Solid-Phase Synthesis of Biphenyls and Terphenyls by the Traceless Multifunctional Cleavage of Polymer-Bound Arenesulfonates

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Nickel-catalyzed reactions between polymer-bound arenesulfonates and aryl Grignard reagents produce unfunctionalized biphenyls and terphenyls in good yields through reductive cleavage/cross-coupling of the C–S bond. This novel traceless multifunctional cleavage strategy appears to be a powerful tool for the preparation of large oligophenyl libraries, because it allows the introduction of diversity concomitantly with the release of the target compounds.

Introduction

Since Merrifield's pioneering work in solid-phase peptide synthesis in the 1960s,[1] solid-phase organic synthesis (SPOS) has formed the core of parallel synthesis and combinatorial chemistry, two areas that play an important role in the discovery and development of new molecules with predetermined profiles of properties.[2] The final step of SPOS always requires the cleavage of a covalent bond linking the product to the resin, prior to the former's isolation, characterization, and biological evaluation. The utilization of suitable linkers that allow facile attachment, functionalization, and release of the molecules of interest is therefore vital to all SPOS methodologies.[3]

Almost all linkers are currently designed to unmask a polar functionality on release of the substrate from the resin, because linkage to the polymeric support is achieved through the functionality already present in the target molecule. However, this polar functionality eventually limits the structure/activity relationships derived from these compounds, so the development of traceless linker strategies that will enable the release of unfunctionalized hydrocarbons from the polymer support represents an important challenge in SPOS.[4] To this end, the traceless cleavage of C–Si[5] and C–N[6] bonds has been extensively studied, although traceless strategies based on the cleavage of C–S bonds have also been investigated.[7] The carbon–sulfur bonds in polymer-bound thioethers,[8] sulfones,[9] thioesters,[10] sulfonamides,[11] and trialkylsulfonium salts[12] could be cleaved without leaving any functional groups under appropriate conditions. Traceless multifunctional cleavage linker systems, allowing the introduction of certain atoms or molecular fragments at the original linking site during the cleavage step, are of particular interest as they allow for the additional diversification of the library with the release of the target compound.[13]

Biphenyl compounds are popular synthetic targets, since the biphenyl moiety is an important pharmacophore present in many biologically active molecules.[14] The biphenyl unit is also represented in a variety of other valuable compounds including liquid crystals and chiral reagents.[15] Terphenyl derivatives are also known to exhibit interesting optical[16] and electrical[17] properties, and are of particular interest in the area of liquid crystals.[18] Moreover, naturally isolated *p*-terphenyl metabolites are known to possess potent biological activities.[19]

There are numerous methods for the preparation of unsymmetrical biphenyls and terphenyls, many of which have been known for several decades. Among these, the use of the palladium- and nickel-catalyzed coupling reactions[20] of aryl halides and pseudohalides with arylboronic acids,[21] arylstannanes,[22] arylzincs,[23] and arylmagnesium halides[24] to produce unsymmetrical oligophenyls has been extensively studied. Since Pd^0-mediated C–C bond-forming reactions were first explored on solid supports in the early 1990s,[25] the repertoire of these reactions in the area of solid-phase parallel synthesis/combinatorial chemistry has steadily increased.[26] Amongst these solid-phase reactions, the preparation of biphenyl libraries is one of the most favored applications of these catalysts.[27] However, there are

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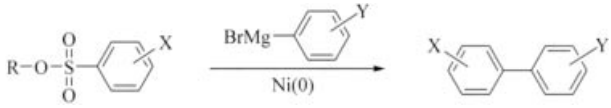
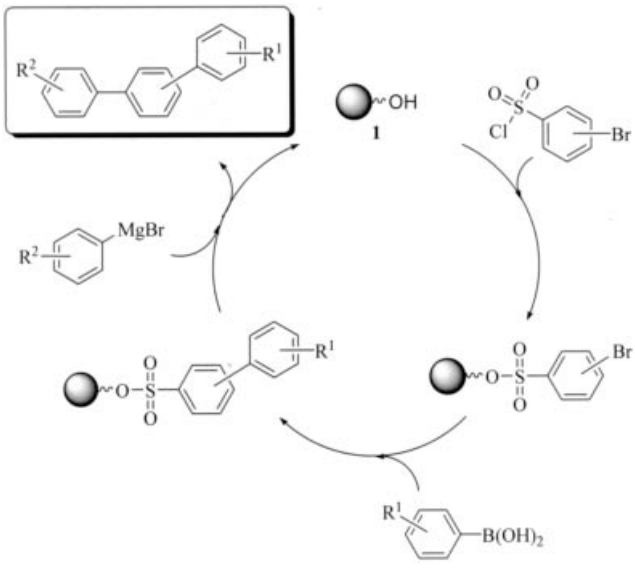
few synthetic strategies for the solid-phase preparation of unfunctionalized biphenyls and terphenyls, due to the absence of efficient traceless linker systems.

Recently, we demonstrated that the nickel-catalyzed cross-coupling reactions of neopentyl arenesulfonates with arylmagnesium bromides, involving the *ipso*-nucleophilic aromatic substitution of alkyloxysulfonyl groups by aryl nucleophiles, efficiently produce unsymmetrical biphenyls and terphenyls (Scheme 1).[28] On the basis of these results, it was anticipated that the aryl moieties of the arenesulfonates attached to the solid support could be liberated without leaving a polar "trace" by use of appropriate nucleophiles.



Scheme 1. Nickel-catalyzed cross-coupling of arenesulfonates with aryl Grignard reagents.

In this paper we report on our attempts to develop a novel sulfonate-based traceless multifunctional linker system through nickel-catalyzed reductive cleavage/cross-coupling of the C–S bond. Under our conditions, reactions between polymer-bound arenesulfonates and aryl Grignard reagents produced unfunctionalized biphenyls and terphenyls in good yields (Scheme 2). While traceless strategies using the famous catalytic cleavage of the C–O bonds of resin-bound arylsulfonates[29] and perfluoroalkylsulfonates[30] have been extensively investigated, the cleavage of the C–S bonds of polymer-bound sulfonates has not, to the best of our knowledge, previously been reported. The results of this study are presented and discussed below.

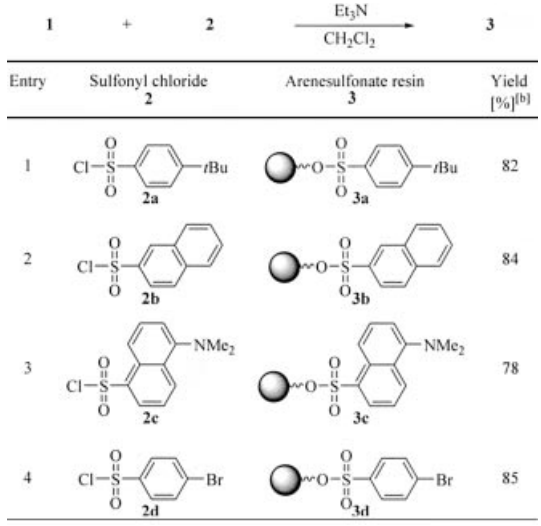


Scheme 2. Preparation of unfunctionalized terphenyls by the traceless multifunctional cleavage strategy.

Results and Discussion

Polymer-bound arenesulfonates **3a**–**d** were prepared by treatment of hydroxyethylmethyl resin **1**[31] with the corresponding arenesulfonyl chlorides **2** in the presence of Et_3N (Table 1). After the reaction had been allowed to proceed for 48 h at room temperature, the resulting arenesulfonate resin **3** was recovered by filtration after standard workup. The isolated yields of **3** were 78–85% based on the loading levels of the resins, which were determined by elemental analysis. The efficient sulfonylation was confirmed by IR analysis, which showed the disappearance of the IR bands at 3583 (sharp) and 3452 cm^{-1} (broad) corresponding to the hydroxy group of **1**, as well as the appearance of new IR bands corresponding to the sulfate group at 1363 and 1177 cm^{-1} (**3a**), 1358 and 1175 cm^{-1} (**3b**), 1358 and 1172 cm^{-1} (**3c**), and 1364 and 1186 cm^{-1} (**3d**) (see the Supporting Information). The remaining hydroxy group of **3** was converted into the methoxy group by treatment with excess CH_3I, before the next step was carried out.

Table 1. Preparation of polymer-bound arenesulfonates **3**.[a]



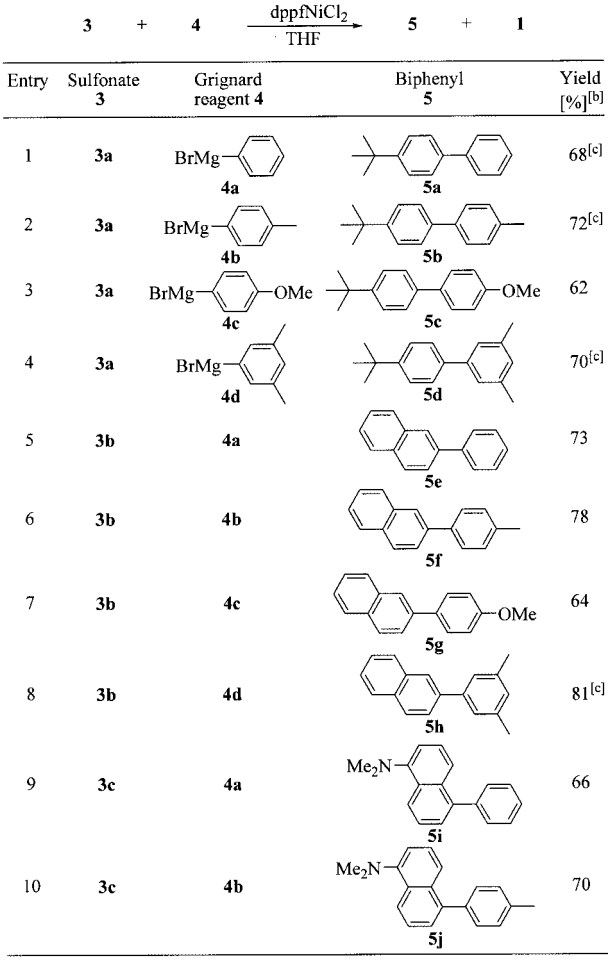
Entry	Sulfonyl chloride 2	Arenesulfonate resin 3	Yield [%][b]
1	2a	3a	82
2	2b	3b	84
3	2c	3c	78
4	2d	3d	85

[a] The reactions between resin **1** (4.6 mmol) and the sulfonyl chlorides (18.2 mmol) were carried out in CH_2Cl_2 (75 mL) in the presence of Et_3N (22.8 mmol). [b] Yields of the isolated products based on the loading level of polymer-bound sulfonate **3** determined by elemental analysis.

The traceless multifunctional cleavage of **3** with aryl Grignard reagents **4** was carried out under the optimized conditions for the corresponding solution-phase reactions.[28b] While organomagnesium reagents have often been used in reactions with polymer-bound aldehydes, ketones, and esters,[32] as well as in the cleavage of products from solid supports,[33] their nickel-catalyzed Kumada coupling reaction with polymer-bound substrates has not been extensively studied.[34] Arenesulfonates **3a**–**c** underwent cleavage/cross-coupling reactions with 15 equivalents of **4** in the presence of [1,1′-bis(diphenylphosphanyl)ferrocene]dichloronickel (dppf$NiCl_2$) to produce the desired unfunctionalized biphenyls **5** in good isolated yields within 48 h (Table 2). The crude products **5** could be purified either by

column chromatography or by preparative HPLC, even though the purification was complicated by the existence of undesired biaryls derived from the homocoupling of **4**. The famous nucleophilic substitution of arenesulfonates by the catalytic cleavage of the C–O bond was not observed by GC or ^{1}H NMR analysis.[35] Additional confirmation of the efficient cleavage of the C–S bond was provided by the IR spectrum of the recovered resin **1**, in which the absorption band corresponding to the hydroxy group was clearly detected.

Table 2. Solid-phase preparation of unfunctionalized biphenyls **5**.[a]

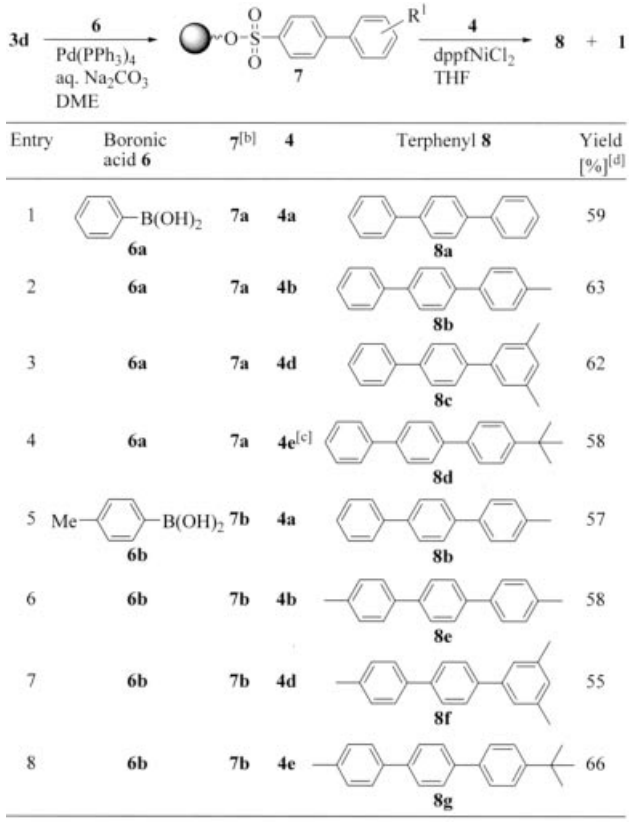


[a] The reactions between resin **3** (0.261 mmol) and **4** (2.61 + 1.31 mmol) were carried out at the reflux temperature of THF (8.0 mL) in the presence of dppfNiCl$_2$ (0.0781 mmol). [b] Yields of isolated products purified by column chromatography on silica gel and based on the loading level of **3**. [c] The yields refer to the isolated products by preparative HPLC and based on the loading level of **3**.

4-Methoxyphenylmagnesium bromide (**4c**) showed slightly diminished efficiency due to the secondary cross-coupling reaction of the initially formed methoxybiphenyls **5c** and **5g** with excess **4c** through the cleavage of the carbon–oxygen bonds (Entries 3 and 7).[36] Naphthalenesulfonate **3b** (Entries 5–8) showed better reactivity than benzenesulfonate **3a** (Entries 1–4), as would be expected given that the faster reaction of the more conjugated arenesulfonates has been consistently observed in corresponding solution-phase reactions.[28] The relatively easier separation of the naphthalene derivatives **5e**–**h** from the biphenyl side product also played an important role in improving their isolated yields, as compared to those of the simple biphenyls **5a**–**d**. Aminonaphthalenesulfonates **3c** also showed competitive reactivity, generating the biaryl compounds **5i** and **5j** in good yields under the standard reaction conditions (Entries 9 and 10).

We further explored the generality of this traceless cleavage/cross-coupling strategy by synthesizing a small library of unfunctionalized terphenyls **8** (Table 3). Thus, resin-bound 4-bromobenzenesulfonate (**3d**) was split into two aliquots, which were separately subjected to the Suzuki coupling reaction with phenylborinic acid (**6a**) and 4-tolylboronic acid (**6b**) in the presence of Pd(PPh$_3$)$_4$ and aqueous Na$_2$CO$_3$ in DME. These palladium-catalyzed coupling reactions produced the biphenylsulfonates **7a** and **7b**, respectively. The liberation of arenesulfonate derivatives via the cleavage of the C–O bond by the Pd catalyst was not detected under our standard reaction conditions.

Table 3. Solid-phase preparation of unfunctionalized terphenyls **8**.[a]



[a] The reactions between resin **7** (0.261 mmol) and **4** (2.61 + 1.31 mmol) were carried out at the reflux temperature of THF (8.0 mL) in the presence of dppfNiCl$_2$ (0.0781 mmol). [b] The reactions between resin **3d** (1.60 mmol) and **6** (5.28 mmol) were carried out in DME (38.0 mL) in the presence of Pd(PPh$_3$)$_4$ (0.144 mmol) and aqueous Na$_2$CO$_3$ (3.2 mmol); **7a**: R^1 = H, **7b**: R^1 = 4-Me. [c] **4e** = *p*-*tert*-butylphenylmagnesium bromide. [d] Overall yields of the isolated products based on the loading level of **3d**.

Polymer-bound biphenylsulfonates **7** were allowed to undergo the nickel-catalyzed coupling reaction with **4** to produce unsymmetrical terphenyl derivatives **8**. The more conjugated biphenylsulfonates **7** showed better reactivity towards the nickel catalyst than the benzenesulfonates **3a** and **3b**, as would be expected. Treatment of the polymer-supported biphenylsulfonates **7** with 15 equivalents of **4** in the presence of dppfNiCl$_2$ at reflux in THF for 30 h afforded the desired unfunctionalized terphenyls **8** in good overall yields from **3d**. The terphenyls **8** were easily isolated from the reaction mixtures by recrystallization from methanol to give white solids. The overall isolated yields of **8**, based on the initial loading of the resin **3d**, were calculated to be 55–65%. The availability of a method for convenient isolation of the final target compounds would make this new traceless strategy useful for the parallel synthesis of relatively large unsymmetrical oligophenyls. Further investigation and optimization of this strategy for preparing unsymmetrical π-conjugated compound libraries is currently underway.

Conclusions

In conclusion, we have demonstrated the application of a novel sulfonate linker offering the possibility of highly efficient traceless multifunctional cleavage to generate biphenyl and terphenyl derivatives, leaving no "memory" of resin attachment. This cleavage/cross-coupling strategy appears to be a powerful tool for the preparation of large oligophenyl libraries, because it allows the introduction of diversity concomitantly with the release of the target compounds. Since no additional reactions are necessary for the preparation of the linker unit, and as the regeneration and reuse of the hydroxy resin seems to be plausible, this traceless process has the potential to be employed for the synthesis of numerous libraries.

Experimental Section

Typical Procedure for the Traceless Multifunctional Cleavage: The aryl Grignard reagent **4b** (2.61 mmol) was added at room temperature to the polymer-bound arenesulfonate **3b** (0.400 g, 0.261 mmol) and dppfNiCl$_2$ (53.4 mg, 0.0781 mmol) in THF (8.0 mL). The reaction mixture was heated at reflux for 24 h and then cooled to room temperature, and additional **4b** (1.31 mmol) was added to the solution. The mixture was heated at reflux for 24 h and then cooled to room temperature. The resulting mixture was filtered through a sintered glass filter with Et$_2$O. The organic filtrate was washed successively with 1% aqueous HCl, water, and brine, dried over MgSO$_4$, and concentrated in vacuo. The crude product was purified by column chromatography (Et$_2$O/*n*-hexane 1:10) to give a white solid **5f** (44.4 mg, 78.0%).

Supporting Information (see footnote on the first page of this article)**:** Spectroscopic and analytical data of synthesized compounds and information on procedures.

Acknowledgments

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