yields (Method B, Scheme 8, Table 6).

4-Biarylacetic acids **6** were finally obtained through a two-step process including a desulfonylation reaction followed by the ester hydrolysis. The desulfonylation reaction of products **22** was performed employing magnesium metal in methanol in the presence of substoichiometric amounts of mercury chloride at room temperature.[45] In the case of compound **20** it was necessary to warm the reaction up to 50 °C for completion. During this desulfonylation step, the intermediate (noncharacterized) methyl esters, formed as a consequence of a transesterification reaction, were detected except for the α-crotyl and α-ethyl derivatives. This side reaction was irrelevant because the next step involved the ester hydrolysis using 1 M methanolic potassium hydroxide at room-temperature overnight. 4-Biphenylacetic acid **6a**,[46] xenbucin **6c**,[47] xenyhexenic acid **6d**[19,48] and the ibuprofen mimetic structure **6b**[49] were isolated in 30−50% overall

(42) (a) Pritykin, L. M.; Selyutin, O. B.; Nikolaev, A. L. *Russ. J. Org. Chem.* **1999**, *35*, 1783−1789. (b) Sengupta, S.; Sadhukhan, S. K.; Battacharyya, S. *Tetrahedron* **1997**, *53*, 2213−2218. (c) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449−7452. (d) Li, G.; Wei, H.-X.; Kim, S. H. *Org. Lett.* **2000**, *2*, 2249−2252. (e) Li, G.; Wei, H.-X.; Kim, S. H. *Tetrahedron Lett.* **2000**, *41*, 8699−8703.

(43) Oxime palladacycles are thermally stable complexes not sensitive to air or moisture. They are inexpensive and very efficient catalysts in the C−C bond forming reactions, even working in water using aryl chlorides as starting materials: (a) Alonso, D.; Nájera, C.; Pacheco, M. C. *Org. Lett.* **2000**, *2*, 1823−1826. (b) Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179−181. (c) Reference 8a.

(44) ref 3, Chapter. 3, p 101 and references therein.

(45) For a review about desulfonylation, see: Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658.

(46) This compound is also commercially known as Felbinac, Dolinac, Flexfree, Napageln, Target, or Traxam: (a) *USP Dictionary of USAN and International Drug Names*; The United States Pharmacopeial Convention, Inc.: Rockville, MD, 1997; p 300. (b) Used as indicator in the titration of lithium alkyls: Juaristi, E.; Martínez-Richa, A.; García Rivera, A.; Cruz-Sánchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603−2606.

(47) (a) Reference 47a, p 788. (b) Uhrich, K.; Macedo, B. Patent WO 041753; *Chem. Abstr.* **2001**, *135*, 51045. (c) Del Soldato, P. Patent WO 012584; *Chem. Abstr.* **2001**, *134*, 178396. (d) Giordano, C.; Castaldi, G.; Casagrande, F.; Abis, L. *Tetrahedron Lett.* **1982**, *23*, 1385−1386. (e) Grovenstein, E., Jr; Lu, P.-C. *J. Org. Chem.* **1982**, *47*, 2928−2939.

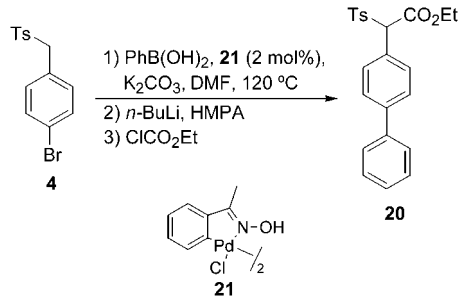
(48) It belongs to the family of diphenesenic acids. It has similar analgesic and antiinflammatory power than ibuprofen: (a) ref 47a, p 789. (b) Cavallini, G.; Massarani, E. US Patent 3043746; *Chem. Abstr.* **1962**, *57*, 9750b. (c) Sestini, G.; Del Vecchio, A. US Patent 4562287; *Chem. Abstr.* **1985**, *102*, 95404. (d) Del Vecchio, A.; Sestini, G. Belg. Patent BE 899,823, 1983; *Chem. Abstr.* **1985**, *102*, 95404.

TABLE 5. Reaction of the α-Sulfonyl Carbanion of Sulfone 4 with Several Electrophiles

entry	base (equiv)	electrophile	*T* (°C)	*t* (h)	product	E	yield (%)[a]
1	P_2-Et (1.2)	MeI	0 to rt	19	**18a**	Me	74
2	P_2-Et (1.2)	EtI	0 to rt	19	**18b**	Et	39
3	P_2-Et (3.0)	$BrCH_2CO_2Et$	0 to rt	19	**19**[b]	–	60
4	P_2-Et (1.2)	PrCHO	−78	0.5	**18c**[c]	PrCH(OH)	54
5	P_2-Et (1.2)	Bu^{t}CHO	−78	0.5	**18d**[d]	Bu^{t}CH(OH)	20
6	P_2-Et (0.1)	CH_2=$CHCO_2Et$	0 to rt	19	**18e**	$CH_2CH_2CO_2Et$	72
7	P_2-Et (0.1)	CH_2=C(Me)CN	0 to rt	19	**18f**	CH_2CH(Me)CN	45
8	BuLi (1.5)[e]	$ClCO_2Et$	−78 to rt	19	**18g**	CO_2Et	62

[a] Isolated yields after purification by flash chromatography (silica gel). [b] *E*-Isomer was exclusively obtained. [c] This compound was isolated as a 1:2.5 *anti*:*syn* mixture of diastereomers. [d] Only the *anti*-isomer was isolated. [e] 1.5 equiv of HMPA were used.

SCHEME 7



SCHEME 8

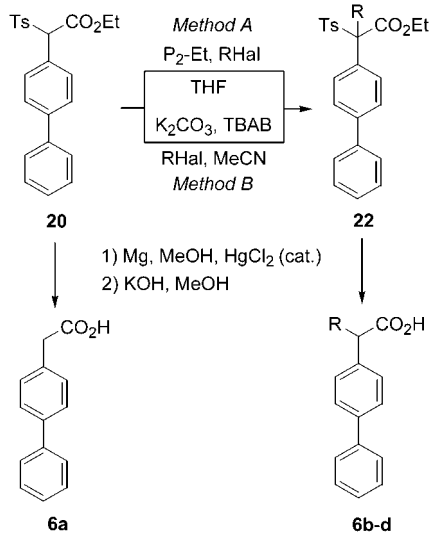


TABLE 6. Alkylation of Compound 20

RHal	method[a]	22	R	yield (%)[b]
MeI	A	**22**[a]	Me	42
MeI	B	**22a**	Me	40
EtI	A	**22b**	Et	70
EtI	B	**22b**	Et	30
(*E*)-CH_3CH=$CHCH_2Br$	A	**22c**	(*E*)-CH_3CH=$CHCH_2$	75
(*E*)-CH_3CH=$CHCH_2Br$	B	**22c**	(*E*)-CH_3CH=$CHCH_2$	40

[a] Method A: P_2-Et (1.1 equiv), RHal (1.1 equiv) in THF at room temperature. Method B: K_2CO_3 (3 equiv), RHal (1.2 equiv), TBAB (5 mol %) in acetonitrile at room temperature. [b] Isolated yields based on sulfone **20** after purification by flash chromatography (silica gel).

yield from the corresponding sulfones **20** and **22** (Scheme 8, Table 7).

In conclusion, we have found that *o*- and *p*-halobenzyl *p*-tolyl sulfones are simple and inexpensive starting materials for the preparation of 1,2- and 1,4-bifunctionalized aromatic systems. They are multifunctional reagents acting as precursors of 1,3- and 1,5-zwitterionic synthons, useful for the synthesis of 2-substituted cinnamic acid derivatives and 4-biarylacetic acids by a two-step sequence of reactions based on a cross-coupling process at the halogen atom and alkylation at the benzylic position.

TABLE 7. Synthesis of 4-Biarylacetic Acids 6

sulfone	product	R	yield (%)[a]
20	**6a**	H	30
22a	**6b**	Me	38
22b	**6c**	Et	50
22c	**6d**	(*E*)-CH_3CH=$CHCH_2$	42

[a] Isolated overall yields based on sulfones **20** or **22** after purification by flash chromatography (silica gel).

Experimental Section

General. Melting points are uncorrected. Only the structurally most important IR peaks are listed. ^1H and ^{13}C NMR spectra were performed using $CDCl_3$ as solvent and TMS as internal standard unless otherwise stated. Low-resolution electron impact (EI) mass spectra were obtained at 70 eV. Microanalyses were performed by the Microanalyses Service of the University of Alicante. Analytical TLC was visualized with UV light at 254 nm. For flash chromatography, silica gel 60 (0.040−0.063 mm) was employed. Anhydrous THF and DMF were purchased, and all the reactions carried out under inert atmosphere (argon) were performed in oven-dried glassware, sealed with a rubber septum.

Alkylation of Sulfone 1a Using *n*-BuLi. Typical Procedure. To a solution of benzyl sulfone **1a** (88 mg, 0.27 mmol) in anhydrous THF (2.5 mL) at −78 °C and under an argon atmosphere was added *n*-butyllithium (1.6 M in hexanes, 200 μL, 0.32 mmol) [for the carboxylation reaction, HMPA (73 μL, 0.41 mmol) and BuLi (1.6M in hexanes, 256 μL, 0.41 mmol) were added]. After the mixture was stirred 10 min at this temperature, the corresponding electrophile (0.32 mmol) was poured into the flask, and the temperature was allowed to rise slowly to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and aqueous phase extracted with ethyl acetate (3 × 5 mL). The combined organic portions were dried ($MgSO_4$) and evaporated, affording crude materials which were purified by flash chromatography, giving products **9** in yields depicted in Table 1.

(49) 2-(1,1′-Biphenyl)propionic acid **6b** has been employed in experiments of structure-based design of COX-2- selectivity into flurbiprofen: (a) Bayly, C. I.; Black, W. C.; Léger, S.; Ouimet, N.; Ouellet, M.; Percival, M. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 307−312. (b) Other applications together with flurbiprofen: Tu, L.; Weng, W.; Xu, H. *Chem. Abstr.* **2001**, *134*, 242773. (c) For the racemic and enantioselective synthesis, see: Hamon, D. P. G.; Massy-Westropp, R. A.; Newton, J. L. *Tetrahedron* **1995**, *51*, 12645−12660.

Alkylation of Sulfone 1a Using NaH. Typical Procedure. To a suspension of sodium hydride (60% dispersion in mineral oil, 6 mg, 0.22 mmol) in anhydrous DMF (2 mL) was added at 0 °C sulfone **1a** (59 mg, 0.18 mmol) in anhydrous DMF (1 mL). After the mixture was stirred at this temperature for 30 min, the electrophile (0.22 mmol) was added and the resulting mixture stirred overnight at room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride (2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic portions were washed with water (4 × 5 mL), dried ($MgSO_4$), and evaporated, affording crude materials which were purified by flash chromatography giving products **9** in yields depicted in Table 1.

Alkylation of Sulfone 1a and 1b Using Phosphazene Base P_2-Et. Typical Procedure. To a cooled solution of the benzyl sulfone **1** (0.26 mmol) in THF (3 mL) was added phosphazene base P_2-Et (105 μL, 0.32 mmol) at 0 °C. After the mixture was stirred for 10 min at the same temperature, the corresponding electrophile (0.32 mmol) was added, and the resulting mixture was stirred at room temperature for times depicted in Table 1. Hydrochloric acid (2 M, 2 mL) was then added, and this phase was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried ($MgSO_4$) and evaporated under vacuum, giving a residue which was purified by flash chromatography to afford pure compounds **9**.

1-(2-Bromophenyl)-1-(*p*-toluenesulfonyl)ethane (9a): colorless oil; R_f 0.58 (AcOEt/*n*-hexane:1/2); IR ν_{max} (neat) 1314, 1285, and 1143 cm^{-1}; ^1H NMR (300 MHz) δ 1.75 (d, J = 7.0 Hz, 3H), 2.45 (s, 3H), 4.97 (q, J = 7.0 Hz, 1H), 7.10−7.27 (m, 3H), 7.32−7.43 (m, 2H), 7.51 (d, J = 8.2 Hz, 2H), and 7.75 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.4, 21.6, 63.3, 126.1, 127.7, 128.8, 129.1, 129.3, 129.9, 130.3, 133.9, 134.6, and 144.6; MS (EI) *m*/*z* 340, 338 (M^+, 2%), 183 (100), 104 (66), 103 (43), and 51 (22); HRMS (EI) calcd for $C_{15}H_{15}BrSO_2$: 337.9902. Found: 337.9976.

Synthesis of Compounds 10a and 10b in the Presence of Phosphazene Base P_2-Et. Typical Procedure. To a solution of *o*-halobenzyl sulfone **1** (0.4 mmol) in THF (4 mL) at 0 °C was added P_2-Et (504 μL, 1.6 mmol), and the resulting mixture was stirred for 10 min. Then, ethyl bromoacetate (53 μL, 0.48 mmol) was added and stirring continued for 24 h at room temperature. Hydrochloric acid (2 M, 2 mL) was added and extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and evaporated under vacuum, giving a residue which was purified by flash chromatography to afford pure compounds **10**.

Ethyl (*E*)-3-(2-bromophenyl)-2-propenoate (10a):[29] colorless oil. R_f 0.75 (AcOEt/*n*-hexane:1/2); IR ν_{max} (neat) 1633, 1713, 1210, and 1144 cm^{-1}; ^1H NMR (300 MHz) δ 1.34 (t, J = 7.3 Hz, 3H), 4.27 (q, J = 7.3 Hz, 2H), 6.39 (d, J = 15.8 Hz, 1H), 7.12−7.32 (m, 3H), and 7.46 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 15.8 Hz, 1H); ^{13}C NMR (75 MHz) δ 30.8, 60.6, 118.9, 124.5, 129.4, 129.5, 132.1, 137.4, 142.3, 143.2, and 166.7; MS (EI) *m*/*z* 256, 254 (M^+, 5%), 215 (65), 213 (71), 199 (30), 185 (64), 183 (62), 175 (48), 171 (43), 169 (37), 155 (37), 147 (75), 139 (94), 118 (78), 91 (100), 89 (74), 77 (45), and 65 (26); HRMS (EI) calcd for $C_{11}H_{11}BrO_2$: 253.9942. Found: 253.9943.

Aldol Reaction of Sulfones 1 Using Phosphazene Base P_2-Et. Typical Procedure. To a solution of sulfone **1** (0.32 mmol) in dry THF (4 mL) at −78 °C and under an argon atmosphere were successively added P_2-Et (129 μL, 0.39 mmol) and the corresponding aldehyde (0.39 mmol). After the mixture was stirred for the times described in Table 2, 2 M hydrochloric acid (2 mL) was added. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic phase was dried ($MgSO_4$) and evaporated under vacuum giving a residue which was purified by flash chromatography to afford pure compounds **11**.

***anti*-1-(2-Bromophenyl)-3,3-dimethyl-1-(*p*-toluenesulfonyl)-2-butanol (11b):** colorless prisms; mp 105−106 °C (AcOEt/*n*-hexane); IR ν_{max} (KBr) 3415, 1318, 1288, and 1134 cm^{-1}; ^1H NMR (300 MHz) δ 0.77 (s, 9H), 2.35 (s, 3H), 4.54 (d, J = 1.8 Hz, 1H), 5.82 (d, J = 1.8 Hz, 1H), 7.12−7.41 (m, 5H), 7.48−7.62 (m, 2H), and 8.20 (dd, J = 7.9 and 1.2 Hz, 1H); ^{13}C NMR (75 MHz) δ 21.6, 26.6, 68.3, 76.1, 125.9, 127.1, 127.6, 128.8, 128.9, 129.2, 130.1, 130.3, 132.8 and 144.9; MS (EI) *m*/*z* 412, 410 (M^+, 5%), 326 (90), 324 (86), 257 (100), 255 (90), 239 (31), 200 (34), 198 (52), 171 (53) 169 (50), 157 (41), 139 (39), 91 (87), and 59 (25). Anal. Calcd for $C_{19}H_{23}BrO_3S$: C, 55.5; H, 5.6; S, 7.8. Found: C, 55.3; H, 5.6; S, 7.5.

Synthesis of Vinyl Sulfones 12. Typical Procedure. A solution of benzylic sulfone **1** (0.34 mmol) in THF (5 mL) was slowly added via syringe pump (over 2 h) onto a solution of THF (10 mL) containing paraformaldehyde (32 mg, 1.02 mmol) and P_2-Et (137 μL, 0.41 mmol). The reaction mixture was stirred at room temperature for 2 h, and 2 M hydrochloric acid (2 mL) was then added. The reaction mixture was extracted with ethyl acetate (3 × 10 mL), and the organic phase was dried ($MgSO_4$) and evaporated under vacuum, giving a residue which was purified by flash chromatography to afford pure compounds **12**.

1-(2-Bromophenyl)-1-(*p*-toluenesulfonyl)ethylene (12a): colorless prisms; mp 142−144 °C (AcOEt/*n*-hexane). IR ν_{max} (KBr) 3101, 1596, 810, 1303, 1149, and 1078 cm^{-1}; ^1H NMR (300 MHz) δ 2.40 (s, 3H), 5.94 (s, 1H), 6.82 (s, 1H), 7.19−7.32 (m, 4H), and 7.42−7.52 (m, 4H); ^{13}C NMR (75 MHz) δ 21.6, 69.9, 124.4, 126.8, 127.8, 128.9, 129.5, 130.2, 130.6, 132.1, 132.9, 135.1, 144.7, and 148.9; MS (EI) *m*/*z* 338, 336 (M^+, <1%), 201 (100), 200 (21), 199 (89), 171 (38), 169 (30), 158 (29), 157 (84), 139 (70), 120 (88), and 119 (49). Anal. Calcd for $C_{15}H_{13}BrO_2S$: C, 53.6; H, 3.9; S, 9.5. Found: C, 53.2; H, 4.1; S, 9.8.

Dimer 13 (major diastereomer): colorless oil; R_f 0.56 (AcOEt/*n*-hexane:3/2); IR ν_{max} (neat) 1312 and 1279 cm^{-1}; ^1H NMR (300 MHz) δ 2.46 (s, 6H), 3.18−3.22 (deform. t, 2H), 4.22−4.34 (deform. t, 2H), 6.91−7.08 (m, 3H), 7.12−7.48 (m, 10 H), and 7.51−7.82 (m, 3H); ^{13}C NMR (75 MHz) δ 21.6, 26.9, 69.9, 106.1, 127.7, 129.1, 129.4, 129.6, 130.7, 133.8, 139.5, 140.5, and 145.; MS (ESI) *m*/*z* 756 (M^+, 2%). HRMS (ESI) calcd for $C_{29}H_{26}I_2O_4S_2$: 755.9362. Found: 755.9360.

Michael-Type Addition Reaction of Sulfones 1 onto Electrophilic Alkenes. Method A. A suspension of sulfone **1** (0.21 mmol), potassium carbonate (88 mg, 0.64 mmol), tetra-*n*-butylammonium bromide (9 mg, 0.021 mmol), and the corresponding electrophilic alkene (0.85 mmol) in DMF (4 mL) was stirred at 120 °C for 24 h. Water (5 mL) was added and extracted with ethyl acetate (3 × 5 mL). The organic phase was washed with water (3 × 5 mL), dried ($MgSO_4$), and evaporated under vacuum, affording a residue which was purified by flash chromatography, giving products **14** in yields showed in Table 3. **Method B.** To a solution of sulfone **1** (0.15 mmol) in THF (3 mL) were successively added phosphazene base P_2-Et (5 μL, 0.015 mmol) and the electrophilic alkene (0.18 mmol) at 0 °C. Stirring was continued at room temperature for 19 h. Hydrochloric acid (2 M, 2 mL) was then added, and the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried ($MgSO_4$) and evaporated under vacuum, giving a residue which was purified by flash chromatography to afford pure compounds **14**.

Ethyl 4-(2-bromophenyl)-4-(*p*-toluenesulfonyl)butanoate (14a): sticky oil; R_f 0.65 (AcOEt/*n*-hexane:1/2); IR ν_{max} (neat) 1735, 1435, 1377, 1318, 1288 and 1182 cm^{-1}; ^1H NMR (300 MHz) δ 1.25 (t, J = 8.4 Hz, 3H), 2.17−2.26 (m, 2H), 2.38−2.42 (m with s at 2.39, 4H), 2.72−2.83 (m, 1H), 4.10 (q, J = 8.4 Hz, 2H), 4.97 (dd, J = 11.0 and 3.7 Hz, 1H), 7.13−7.20 (m, 3H), 7.35−7.50 (m, 4H) and 7.68 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.1, 21.6, 24.1, 30.9, 60.6, 67.2, 127.3, 127.9, 128.9, 129.2, 129.8, 130.2, 131.7, 132.9, 134.6, 144.7 and 171.8; MS (EI) *m*/*z* 426, 424 (M^+, 2), 411 (46), 371 (56), 370 (54), 325 (74), 323 (82), 297 (65), 295 (71), 277 (45), 271 (90), 269 (88), 251 (96), 249 (95), 241 (49), 223 (80), 221 (79), 209 (80), 207 (82), 197 (63), 195 (67), 184 (48), 171 (95), 169 (100), 157 (45), 144 (69), 139 (97), 128 (79), 117 (69), 115 (68), 103 (55), 91 (75), 90 (65), 89 (59), 62 (52) and 55 (41); HRMS (EI) calcd for $C_{19}H_{21}BrO_4S$: 424.0344. Found: 424.0339.

Suzuki−Miyaura Cross-Coupling Reaction of *o*-Halobenzyl Sulfones 1. Synthesis of Compound 15. A solution of benzyl sulfone **1** (0.75 mmol), phenylboronic acid (142 mg, 1.13 mmol), potassium carbonate (512 mg, 3.75 mmol), palladium acetate (12 mg, 0.038 mmol), and triphenylphosphine (20 mg, 0.075 mmol) in DMF (15 mL) was stirred at 120 °C for 24 h. Ethyl acetate (50 mL) was added and washed with water (3 × 10 mL), dried ($MgSO_4$), and evaporated under vacuum. The residue was purified by flash chromatography affording pure compound **15** (see text) as colorless prisms; mp: 115−116 °C (AcOEt/*n*-hexane); IR ν_{max} (KBr) 1315, 1290 and 1148 cm^{-1}; ^1H NMR (300 MHz) δ 2.43 (s, 3H), 4.39 (s, 2H), 6.85 (d, J = 7.3 Hz, 2H), 7.15 (d, J = 7.3 Hz, 2H), 7.25−7.31 (m, 7H), 7.36−7.39 (m, 1H) and 7.61−7.64 (m, 1H); ^{13}C NMR (75 MHz) δ 21.6, 58.9, 127.2, 127.6, 127.8, 128.1, 128.2, 128.4, 128.5, 128.6, 129.1, 129.6, 130.3, 131.5, 139.8 and 144.4; MS (EI) *m*/*z* 322 (M^+, 8%), 168 (100), 167 (22), 166 (20), 165 (32), 152 (75), 115 (15) and 91 (22). Anal. Calcd for $C_{20}H_{18}O_2S$: C, 75.0; H, 5.1; S, 10.0. Found: C, 74.8; H, 5.0; S, 9.9.

Sonogashira Cross-Coupling Reaction of Benzyl Sulfone 1b. Synthesis of Compound 16. A suspension of palladium acetate (4.5 mg, 0.015 mmol), triphenylphosphine (7.5 mg, 0.029 mmol), sulfone **1b** (108 mg, 0.29 mmol), copper iodide (6 mg, 0.029 mmol), and phenylacetylene (32 μL, 0.29 mmol) in diethylamine (5 mL) was stirred at 60 °C for 24 h. Solvent was evaporated under vacuum and the residue purified by flash chromatography giving pure compound **16** (see text) as colorless needles; mp 113−114 °C (AcOEt/*n*-hexane). IR ν_{max} (KBr) 1315, 1285, and 1138 cm^{-1}; ^1H NMR (300 MHz) δ 2.31 (s, 3H), 4.66 (s, 2H), 7.07 (d, J = 8.5 Hz, 2H), 7.30−7.52 (m, 1H); ^{13}C NMR (75 MHz) δ 21.5, 60.8, 86.4, 96.5, 122.6, 124.6, 128.1, 128.3, 128.5, 128.7, 129.0, 129.3, 130.1, 131.4, 131.5, 132.1, 135.2, and 144.5; MS (EI) *m*/*z* 346 (M^+, 100%), 265 (17), 193 (23), 192 (37), 189 (22), 166 (23), 163 (20), 152 (31), and 139 (15). Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.3; H, 5.2; S, 9.2. Found: C, 76.4; H, 5.1; S, 9.6.

Heck Reaction of *o*-Iodobenzyl Sulfone 1b. Typical Procedure. A suspension of sulfone **1b** (100 mg, 0.27 mmol), potassium carbonate (75 mg, 0.55 mmol), TBAB (8.5 mg, 0.027 mmol), palladium acetate (4.2 mg, 0.014 mmol), triphenylphosphine (8 mg, 0.027 mmol), and the alkene (0.33 mmol) in acetonitrile (6 mL) was refluxed for 24 h. Solvent was evaporated under vacuum, and water (10 mL) was added. The resulting solution was extracted with ethyl acetate (2 × 20 mL), and the combined organic phase was dried ($MgSO_4$) and evaporated, giving a residue which was purified by flash chromatography to afford pure compounds **17**.

(*E*)-2-Phenyl-1-[2-(*p*-toluenesulfonylmethyl)phenyl]-1-ethene (17a): colorless prisms; mp 139−140 °C (AcOEt/*n*-hexane). IR ν_{max} (KBr) 1320, 1285, and 1139 cm^{-1}; ^1H NMR (300 MHz) δ 2.41 (s, 3H), 4.49 (s, 2H), 6.65, 6.93 (2d, J = 15.9 Hz, 2H), and 7.04−7.61 (m, 13H); ^{13}C NMR (75 MHz) δ 20.9, 62.8, 124.5, 126.1, 126.6, 127.6, 127.9, 128.6, 129.1, 129.4, 129.6, 130.7, 131.7, 132.6, 134.9, 136.8, 138.1 and 144.8; MS (EI) *m*/*z* 348 (M^+, 100%), 217 (46), 194 (40), 193 (29), 192 (24), 191 (22), 190 (23), 189 (69), 179 (24), 178 (31), and 165 (63). Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.8; H, 5.8; S, 9.2. Found: C, 75.5; H, 5.7; S, 9.7.

Synthesis of 1,2-Disubstituted Benzenes 3a−c. The synthesis was accomplished according to the previously described cross-coupling reactions followed by the alkylation−β-elimination step (see above).

Ethyl (*E*)-3-{2-[(*E*)-2-(*tert*-butoxycarbonyl)-1-ethenyl]-phenyl}-2-propenoate (3a): colorless oil; R_f 0.75 (AcOEt/*n*-hexane:1/1); IR ν_{max} (neat) 1712, 1633, 1455, 1311, and 1151 cm^{-1}; ^1H NMR (300 MHz) δ 1.35 (t, J = 6.2 Hz, 3H), 1.60 (s, 9H), 4.32 (q, J = 6.2 Hz, 2H), 6.26, 6.34 (2d, J = 15.9 Hz, 2H), 7.30−7.48 (m, 2H), 7.56−7.68 (m, 2H), 7.95 and 8.04 (2 × d, J = 15.9 Hz, 2H); ^{13}C NMR (75 MHz) δ 14.3, 28.2, 60.6, 80.8, 121.8, 123.7, 127.5, 127.5, 127.6, 129.6, 129.7, 129.9, 140.2, 141.3, 165.7, and 166.4; MS (EI) *m*/*z* 302 (M^+, 5%), 201 (49), 172 (49), 155 (52), 129 (100), 128 (73), 127 (36), 57 (99), and 41 (93); HRMS (EI) calcd for $C_{18}H_{22}O_4$: 302.1518. Found: 302.1508.

Synthesis of *p*-Bromobenzyl Sulfone 4. Typical Procedure. To a solution of commercially available *p*-bromobenzyl bromide (5.25 g, 21 mmol) in methanol (200 mL) was added sodium *p*-toluenesulfinate (16 g, 65 mmol). The suspension was refluxed for 24 h and solvent evaporated under vacuum. Water was added (50 mL) and the aqueous phase extracted with ethyl acetate (3 × 20 mL), affording compound **4** which was recrystallized in AcOEt/*n*-hexane as colorless solids (needles) (5.19 g, 76%). mp 152−153 °C; IR ν_{max} (KBr) 1314, 1282, 1147 cm^{-1}; ^1H NMR (300 MHz) δ 2.43 (s, 3H), 4.23 (s, 2H), 6.97 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H) and 7.52 (d, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz) δ 21.6, 62.2, 123.2, 127.3, 128.6, 129.6, 131.7, 132.5, 134.7, and 145.0; MS (EI) *m*/*z* 326, 324 (M^+, 33%), 172 (87), 170 (100), 169 (25), 166 (23), and 165 (27). Anal. Calcd for $C_{14}H_{13}BrO_2S$: C, 51.9; H, 4.0; S, 9.9. Found: C, 51.3; H, 3.9; S, 10.4.

Alkylation Reaction, Aldol Reaction, Michael Addition Reaction and Carboxylation Reaction of Sulfone 4 Using Phosphazene Base P_2-Et. All these reactions were performed as it was described, respectively, for *o*-halobenzyl sulfones **1** (see above).

1-(4-Bromophenyl)-1-(*p*-toluenesulfonyl)ethane (18a): colorless oil; R_f 0.58 (AcOEt/*n*-hexane:1/2); IR ν_{max} (neat) 1314, 1285, and 1143 cm^{-1} (SO_2); ^1H NMR (300 MHz) δ 1.75 (d, J = 6.8 Hz, 3H), 2.45 (s, 3H), 4.97 (q, J = 6.8 Hz, 1H), 7.10−7.27 (m, 3H), 7.32−7.43 (m, 2H), 7.51 (d, J = 8.2 Hz, 2H), and 7.75 (d, J = 7.3 Hz, 1H); ^{13}C NMR (75 MHz) δ 14.4, 21.6, 63.3, 126.1, 127.7, 128.8, 129.3, 129.9, 130.3, 132.7, 133.9, 134.6, and 144.6; MS (EI) *m*/*z* 340, 338 (M^+, 2%), 185 (97), 183 (100), 104 (66), 103 (43), 77 (42), and 51 (22); HRMS (EI) calcd for $C_{15}H_{15}BrO_2S$: 337.9976. Found: 337.9225.

Ethyl (*E*)-3-(4-bromophenyl)-2-propenoate (19):[42] colorless oil; R_f 0.75 (AcOEt/*n*-hexane:1/2); IR ν_{max} (neat) 1633, 1713, 1210 and 1144 cm^{-1}; ^1H NMR (300 MHz) δ 1.34 (t, J = 7.3 Hz, 3H), 4.27 (q, J = 7.3 Hz, 2H), 6.42 (d, J = 16.5 Hz, 1H), 7.37−7.53 (m, 4H), and 7.62 (d, J = 16.5 Hz, 1H); ^{13}C NMR (75 MHz) δ 30.8, 60.6, 118.9, 124.5, 129.4, 132.1, 133.4, 143.2, and 166.7 (C=O); MS (EI) *m*/*z* 256, 254 (M^+, 5%), 215 (65), 213 (71), 199 (30), 185 (64), 183 (62), 175 (48), 171 (43), 169 (37), 155 (37), 147 (75), 139 (94), 118 (78), 91 (100), 89 (74), 77 (45), and 65 (26); HRMS (EI) calcd for $C_{11}H_{11}BrO_2$: 253.9942. Found: 253.9923.

Synthesis of Compound 20. A solution of benzyl sulfone **4** (244 mg, 0.75 mmol), phenylboronic acid (142 mg, 1.13 mmol), potassium carbonate (512 mg, 3.75 mmol), oxime carbapalladacycle **21** (4×10^{-3} mmol, 2.5 mg) in DMF (15 mL) was stirred at 120 °C for 12 h. Ethyl acetate (50 mL) was added, washed with water (3 × 10 mL), dried ($MgSO_4$), and evaporated under vacuum. The crude residue was immediately dissolved in anhydrous THF (5 mL) and treated with HMPA (1.13 mmol, 210 μL) and BuLi (1.6 M solution in hexanes, 1.13 mmol, 706 μL) at −78 °C. The reaction was stirred at this temperature for 10 min, and ethyl chloroformate (1.13 mmol, 110 μL) was added. The temperature was allowed to rise slowly to room temperature, and stirring was continued overnight. Water (40 mL) and ethyl acetate (50 mL) were added, washed with water (3 × 10 mL), dried ($MgSO_4$), and evaporated under vacuum. The resulting residue was chromatographed (flash silica gel), obtaining **20** (163 mg, 54%) as pale yellow oil; R_f 0.76 (AcOEt/*n*-hexane): IR ν_{max} (neat) 1725, 1250, 1315, 1290, and 1148 cm^{-1}; ^1H NMR (300 MHz) δ 1.25 (t, J = 7.3 Hz, 3H), 2.42 (s, 3H), 4.15 (q, J = 7.3 Hz, 4H), 5.12 (s, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.34−7.44 (m, 5H), and 7.52−7.59 (m, 6H); ^{13}C NMR (75 MHz) δ 13.9, 21.7, 62.5, 75.1, 126.7, 127.1, 128.8, 129.2, 129.5, 130.0, 130.6, 133.5, 133.8, 140.1, 142.4, 145.3, and 165.0; MS (EI) *m*/*z* 394 (M^+, 47%), 241 (60), 240 (45), 211 (41), 168 (32), 167 (86), 165 (79), and 155 (100); HRMS (EI) calcd for. $C_{23}H_{22}O_4S$: 394.1239. Found: 394.1139.

Alkylation Reaction of Compound 20 in the Presence of Phosphazene Base P_2-Et. This procedure is identical to that described for the alkylation of sulfones **1** and **4** (see above).

Ethyl 2-(*p*-toluenesulfonyl)-2-(4-biphenyl)propanoate (22a): colorless oil; R_f 0.30 (AcOEt/*n*-hexane:1/4); IR ν_{max} (neat) 1737, 1463, 1315, 1228, and 1145 cm^{-1}; ^1H NMR (300 MHz) δ 1.33 (t, $J = 7.3$ Hz, 3H), 2.16 (s, 3H), 2.37 (s, 3H), 4.29 (q, $J = 7.3$ Hz, 2H), 7.12 (d, $J = 8.5$ Hz, 2H), and 7.39−7.62 (m, 8H); ^{13}C NMR (75 MHz) δ 13.9, 18.4, 21.6, 62.4, 75.9, 126.7, 127.1, 127.2, 127.8, 128.6, 129.1, 129.5, 131.2, 132.1, 133.2, 141.9, 144.7, and 168.3; MS (EI) *m*/*z* 408 (M^+, <1), 393 (54), 379 (85), 253 (37), 212 (85), 185 (28), 165 (58), 139 (100), and 109 (72); HRMS (EI) calcd for. $C_{24}H_{24}O_4S$: 408.1395. Found: 408.1389.

Synthesis of Biarylacetic Acids 6. Typical Procedure. To a suspension of magnesium powder (20 mg, 0.8 mmol) and mercury(II) chloride (2 mg, 0.014 mmol) in dry methanol (2 mL) at 0 °C and under an argon atmosphere was slowly added the corresponding sulfone **20** or **22** (0.14 mmol) in methanol (0.5 mL). The reaction mixture was stirred at room temperature for 24 h (except for substrate **20**, which required 50 °C for completion). The reaction mixture was filtered through a Celite pad, the solvent evaporated under vacuum, and the residue partitioned in water (5 mL) and ethyl acetate (5 mL). The aqueous phase was extracted with ethyl acetate (2 × 5 mL) and the organic solvent dried ($MgSO_4$) and evaporated under vacuum affording a residue which was dissolved in 0.5 M solution of methanolic KOH (10 mL). After the mixture was stirred at room temperature for 24 h, methanol was evaporated, water was added (5 mL), and ethyl acetate was added (2 × 5 mL). The aqueous phase was acidified, adding 1 M solution of $KHSO_4$ (5 mL), and extracted with ethyl acetate (3 × 2 mL). The organic phase was dried ($MgSO_4$) and evaporated affording pure compounds **6**.

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Supporting Information Available: Physical and spectroscopic data of compounds **1a**,**b**, **3b**,**c**, **9b**−**m**, **10b**, **11a**,**c**−**f**, **12b**, **14b**−**l**, **17b**−**d**, **18b**−**g**, **22b**,**c**, **6a**−**d**, and ^1H NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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