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Solid-phase cross-coupling reaction of aryl(fluoro)silanes with 4-iodobenzoic acid

Fadi Homs, Kyoko Nozaki and Tamejiro Hiyama*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

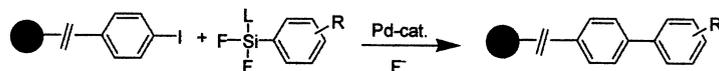
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Abstract

Aryl(alkyl)(difluoro)silanes undergo a facile and efficient palladium-catalyzed cross-coupling reaction with iodobenzoic acid tethered to the Wang resin. Acid cleavage releases unsymmetrical biaryl carboxylic acids with high conversions, purities, and yields. © 2000 Elsevier Science Ltd. All rights reserved.

The recent advances made in high-throughput screening have sparked renewed interest in solid-phase organic synthesis as a powerful tool for combinatorial chemistry. With this renewed interest came new challenges for the organic chemist: developing solid-phase reactions, transferring successful solution-phase reactions to solid phase, and developing new protocols for the characterization of such reactions. In testimony for this very active new research area, publications of many review articles¹ and books² have appeared in the past few years. The biaryl subunit, being an important pharmacophore in a variety of biologically active compounds³ as well as a key mesogenic unit in the liquid crystalline technology, it is no wonder that some of the earliest efforts were aimed at transferring several of the well-known Pd-catalyzed coupling reactions to solid phase.⁴ Since then, several articles have been published.⁵ In addition, a recent comprehensive review on transition metal-catalyzed reactions to solid-phase synthesis has also been published.⁶

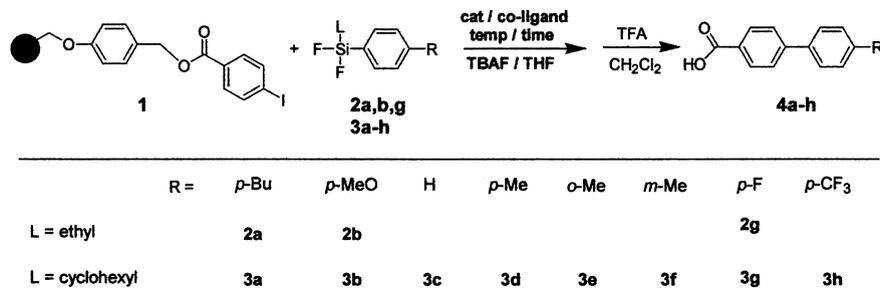
The palladium-catalyzed cross-coupling reaction of aryl(difluoro)silanes with iodoarenes has been shown to give good to high yields of unsymmetrical biaryls.⁷ Our research goal was to transfer this reaction from solution phase to solid phase and identify a general set of conditions that allow complete conversion to products from a wide range of substrates (Scheme 1).



Scheme 1.

* Corresponding author. Tel: 81-75-753-5555; fax: 81-75-753-5555; e-mail: thiyama@npc05.kuic.kyoto-u.ac.jp

Optimization of conditions was carried out based on our model reaction (Scheme 2). Resin **1** was obtained by esterification of the Wang resin⁸ with 4-iodobenzoic acid according to the standard literature procedure.⁹



Scheme 2.

Initially, we synthesized compounds **2a,b,g** as the representative silanes^{7a} and used **2a** for reaction optimization. The intermediate resin, obtained after coupling, was cleaved with TFA in dichloromethane, and the product analyzed by proton NMR.

After considerable experimentation, our results can be conveniently summarized as follows:

- Of the three catalysts tested ($(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$, $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{PPh}_3)_4$), $\text{Pd}(\text{PPh}_3)_4$ gave the highest conversion and purity.
- In the presence of a co-ligand (PPh_3 or $\text{P}(2\text{-Furyl})_3$), cross-coupling of the ethyl dummy ligand was observed.
- Higher conversions and cleaner product were obtained with TBAF than KF.
- Temperature: below 50°C, no conversion observed; 50°C to 70°C, low conversion; 80°C, highest conversion; above 90°C, resin degradation during long reaction time.
- Time: minimum 30 h.
- Thus, 100% conversion was obtained with the following optimized conditions: 5 equiv. of silane, 5 equiv. of TBAF, 5 mol% $\text{Pd}(\text{PPh}_3)_4$, THF, 80°C, 30 h.

When we tested the optimized reaction conditions, with *p*-methoxyphenyl derivative **2b**, we obtained product **4b** with quantitative conversion in 98% yield. With *p*-fluorophenylsilane derivative **2g**, a complex mixture resulted including an ethyl-coupling product as an important byproduct. This competitive reaction of the ethyl group precludes the use of any electron-deficient partner on the silane and, therefore, prompted us to search for an alternative dummy ligand. As a replacement for the ethyl ligand we chose a cyclohexyl group. In addition to commercial availability of (cyclohexyl)trichlorosilane, this dummy ligand has advantages of being more stable and less prone to migration since the cross-coupling step proceeds with an organosilicon reagent as a nucleophile. In addition to the previously prepared derivatives, we have prepared several additional silanes **3a–h** (Scheme 2). Their coupling results are shown in Table 1.

As seen from Table 1, with *p*-butylphenyl derivative **3a**, we obtained **4a** with over 99% conversion in quantitative yield (entry 1). Similar results were obtained for *p*-methoxyphenyl derivative **3b**: over 99% conversion and quantitative yield of **4b** resulted (entry 2). With phenyl-**3c**, *p*-methylphenyl-**3d**, or *o*-methylphenylsilane **3e**, we obtained low conversions under the optimized

Table 1
Cross-coupling of aryl(cyclohexyl)(difluoro)silanes with resin-tethered 4-iodobenzoic acid

entry	silane	R	eq. silane	eq. TBAF	time/h	% conv ^a (%yield of 4) ^b
1	3a	<i>p</i> -Bu	5	5	30	> 99 (quant.)
2	3b	<i>p</i> -MeO	5	5	30	> 99 (quant.)
3	3c	H	10	10	48	> 99 (96)
4	3d	<i>p</i> -Me	10	10	48	> 99 (94)
5	3e	<i>o</i> -Me	10	10	48	> 99 (93)
6	3f	<i>m</i> -Me	10	10	48	> 98 (94)
7	3g	<i>p</i> -F	10	10	48	< 40
8			10	10	72	> 94 (91)

All reactions were run at 80 °C in THF, with 5 mol% Pd(PPh₃)₄. ^aConversion based on ¹H NMR and HPLC. All compounds showed satisfactory analytical data. ^bBased on the incorporation of 4-iodobenzoic acid on the resin.

conditions. However, when the number of equivalents of both the silane and TBAF was increased to 10, and the reaction time to 48 h, over 99% conversions were obtained for all three derivatives, with yields of 96, 94, and 93%, respectively (entries 3–5). With *m*-substituted phenylsilane **3f**, the conversion was only 15% with 5 equiv. of silane. However, with 10 equiv. of **3f** and longer reaction time, we attained 98% conversion and 94% yield of **4f** (entry 6). With *p*-fluorophenylsilane **3g**, under the optimized conditions, low conversion in **4f** was observed. Under the modified conditions (entry 7) the conversion was improved to 40%. When we further increased the reaction time to 72 h (entry 8), the conversion exceeded 94% with 91% yield. Finally, with *p*-(trifluoromethyl)phenylsilane **3h**, 30% conversion at best was obtained even after 48 h or 72 h of a reaction period.

A typical procedure for the cross-coupling is as follows: To 0.1 g of resin **1** (0.88 mmol/g, 0.088 mmol) was added 5 ml of dry THF. After swelling for 30 min, were added in sequential order 5 ml of 5 mol% Pd(PPh₃)₄, 5 equiv. of silane, and 5 equiv. of TBAF. The test tube was then capped, and the reaction mixture was stirred at 80 °C for 30 h. Subsequently, the resin was filtered and washed successively with 3×THF, 3×DMF, briefly with 2×dilute KCN in DMSO,¹⁰ 3×DMF, 3×MeOH, 3×CH₂Cl₂, and finally 2×MeOH. After drying to a constant weight, the resin was cleaved with 4 ml of TFA:CH₂Cl₂ (1:3) for 1 h. After filtering and drying, the crude product was analyzed by ¹H NMR and HPLC. When the conversion and purity were higher than 90%, the final product was purified by column chromatography (eluent: 2-propanol/hexane).

In summary, we have shown that, under the appropriate set of conditions, the palladium-catalyzed cross-coupling reaction of aryl(alkyl)(difluoro)silanes with 4-iodobenzoic acid tethered to the Wang resin proceeds with high efficiency.

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