



Accepted Article

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To be cited as: Adv. Synth. Catal. 10.1002/adsc.201801733

Link to VoR: http://dx.doi.org/10.1002/adsc.201801733

Nickel-Catalyzed Intramolecular Coupling of Sulfones via the Extrusion of Sulfur Dioxide

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201#######.

Abstract. We describe a method for intramolecular desulfonylative coupling using bis(cyclooctadiene)nickel as a catalyst. A broad range of aromatic, heteroaromatic and aliphatic sulfones can be utilized as substrates in this process. This method provides an atom-economical route to the synthesis of various biaryls and an efficient tool for the catalytic conversion of sulfonyl groups, representing a significant advancement in organic synthesis

Keywords: Desulfonylative coupling; Nickel-catalysis; Biaryl; Sulfone; C–S activation

The development of new methods for carbon-carbon (C–C) bond formation is currently an important goal in organic chemistry. Transition metal-catalyzed C–C bond-forming reactions have emerged as a powerful synthetic tool in this regard.^[1] Among these new methods, the extrusion of CO from ketones has attracted much attention in recent decades, and has been investigated in pioneering works by Murai,^[2] Chatani,^[3] Shi,^[4] Dong,^[5] and own our group.^[6] The extension of this strategy to other functional groups is highly desirable,^[7] because this would represent a new aproach to the formation of C–C bonds.

Sulfonyl compounds are a versatile class of organic compounds^[8] and the sulfonyl moiety can be employed as a directing group to allow the functionalization of adjacent positions on an aromatic ring structure.^[9] Therefore, the development of new methods for the conversion of sulfonyl groups would provide significant opportunities for the facile construction of complex molecules. To date, various intermolecular cross-coupling reactions involving sulfone moieties have been reported.^[10] However, in these cases, only one part of the sulfonyl molecule is involved, which is undesirable with regard to atom economy (Scheme 1).

a. Intermolecular cross-coupling reactions involving sulfone



b. Application of extrusion strategy to sulfone



c. This work:



Scheme 1. Two types of desulfonylative coupling and this work

Based on our previous work,^[6] it is apparent that the application of the extrusion strategy to sulfones could be highly useful. Employing this strategy allows both parts of the sulfone to be fully used in one transformation, such that a single, common sulfonyl group becomes the site for C-C bond formation. However, compared with intermolecular desulfonylative couplings, intramolecular reactions face additional challenges. These difficulties are associated with the activation of both C-S bonds, which may be at different positions, under the same conditions. To date, only few methods have been reported for this type of reaction,^[11] and so the intramolecular desulfonylative coupling of sulfones is still a relatively unexplored research area. The present research demonstrates a nickel-catalyzed intramolecular desulfonylative coupling with a broad substrate scope and satisfactory yields, based on the

use of a directing group (Scheme 1). This reaction offers an efficient catalytic system for desulfonylative coupling and is expected to significantly mitigate the limitations currently associated with this field.

Table 1. Optimization of the reaction conditions.^[a]



Entry	Ligand	Solvent	T (°C)	Yield (%) ^[b]
1	PCy ₃	1,4-dioxane	150	56
2	PMe ₃	1,4-dioxane	150	43
3	$P(i-Pr)_3$	1,4-dioxane	150	12
4	$P(n-Bu)_3$	1,4-dioxane	150	72
5	$P(n-Bu)_3$	toluene	150	63
6	$P(n-Bu)_3$	THF	150	11
7	$P(n-Bu)_3$	CH ₃ CN	150	trace
8	$P(n-Bu)_3$	1,4-dioxane	130	34
9 ^[c]	$P(n-Bu)_3$	1,4-dioxane	150	n.d.
10		1,4-dioxane	150	19
$11^{[d]}$	$P(n-Bu)_3$	1,4-dioxane	150	68
12 ^[e]	$P(n-Bu)_3$	1,4-dioxane	150	n.r.
13 ^[f]	$P(n-Bu)_3$	1,4-dioxane	150	n.r.
14 ^[g]	$P(n-Bu)_3$	1,4-dioxane	150	trace

^[a] Unless otherwise noted, the reactions were carried out with 1a (0.1 mmol), Ni(cod)₂ (0.01 mmol) and ligand (0.02 mmol) in the indicated solvent (0.5 mL) for 36 h.
^[b] Isolated yield after flash chromatography.

^[c] Without Ni(cod)₂.

^[d] Using **1i** as starting material.

^[e] Using **3a** as starting material.

^[f] Using **3b** as starting material.

^[g] Using DABCO as additive.

 $Ni(cod)_2 = bis(cyclooctadiene)nickel, n. r. = no reaction.$

initial In 2 - (2 trials. (phenylsulfonyl)phenyl)pyridine (1a) was used as a model substrate to optimize the reaction conditions. The reaction proceeded smoothly to provide the desired product 2a in the presence of catalytic amounts of Ni $(cod)_2$ and PCy₃ (Table 1, entry 1). This result encouraged us to pursue further optimization and a variety of phosphine ligands were assessed (Table 1, entries 1-4), showing that P(n-4) Bu_{3} was more efficient than other ligands (Table 1, entry 4). Several solvents were subsequently screened and 1,4-dioxane was found to be optimal (Table 1, entries 5–7). Attempts to lower the temperature (to 130 °C) led to a lower yield (Table 1, entry 8), while control experiments showed that both Ni $(cod)_2$ and PCy₃ were necessary for an efficient catalytic system (Table 1, entries 9–10). Finally, the efficiencies of various directing groups were investigated, and substrate **1a** with pyridine as the directing group gave the best result (Table 1, entries 11–13). We also attempted to capture SO₂ released from the reaction using DABCO,^[12] but the results were not satisfactory (Table 1, entry 14).

Table 2. Scope of intramolecular desulfonylative coupling.^[a,b]



^[a] Unless otherwise noted, the reactions were carried out with 1 (0.1 mmol), Ni(cod)₂ (0.01 mmol) and P(*n*-Bu)₃ (0.02 mmol) in 1,4-dioxane (0.5 mL) at 150 °C for 36 h.
^[b] Isolated yields.

^[c] 1.0 mmol scale.

Having determined the optimized reaction conditions, variations of the substituted phenyl sulfone 1 were investigated to assess the versatility of this catalytic system. Substrates having different substituents at the para-position of the benzene ring were initially examined. As shown in Table 2, regardless of the electronic properties of the substituents, moderate to good yields were obtained with this desulfonylative reaction, although, the yields of some substrates (2b, 2c, 2g) were relatively low, due to lower degrees of conversions. The reaction also exhibited excellent compatibility with a variety of functional groups, including trifluoromethyl (2e), nitrile (2d) and fluoride (2f). A substrate with a substituent at the meta-position also

worked to give the product (2g). Notably, a heteroaromatic sulfone (2h) also showed satisfactory reactivity and gave the desired product in good yield.

Table 3. Scope of intramolecular desulfonylative coupling with indolyl sulfones. ^[a,b]



^[a] Unless otherwise noted, the reactions were carried out with 4 (0.1 mmol), Ni(cod)₂ (0.01 mmol) and P(*n*-Bu)₃ (0.02 mmol) in 1,4-dioxane (0.5 mL) at 150 °C for 40 h.
^[b] Isolated yields.

To further explore the generality of this novel method, we applied this technique to various substituted indolyl sulfones. As shown in Table 3, substrates with either electron withdrawing or donating substituents all worked well to afford the desired products in moderate to good yields, and a variety of functional groups were also well tolerated. Notably, fluoride and chloride substituents provided good results (5e, 5j and 5k), demonstrating the possibility of a wide range of functionalization. In addition, ether (5d, 5n) and ester groups (5l) were also compatible under these conditions. The data show that the position of the substituent had little effect on the yield (5f-5i). Finally, sulfone substrates with other directing groups also worked well (5m, 5n). A crossover experiment was also conducted and no intermolecular disulfenylation was observed, please see supporting information for details.

To the best of our knowledge, the direct construction of $C(sp^3)-C(sp^2)$ bonds via metalcatalyzed intramolecular desulfonylative coupling has not yet been reported. Thus, we attempted to apply this method to alkyl sulfones (**1j** and **1k**). The reaction of alkyl sulfone **1j** proceeded smoothly to give the desired product in 74% yield using this catalytic system. Unfortunately, alkyl sulfone **1k** did not work well, presumably due to steric hindrance (Scheme 2).



Scheme 2. Intramolecular desulfonylative coupling of 1j and 1k.

This new method was also applied to substrates with no directing groups. Under standard conditions, the reaction did not work well, and only a trace amount of product was observed (**6a**), although the yield was improved to 80% when a stoichiometric amount of Ni(cod)₂ was employed. We also assessed the performance of a benzothiophene sulfone (**6b**) and the desired product was obtained in 53% yield (Scheme 3).



Scheme 3. Application to substrates with no directing group.

Based on these data and previous publications,^[6,11b] a possible mechanism is proposed. As shown in Scheme 4, initially, with the assistance of the directing group, the Ni(0) complex coordinates with substrate **1a** to form intermediate **M1**. Intermediate **M2** is then formed via the oxidative cleavage of one C–S bond by the complex. Subsequently, a desulfonylative reaction produces the corresponding

nickel complex M3. Finally, M3 undergoes reductive elimination to afford product 2a, along with the regeneration of the Ni(0) catalyst.



Scheme 4. Proposed mechanism.

In summary, we have demonstrated the efficient, high atom-economy, nickel-catalyzed intramolecular desulfonylative coupling of sulfonyl compounds. This approach can also employ a broad range of substrates. This methodology not only provides a novel pathway for the catalytic conversion of sulfonyl groups, but is also expected to facilitate the discovery of important trends in nickel-catalyzed C–S bond activation.

Experimental Section

In a glovebox, $P(n-Bu)_3$ (0.02 mmol) was added to a solution of Ni(cod)₂ (0.01 mmol) and sulfone (0.1 mmol) in 1,4-dioxane (0.5 mL). Then the vessel was sealed and removed from glovebox. The mixture was stirred at 150 °C for 36 or 40 h. After completion of reaction, the solvent was removed and the residue was purified by flash column chromatography to afford desired product.

Acknowledgements

We are grateful to the financial support from the National Natural Science Foundation of China (NSFC 21502149 and 21632003) and the Key Science and Technology Innovation Team of Shaanxi Province (2017KCT-37).

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