Communication

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Preparation of Quaternary Centers via Nickel-Catalyzed Suzuki-Miyaura Cross-Coupling of Tertiary Sulfones

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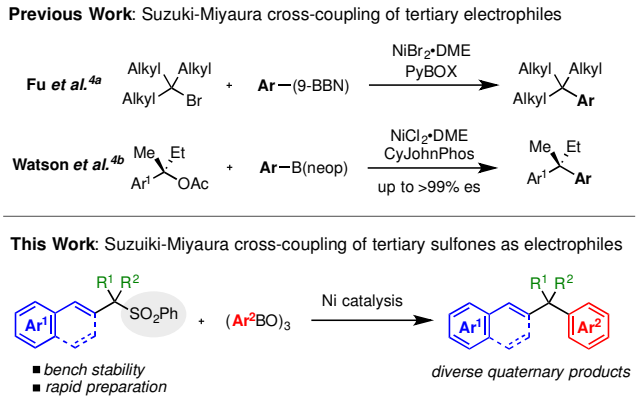
Supporting Information Placeholder

ABSTRACT: We describe the development of a nickel-catalyzed Suzuki-Miyaura cross-coupling of tertiary benzylic and allylic sulfones with arylboroxines. A variety of tertiary sulfones, which can easily be prepared via a deprotonation-alkylation route, were reacted to afford symmetric and unsymmetric quaternary products in good yields. We highlight the use of either BrettPhos or the Doyle's phosphines as effective ligands for these challenging desulfonative reactions. The utility of this methodology was demonstrated in the concise synthesis of a vitamin D receptor modulator analogue.

The Suzuki-Miyaura cross-coupling reaction is a powerful method for the formation of carbon-carbon bonds[1] that has found utility in the synthesis of bioactive compounds, materials, dyes, and natural products.[2] While there are many effective examples of the cross coupling of secondary electrophiles to furnish tertiary products,[3] there are only limited examples of Suzuki-Miyaura cross-couplings of tertiary electrophiles.[4] Since slow oxidative addition and facile β-hydride elimination reactions are difficulties associated with tertiary electrophiles, it is unsurprising that this is a challenging reaction. The quaternary center motif is, however, prevalent in bioactive compounds and natural products[5] and thus other valuable methods have been developed to access this functional group.[5,6,7,8] For allylic substrates, these methods include substitution reactions of secondary allylic electrophiles[9] and Morken's cross-coupling of allylic boronate esters.[10] Suzuki-Miyaura cross-coupling methodologies to prepare quaternary centers employing tertiary electrophiles are limited to only two reports by Fu[4a] and Watson[4b] (Scheme 1).

In order to address the deficiency in cross-coupling approaches to quaternary centers, we employed our recently developed sulfone electrophiles along with typical boron-based coupling partners (Scheme 1).[11] Previously, our group has reported the synthesis of multiply-arylated methanes via α-arylation followed by Suzuki-Miyaura cross-couplings with methyl sulfone derivatives.[11] If these sulfones could be prepared rapidly via deprotonative functionalizations it would be a useful method to access complex molecules in few steps. However, cross-coupling had not been demonstrated on sulfones bearing alkyl groups on the benzylic carbon, and the preparation of quaternary centres was similarly unknown. With benzylic functionalization facilitated due to the inherent acidity of hydrogens α to the sulfonyl group,[12] the challenge entailed the use of these species in cross-coupling chemistry to generate quaternary centres. Herein, we describe cross coupling of tertiary benzylic and allylic sulfones with arylboron compounds catalyzed by Ni

Scheme 1. Preparation of quaternary centres via metal-catalyzed cross-coupling reactions of tertiary electrophiles.



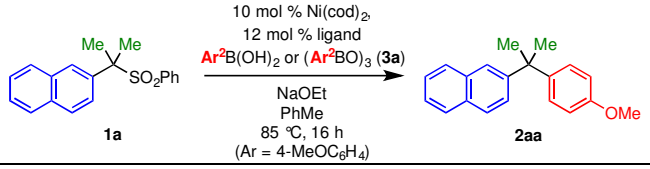
(Scheme 1). A variety of functionalized methane derivatives were easily obtained from readily available building blocks.

We began our investigation into the desulfonative cross-coupling reaction of dimethyl(naphthyl)methyl phenyl sulfone **1a** with 4-methoxyphenylboronic acid. For our first attempts, bis(1,5-cyclooctadiene)nickel ($Ni(cod)_2$) was selected as the catalyst and the electron-rich and bulky Buchwald biaryl phosphine, RuPhos[13] (**L1**), as ligand (Chart 1). Using NaOEt as the base at 85 °C in toluene, we were delighted to obtain the desired quaternary cross-coupled product **2aa** in 40% yield (Table 1, entry 1). A significant improvement was observed when the corresponding boroxine **3a** was used in place of the boronic acid, giving **2aa** in 86% yield (entry 2). Examination of other biaryl(dialkyl)phosphine ligands led us to identify BrettPhos (**L2**) as a superior ligand giving the quaternary product **2aa** in 91% yield (entry 3).

Recently, Doyle reported a novel class of dialkyl aryl phosphine ligands designed for nickel-catalyzed reactions.[14] We were delighted to find that one of these ligands, **L3** (Chart 1) gave the desired product in near quantitative yield (entry 4). Thus either this ligand, or Brettphos were employed for further optimization. Ethereal solvents did not promote the reaction (entry 6) and further studies showed that the arylboroxine loading could be reduced to 0.7 equivalents relative to the sulfone (entries 3, 5-8). Lowering or raising the reaction temperature to 60 °C or 120 °C, respectively, diminished the yield of quaternary product (entries 9

and 10). The use of electron-donating *N*-heterocyclic carbene ligands such as **L4** and **L5** afforded reduced amounts of **2aa** (entries 11 and 12). Finally, control reactions confirmed the requirement of both the nickel catalyst and ligand (entries 13 and 14).

Table 1. Optimization of the Suzuki-Miyaura cross-coupling reaction of **1a** with **3a**.[a]



1a **2aa**

Entry	Arylboron (equiv)	Ligand	NaOEt (equiv)	Yield[b]
1	$ArB(OH)_2$ (2.0)	RuPhos (**L1**)	1.5	40%
2	$(ArBO)_3$ (**3a**) (1.0)	**L1**	2.25	86%
3	**3a** (0.7)	BrettPhos (**L2**)	2.2	91%
4[c]	**3a** (0.7)	Doyle (**L3**)	2.2	98%[d]
5	**3a** (1.0)	**L2**	2.25	88%[d]
6[e]	**3a** (1.0)	**L2**	2.25	32%
7	**3a** (0.3)	**L2**	0.75	55%
8	**3a** (0.3)	**L2**	1.1	71%
9[f]	**3a** (0.7)	**L2**	2.2	80%
10[g]	**3a** (0.7)	**L2**	2.2	80%
11	**3a** (0.7)	SIPr·HCl (**L4**)	4.1	<5%
12	**3a** (0.7)	SICy·HCl (**L5**)	4.1	62%[d]
13[h]	**3a** (0.7)	**L2**	2.2	n.d.
14	**3a** (0.7)	--	2.2	trace

[a] Conditions: **1a** (0.1 mmol), $ArB(OH)_2$ or $(ArBO)_3$ (**3a**) (0.7–2.0 equiv), $Ni(cod)_2$ (10 mol %), ligand (12 mol %), NaOEt (1.1-4.1 equiv), PhMe (0.2 M). [b] Determined by GC-MS integration; dodecane was used as an internal standard. [c] Reaction conducted at 0.05 mmol scale. [d] Isolated yield. [e] THF was used in place of PhMe. [f] Reaction conducted at 60 °C. [g] Reaction conducted at 120 °C. [h] Reaction conducted without $Ni(cod)_2$. n.d. = not detected.

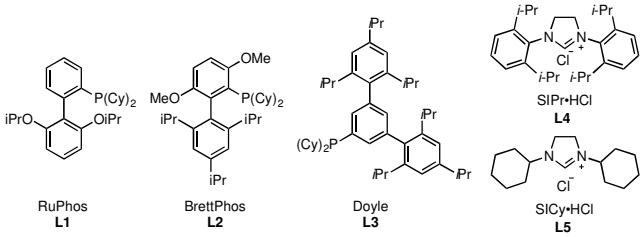
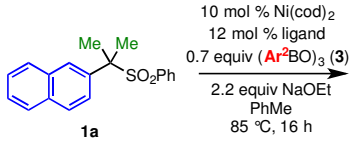


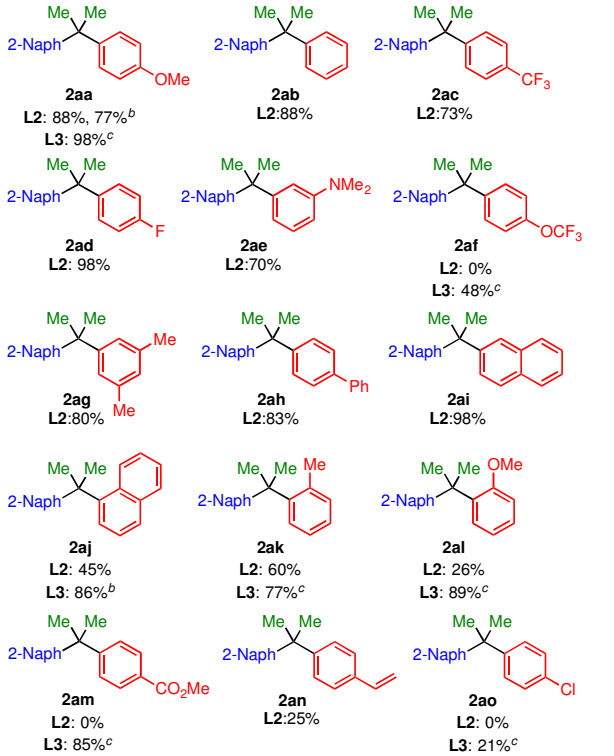
Chart 1. Ligands employed in screening study.

Having identified two ligands, **L2** and **L3,** capable of promoting the desulfonative cross-coupling reaction under the optimized conditions (entries 3 and 4), we then examined the scope of arylboroxines (Table 2). Electron-rich (**3a**, **3e**), neutral (3**b**, **3d**, **3g**), and electron-deficient (**3c**) arylboroxines afforded the corresponding quaternary products in good yields. To demonstrate the effectiveness of the reaction on a larger scale, 1 g of **1a** was cross-coupled to afford **2aa** in 77% yield. For this reaction, the commercially available ligand Brettphos was employed. Conjugated and π-extended aryl boroxines also cross-coupled efficiently (**3h**,**3i**, **3j**). The Doyle ligand **L3** proved advantageous when sterically hindered arylboroxines (**3j**, **3k**, **3l**) were used, providing significantly improved yields. Additionally, BrettPhos **L2** did not promote the cross couplings of 4-trifluoromethoxyphenylboroxine (**3f**), (4-methoxylcarbonyl)phenylboroxine (**3m**), or 4-chlorophenylboroxine (**3o**) and no quaternary products were detected. However, when **L3** was employed as the ligand, the corresponding products were obtained in modest to good yields. 4-Vinylphenylboroxine (**3n**) reacted in low yield likely due to the formation of by-products by reaction at the vinyl moiety.[15] Unfortunately, electron-deficient heteroarylboroxines such as 3-pyridylboroxine (**3p**), 3-thiophenylboroxine (**3q**), and 2-furylboroxine (**3r**) were not effective cross-coupling parnters.[4b,14,16]

Table 2. Scope of Suzuki-Miyaura cross-coupling reaction of **1a** with arylboroxines **3**.[a]



1a **2**

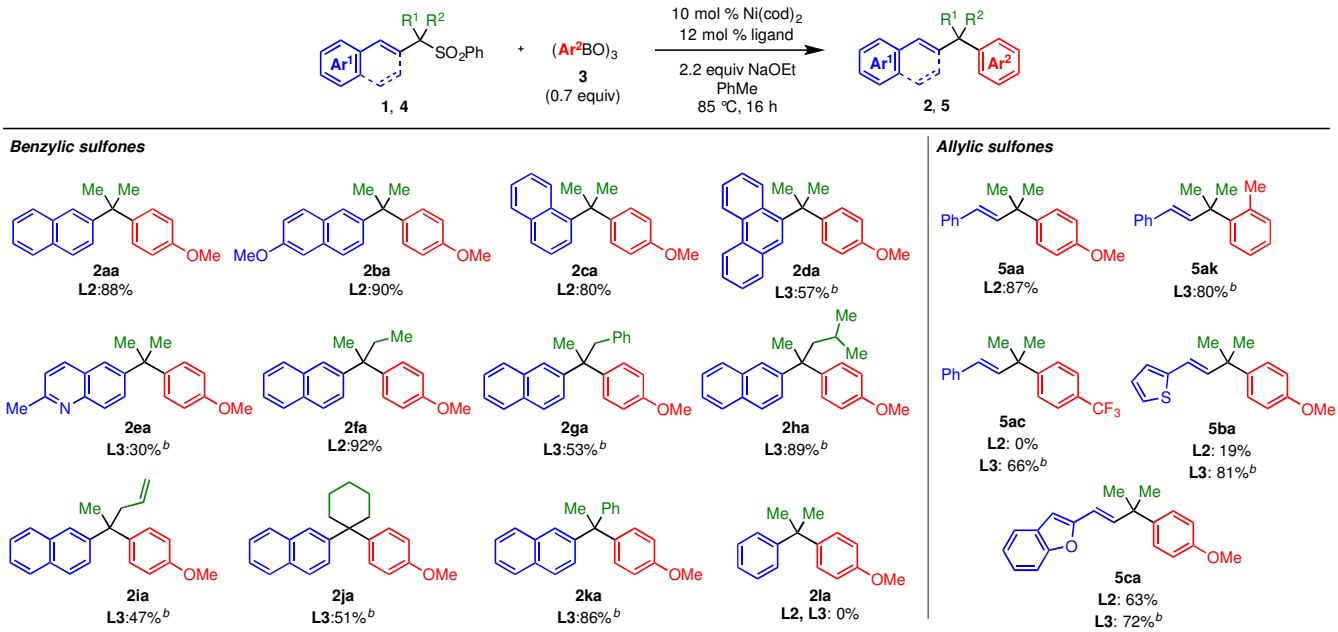


[a] Conditions: **1a** (0.1 mmol), **3** (0.7 equiv), $Ni(cod)_2$ (10 mol %), ligand (12 mol %), NaOEt (2.2 equiv), PhMe (0.2 M). [b] Reaction conducted at 3.22 mmol (1.0 g) scale. [c]Reaction conducted at 0.05 mmol scale.

Next, we sought to examine the scope of the tertiary benzylic sulfone electrophiles (Table 3). These compounds were readily prepared by deprotonative alkylation of benzyl sulfones (details in Supporting Information). With respect to the aryl substituent, electron-rich (**2ba**) and sterically hindered (**2ca**, **2da**) π-extended aromatics were well tolerated. 6-Quinolinyl sulfone **1e** also underwent cross-coupling albeit in modest yield (**2ea**). Unfortunately, when the naphthyl group was substituted with a phenyl group, no cross- coupled product (**2la**) was detected using either **L2** or **L3**, consistent with a likely requirement for a π-benzyl nickel intermediate.[4b,17] In terms of the alkyl substituents, primary alkyl

chains of increasing steric hindrance (**2fa**, **2ga**, **2ha**) were well tolerated to afford interesting unsymmteric methane derivatives. And a synthetically useful allyl group could be introduced into product (**2ja**) in moderate yield.

Table 3. Scope of tertiary benzylic (**1**) and allylic sulfones **3**.[a]



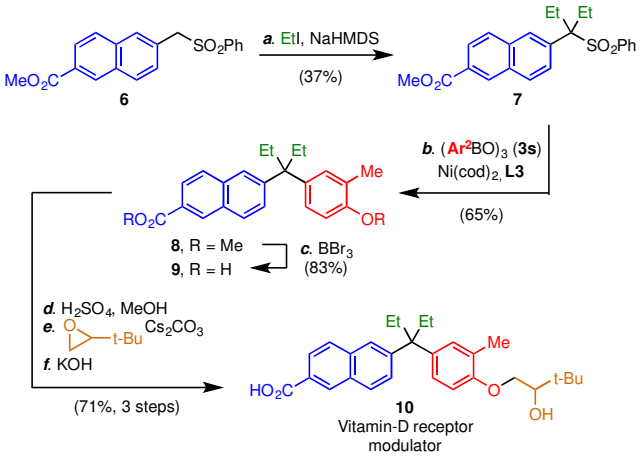
[a] Conditions: sulfone **1** or **4** (0.1 mmol), **3** (0.7 equiv), $Ni(cod)_2$ (10 mol %), ligand (12 mol %), NaOEt (2.2 equiv), PhMe (0.2 M). [b] Reaction conducted at 0.05 mmol scale

A sulfone bearing a cyclic alkyl group (**1j**) was also cross-coupled in good yield. As well, a diarylalkylmethyl sulfone **1k** was cross-coupled to afford the corresponding triarylalkyl methane **4ka** in good yield. Analogously to the cross-coupling of arylboroxines, the cross-coupling of sterically hindered sulfones was most effective with **L3**.

In addition to these results employing π-extended tertiary sulfones, we were intrigued to find that tertiary allylic sulfones could also be cross-coupled to afford the corresponding quaternary allylic products. With respect to the arylboroxine, electron rich (**3a**), electron-poor (**3c**), and bulky (**3k**) substrates underwent cross-coupling in good yields. With the use of the ligand **L3**, we were excited to find that heteroaromatic moieties were well tolerated, giving quaternary products **5ba** and **5ca**. For these substrates, interestingly, no isomerization of the alkene was observed and the linear cross-coupled product was exclusively obtained. We assume that by coupling at the linear position, conjugation with the aromatic system is maintained. Indeed, when the cross coupling reaction of allyl phenyl sulfone was conducted under the standard reaction conditions, the linear and branched products were obtained in nearly 1:1 ratios (see Supporting Information).

To demonstrate the utility of present cross-coupling reaction, we selected the vitamin D receptor modulator **10** as a synthetic target (Scheme 2).[18] Tertiary benzylic sulfone **7** was prepared via the double-alkylation of benzyl sulfone **6** using NaHMDS and iodoethane. Subjecting the tertiary benzylic sulfone to our optimized cross-coupling conditions gave the quaternary product **8** in good yield. Subsequent deprotection was promoted by BBr_3. Since treating compound **9** with 2-*tert*-butyl oxirane directly afforded two products resulting from alkylation at the carboxylate and phenolate, **9** was protected as the methyl ester prior to alkylation. Subsequent deprotection afforded the desired product **10** in good yield in 6 total steps from the primary benzylic sulfone indicating that our method can be used to prepare such biologically-active molecules having quaternary centres in a modular manner.

Scheme 2. Synthesis of vitamin-D receptor modulator.[a]



[a] Reaction conditions: (a) EtI, NaHMDS, THF, 0 °C; (b) 4-Methoxy-3-methylphenyl-boroxine (**3s**), $Ni(cod)_2$, **L3**, NaOEt, PhMe, 85 °C; (c) BBr_3, CH_2Cl_2, -78 °C; (d) H_2SO_4, MeOH; (e) 2-*tert*-butyl oxirane, Cs_2CO_3; (f) KOH, THF.

In conclusion, we have developed a Suzuki-Miyaura cross-coupling of tertiary benzylic and allylic sulfones as new electrophiles to yield structurally diverse quaternary products. Tertiary sulfones can be prepared by a simple alkylation procedure rendering the modular synthesis of diaryl-dialkyl methane products in short steps. With the prevalence of the quaternary benzylic centre motif in bioactive molecules and natural products, we demonstrated the utility of the cross-coupling methodology in the synthesis of a bioactive molecule. Importantly, our strategy for the present sequential functionalization of sulfones can provide a new syn-

thetic route for complex molecules. Investigations to elucidate the mechanism, asymmetric transformations, and other desulfonative cross-couplings are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Synthetic and spectral data

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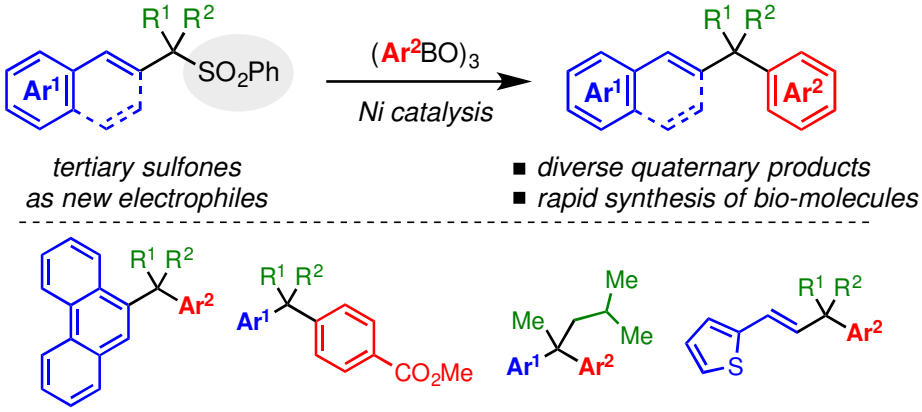
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Ar2
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as new electrophiles
diverse quaternary products
rapid synthesis of bio-molecules
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Ar2
R1 R2
Ar1
CO2Me
Me
Me
Me
Ar1
Ar2
R1 R2
Ar2
S