

Nickel(II)-Catalyzed Addition of Aryl and Heteroaryl Boroxines to the Sulfinylamine Reagent TrNSO: The Catalytic Synthesis of Sulfinamides, Sulfonylamides and Primary Sulfonamides

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ABSTRACT: We report a redox-neutral Ni(II)-catalyzed addition of (hetero)aryl boroxines to *N*-sulfinyltritylamine (TrNSO). The reactions use a catalyst generated from the combination of commercial, air-stable NiCl₂·(glyme), and a commercially available bipyridine ligand, and deliver sulfinamide products. The scope of the reaction is established using a sulfonylamide synthesis, in which the initially formed sulfinamides undergo oxidative chlorination with the inexpensive and safe chlorinating agent, trichloroisocyanuric acid (TCCA), to produce sulfonyl chlorides as key intermediates. These are combined, in situ, with a range of amines to deliver sulfonylamides. The sulfonyl chlorides can also be elaborated into primary sulfonamides *via* hydrolysis, and sulfonyl fluorides *via* treatment with fluoride. These transformations are all achieved using one-pot procedures. Unprotected, primary sulfinamides are also available. For larger-scale reactions the catalyst loading can be reduced to 1 mol%.

Sulfinamides have found widespread applications in organic synthesis. For example, chiral sulfinamides are employed as chiral auxiliaries,¹ as ligands in transition-metal catalysis,² and as organocatalysts.³ Sulfinamides are also versatile synthetic intermediates and are commonly used to prepare a range of other sulfur functional groups, including sulfonamides,⁴ sulfonylamides⁴⁻⁵ and sulfonyl fluorides.^{4, 6} Of these, sulfonamides are the most well established as medicinal agents,⁷ and feature in 25% of sulfur-containing FDA-approved drugs.⁷ Sulfonylamides, the mono aza-analog of sulfonamides, have shown potential in medicinal and agrochemical applications recently.^{5, 8} Sulfonyl fluorides are chiral isosteres of sulfonyl chlorides, and have attracted significant interest as tools in chemical biology.^{6b, 9}

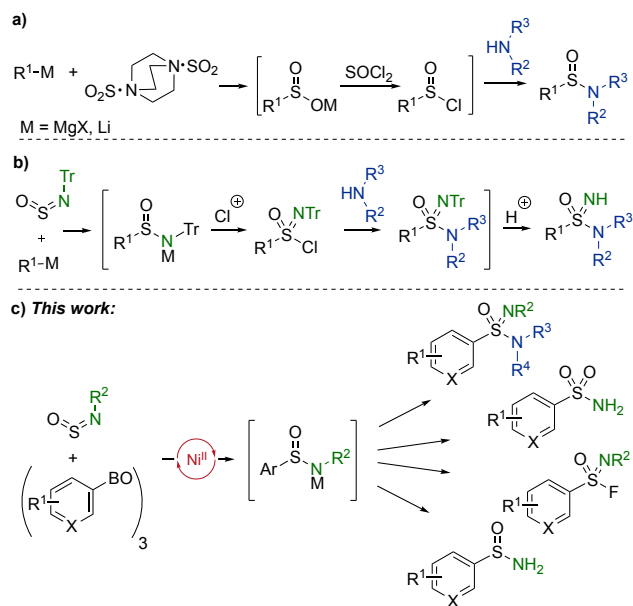
The synthesis of sulfonylamides, sulfonamides and sulfonyl fluorides from sulfinamides can be divided into two strategies. In one approach, sulfinamides undergo direct oxidative transformation to produce these compounds. For example, sulfinamides can react with PhI(OAc)₂ and NH₂CO₂NH₄ to afford sulfonylamides,¹⁰ with *meta*-chloroperoxybenzoic acid (*m*-CPBA) to form sulfonamides,¹¹ and with Selectfluor to generate sulfonyl fluorides.^{6b} Alternatively, sulfinamides can be converted into sulfonyl chlorides, using chlorine,¹² *N*-chlorobenzotriazole,¹² *tert*-butyl hypochlorite (*t*-BuOCl)¹³ or *N*-chlorosuccinimide (NCS)¹⁴ as an oxidative chlorinating reagent.⁴⁻⁵ These sulfonyl chlorides then further react with amines to produce sulfonylamides,⁴⁻⁵ with H₂O to form sulfonamides,⁴ or with fluoride to generate sulfonyl fluorides.^{4, 6} The synthesis of

sulfonylamides *via* the amination of sulfonyl chlorides (or fluorides) remains the most commonly used approach to these molecules.⁵

Previous methods to access sulfonamides are generally limited to substrates with pre-installed sulfur functional groups, such as sulfinate salts (or their acids),¹⁵ thiols,¹⁶ and disulfides,^{16a} which, in general, have limited availability from commercial vendors.¹⁷ Our laboratory has explored approaches to sulfonamides that do not rely on substrates with a pre-installed C-S bond, and which are based on the introduction of high oxidation state sulfur functional groups to a nucleophilic carbon-fragment. For example, the combination of pre-formed organometallic reagents, DABSO, as a sulfur dioxide surrogate, and nitrogen nucleophiles, by way of reactive sulfinyl chloride intermediates (Scheme 1a).¹⁷ A more direct approach replaces sulfur dioxide with an isoelectronic sulfinylamine reagent.^{18,19} We exploited this in a sulfonylamide synthesis, in which the sulfinylamine reagent TrNSO was combined with organometallic reagents in the first step, to form sulfonamide intermediates (Scheme 1b).²⁰ We have recently shown that a sulfinylamine reagent can also be used as the key component in a synthesis of sulfonamides,²¹ and that related hydroxylamine-derived reagents can be used to access sulfonylamides,²² sulfoximines,²² and primary sulfonamides.²³ In all of these examples the carbon fragment is introduced as a preformed organometallic, such as a Grignard or an organolithium reagent. These methods are all effective, but reactive organometallic reagents are generally air- and moisture-sensitive, and they can limit functional group compatibility.

A more attractive approach would employ stable, widely available substrates such as aryl halides or aryl boronic acids, in combination with transition-metal catalysis. Although our laboratory,²⁴ and others,²⁵ have developed methods that are effective for the addition of these substrates into sulfur dioxide, no such approaches with a sulfinylamine reagent have been described. The copper-catalyzed addition of arenediazonium salts into TrNSO has been reported, and applied to the synthesis of sulfonimidamides,²⁶ and sulfonimidoyl fluorides.²⁷ However, there are potential safety issues associated with the use of diazonium salts, which may be an obstacle to their widespread application.²⁸ In this Communication we show that a Ni(II) catalyst, constructed from commercial components, is effective for the addition of (hetero)aryl boroxines to the sulfinylamine TrNSO, to provide sulfnamides, and after in situ derivatization, sulfonimidamides, primary sulfonamides, and sulfonimidoyl fluorides (Scheme 1c).

Scheme 1. (a) Sulfnamides via organometallic addition to DABSO (SO₂); (b) Sulfnamides from the combination of TrNSO and organometallics; (c) This work: Nickel-catalyzed addition of boroxines to sulfinylamine reagents.



Our prior report of the Ni-catalyzed addition of boronic acids to DABSO was effective for a broad range of electronically varied and pharmaceutically relevant (hetero)aryl boronic acids,²⁹ and as such we selected this method as a starting point for the present study. Despite some initial success exploring the addition of 4-fluorophenylboronic acid to TrNSO,³⁰ we observed irreproducible results which were dependent on the batch of boronic acid used. It became apparent that the variation was due to differing proportions of boronic acid and boroxine, along with associated water, in individual batches, which resulted in degradation of TrNSO.³¹ This could be avoided if boroxines were used directly as reagents; these could be conveniently prepared from simple dehydration of the relevant boronic acids.³² Using the reaction conditions from the related DABSO chemistry,²⁹

but replacing the boronic acid with 4-fluorophenylboroxine, and DABSO with TrNSO, led to initial success, with small amounts of sulfnamide **1a** being observed at 100 °C. Lowering the reaction temperature to 80 °C improved this to 19%, while only trace product was observed at 60 °C.

We optimized the reaction conditions and found that using 10 mol% of commercially available and air-stable NiCl₂·(glyme), in combination with 10 mol % of 4,4'-dinonyl-2,2'-dipyridyl (dNbpy) as ligand, was effective, producing the desired sulfnamide in 85% yield (Table 1). The reaction used dioxane as a solvent at 80 °C and required only 1 equiv. of TrNSO and 1 equiv. of Cs₂CO₃. Although replacing dNbpy with inexpensive 2,2'-bipyridine (bpy) was detrimental (entry 2), if the equivalents of TrNSO were increased to two, the yield of sulfnamide **1a** was raised when using both dNbpy (89%) and bpy (84%) (entries 3–4). However, conscious of total mass balance, we elected to employ dNbpy as the ligand and 1 equiv. of TrNSO (entry 1). Higher loading of ligand, or lowering the reaction temperature resulted in less efficient reactions (entries 5 and 6). Using more equivalents of Cs₂CO₃ had no impact (entry 7). As expected, the nickel salt, ligand, and base were essential for reactivity (entry 8–10). Replacing the arylboroxine with a boronic ester, or a potassium trifluoroborate salt, were both unproductive (entry 11–12). Substituting dioxane with DMI (1,3-dimethyl-2-imidazolidinone), or Cs₂CO₃ with K₂CO₃, resulted in diminished yields (entry 13–14). The optimized reaction conditions could also be applied to the alternative sulfinylamine reagent *t*-OctNSO,²¹ producing 68% of the corresponding sulfnamide (entry 15).

Table 1. Optimization of reaction conditions for the formation of sulfnamide **1a from 4-fluorophenylboroxine and TrNSO.^a**

Entry	Variation from above	Yield of 1a (%)
1	none	85
2	bpy as ligand	67
3	2 equiv. TrNSO	89
4	2 equiv. TrNSO, bpy as ligand	84
5	15 mol% dNbpy	77
6	70 °C	70
7	1.5 equiv. Cs ₂ CO ₃	85
8	No NiCl ₂ ·(glyme)	<1
9	No dNbpy	<1
10	No Cs ₂ CO ₃	1
11	4-F-Ph-Bpin instead of (4-F-Ph-BO) ₃	<1
12	4-F-Ph-BF ₃ K instead of (4-F-Ph-BO) ₃	<1
13	DMI instead of dioxane	55
14	K ₂ CO ₃ instead of Cs ₂ CO ₃	9
15	<i>t</i> -OctNSO instead of TrNSO	68 ^b

dNbpy

bpy

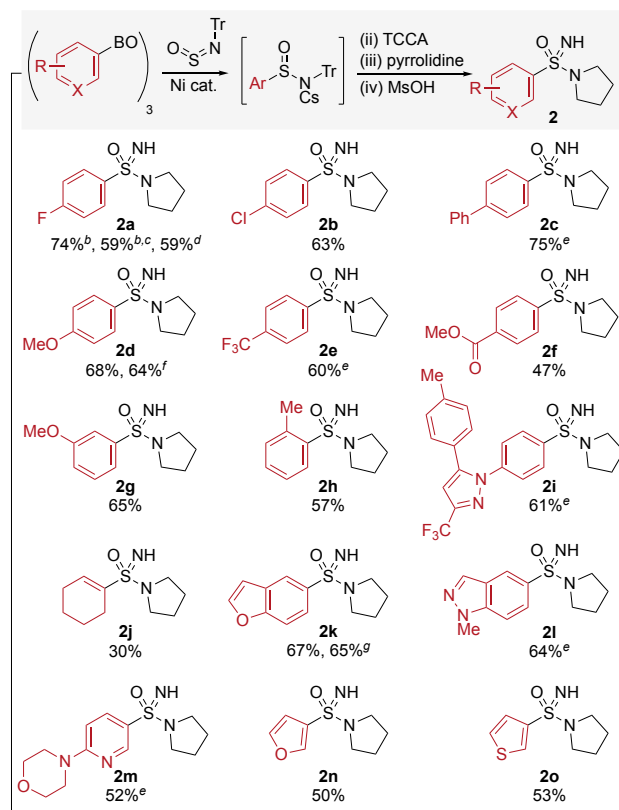
t-OctNSO

^a Reaction conditions: tris(4-fluorophenyl)boroxine (0.38 equiv.), NiCl₂·(glyme) (10 mol%), dNbpy (10 mol%), TrNSO (1.0 equiv.), Cs₂CO₃ (1.0 equiv.), dioxane (0.17 M), 80 °C, 16 h. Yields of **1a** were calculated from HPLC analysis using

1,3,5-triisopropylbenzene as an internal standard. ^bYield of the corresponding *t*-octyl sulfonimide.

To demonstrate the utility of the developed reaction, and to explore the substrate scope, we prepared a series of sulfonimidamides using a sequence similar to that shown in Scheme 1b. In our original sulfonimidamide synthesis we used *t*-BuOCl for the oxidative chlorination of sulfonamides; however, *t*-BuOCl is light-sensitive and presents an explosion risk,³³ and so we sought a more attractive alternative. We settled on trichloroisocyanuric acid (TCCA), which is a safe, stable and inexpensive reagent that is produced in a hundred thousand tonnes per year and is widely used as a disinfectant and bactericide in swimming pools, bathrooms, and laundry bleach.³⁴ Accordingly, direct treatment of the in situ, catalytically generated sulfonamide salt with TCCA, followed by the addition of pyrrolidine and triethylamine, provided the trityl-sulfonimidamide in 1 h. Subsequent treatment with MsOH at rt afforded the deprotected NH sulfonimidamide **2a** in a 74% isolated yield (Table 2). This represents an average of 96% for each of the three steps in the chlorination/amination/deprotection sequence. All four steps were performed in a one-pot reaction, providing a convenient synthesis of NH sulfonimidamides. The reaction can also be scaled to 1 mmol scale using only 5 mol% catalyst, producing a 59% isolated yield of the sulfonimidamide **2a**. Using *t*-OctNSO as the sulfenylamine reagent provided the same NH sulfonimidamide (**2a**) in 59% yield. This sequence was then applied across a range of boroxines (Table 2). Electronically varied 4-arenes were well tolerated, with chloro, phenyl, methoxy, trifluoromethyl, and methyl ester substituents delivering good to moderate isolated yields (**2b–f**). *Meta*- and *ortho*-substituted boroxines (**2g, h**) also reacted well. A boroxine bearing the arene core of the COX2 inhibitor Celecoxib was well-tolerated (**2i**). Alkenyl boroxine (**2j**) was a less successful coupling partner. A range of nitrogen-, oxygen-, and sulfur-containing heteroaryl boroxines were also suitable substrates, including benzofuran (**2k**), indazole (**2l**), pyridine (**2m**), furan (**2n**) and thiophene (**2o**), providing useful yields of the desired sulfonimidamides. The benzofuran example (**2k**) was also performed on an increased scale (0.4 mmol), which, provided the reaction temperature was increased to 100 °C, allowed the catalyst loading to be reduced to just 1 mol% nickel, and which provided the sulfonimidamide in 65% yield. With the addition of a dehydration step, the reaction sequence could also start directly from the boronic acid. For example, sulfonimidamide **2d** was obtained in 64% yield, using a one-pot reaction sequence commencing from the boronic acid, which compares well with the 68% achieved from the boroxine.

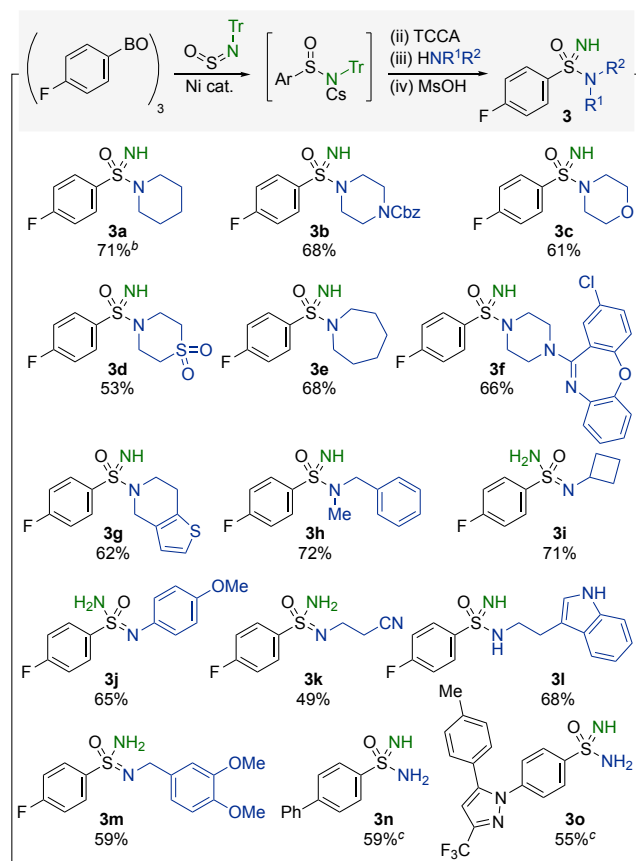
Table 2. Scope of the boroxines in the Ni-catalyzed synthesis of sulfonimidamides **2.^a**



^a Reaction conditions: (i) (hetero)aryl boroxine (0.33 equiv.), NiCl₂·(glyme) (10 mol%), dNbpy (10 mol%), TrNSO (1.0 equiv.), Cs₂CO₃ (1.0 equiv.), dioxane (0.17 M), 80 °C, 16 h. (ii) TCCA (0.5 equiv.), rt, 20 min. (iii) Pyrrolidine (2.0 equiv.), Et₃N (2.0 equiv.), rt, 1 h. (iv) MsOH, rt, 20 min. ^b boroxine (0.38 equiv.). ^c 1 mmol scale with 5 mol% NiCl₂·(glyme) and dNbpy, 100 °C. ^d Using *t*-OctNSO. ^e (hetero)aryl boroxine (0.67 equiv.), 100 °C. ^f Boroxine prepared directly from the dehydration of commercial aryl boronic acid (0.20 mol, 1.0 equiv.) in a one-pot reaction. ^g 0.4 mmol scale with heteroaryl boroxine (0.50 equiv.), 1 mol% NiCl₂·(glyme) and dNbpy, 100 °C, 48 h.

We next examined the scope of nitrogen-based nucleophiles that could be used, with tris(4-fluorophenyl)boroxine fixed as the carbon-coupling partner (Table 3). A range of secondary amines, including biologically relevant examples (**3f, g**), reacted smoothly to produce the corresponding sulfonimidamides (**3a–h**). Primary amines (**3i–m**), including anilines (**3j**) were also suitable nucleophiles. We then investigated the synthesis of primary sulfonimidamides. In our original sulfonimidamide synthesis (Scheme 1b),²⁰ we were unable to use ammonia as the amine component, and 3,4-dimethoxybenzylamine was used as a surrogate. Striving for greater efficiency, we revisited the use of ammonia; using NH₃ in dioxane, again produced a complex reaction mixture. However, guided by our earlier sulfonamide synthesis (Scheme 1a),¹⁷ a biphasic mixture of ammonium hydroxide and ethyl acetate cleanly produced the primary sulfonimidamides (**3n** and **3o**) in good yields.³⁵

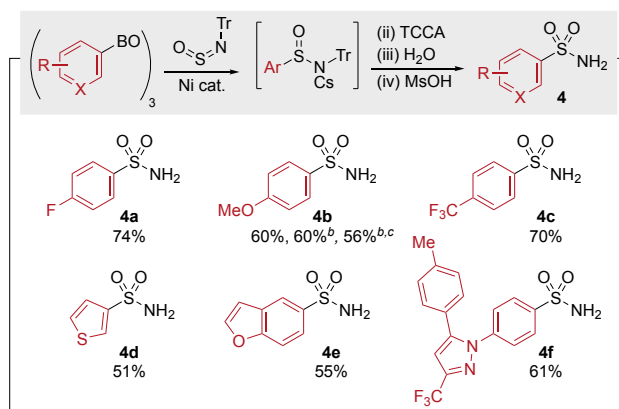
Table 3. Scope of the amine component in the Ni-catalyzed synthesis of sulfonimidamides 3.^a



^a Reaction conditions for step (iii) (amination step): R¹R²NH (2.0 equiv.), Et₃N (2.0 equiv.), rt, 24 h. ^b 5 h for step (iii). ^c Using biphasic mixture of aq. NH₃/ethyl acetate.

During the sulfonimidamide synthesis shown in Table 3, when less nucleophilic amines were used (e.g., for sulfonimidamides **3d** and **3k**) we observed significant quantities of sulfonamides as side products. Although this hydrolysis was detrimental in the context of sulfonimidamide syntheses, it suggested a convenient route to primary sulfonamides. We found that the intentional hydrolysis of sulfonimidoyl chlorides, generated in situ from the corresponding sulfonamides, could be achieved in high yields in a simple one-pot procedure (Table 4).⁴ Substrates bearing electron-poor (**4a**, **c**) and electron-rich arenes (**4b**), and heterocyclic examples (**4d**, **e**), were all smoothly converted to the corresponding primary sulfonamides. The COX-2 inhibitor celecoxib (**4f**) could be prepared using this method. The sequence could be performed on a 1 mmol scale using just 1 mol% of the Ni catalyst in the first step, to produce the sulfonamide **4b** in 60% yield. Additionally, sulfonamide **4b** could be prepared directly from the boronic acid, with the addition of a dehydration step, in 56% yield, again using just 1 mol% of catalyst.

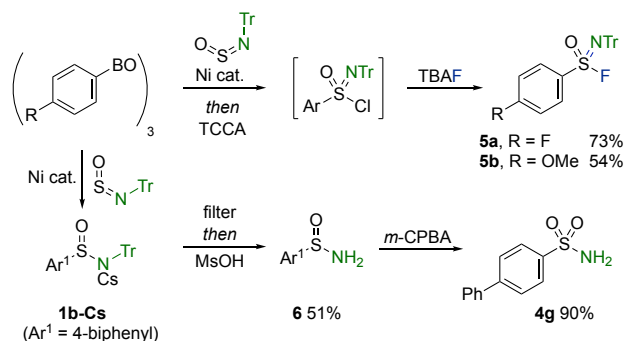
Table 4. The Ni-catalyzed synthesis of primary sulfonamides 4.^a



^a Reaction conditions: (iii) H₂O (2.0 M), rt, 24 h. (iv) MsOH, rt, 20 min. ^b 1 mmol scale with 1 mol% NiCl₂·(glyme) and dNbpy, aryl boronate (0.36 equiv.), 100 °C and 48 h. ^c Boronate prepared from the dehydration of commercial aryl boronic acid (1.1 mol, 1.1 equiv.) in a one-pot reaction.

To further expand the utility of the catalytically generated sulfonimidoyl chloride intermediates, we turned our attention to the synthesis of sulfonimidoyl fluorides. The desired halogen exchange was achieved by using TBAF as a soluble fluorine source, in a one-pot reaction (Scheme 2). Finally, we found that neat MsOH was effective for the deprotection of the N-trityl sulfonamide **1b**, to form primary sulfonamide **6** in a 51% yield. Primary sulfonamide **6** could be smoothly oxidized to the primary sulfonamide **4g** using *m*-CPBA, providing an alternative pathway to access primary sulfonamides.^{11b} However, the hydrolysis of sulfonimidoyl chlorides, shown in Table 4, provides a more efficient route to these important targets.

Scheme 2. Sulfonimidoyl fluoride and primary sulfonamide synthesis.



In summary, the nickel-catalyzed synthesis of sulfonamides has been developed. The method is redox-neutral, and uses (hetero)arylboroxines and TrNSO as the substrates. The nickel-catalyzed method can be scaled to 1 mmol using just 1 mol% catalyst. The in situ formed trityl-sulfonamides are efficiently chlorinated to the corresponding sulfonimidoyl chlorides using TCCA as an inexpensive and safe oxidant. A range of S(VI)-derivatives, including sulfonimidamides, sulfonamides and sulfonimidoyl fluorides, are prepared from the sulfonimidoyl chlorides in a series of one-pot reactions. Deprotection of the trityl-sulfonamide was also feasible to produce the primary sulfonamide. Several biologically relevant amines, and an

aryl core, were employed, demonstrating the utility of this method for the preparation of medicinally relevant molecules. Given the increasing attention on aza-S(IV) and aza-S(VI) derivatives in both pharmaceuticals and agrochemicals, we anticipate the broad uptake of the reported methods.

ASSOCIATED CONTENT

Experimental procedures and supporting characterization data and spectra (pdf). "This material is available free of charge via the Internet at <http://pubs.acs.org>."

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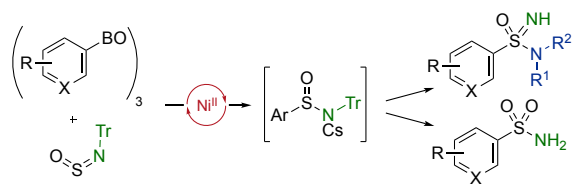
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