Stereoconvergent Arylations and Alkenylations of Unactivated Alkyl Electrophiles: Catalytic Enantioselective Synthesis of Secondary Sulfonamides and Sulfones

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Ⓢ Supporting Information

ABSTRACT: The development of efficient methods for the generation of enantioenriched sulfonamides and sulfones is an important objective for fields such as organic synthesis and medicinal chemistry; however, there have been relatively few reports of direct catalytic asymmetric approaches to controlling the stereochemistry of the sulfur-bearing carbon of such targets. In this report, we describe nickel-catalyzed stereo-

convergent Negishi arylations and alkenylations of racemic α-bromosulfonamides and -sulfones that furnish the desired cross-coupling product in very good ee and yield for an array of reaction partners. Mechanistic studies are consistent with the generation of a radical intermediate that has a sufficient lifetime to diffuse out of the solvent cage and to cyclize onto a pendant olefin.
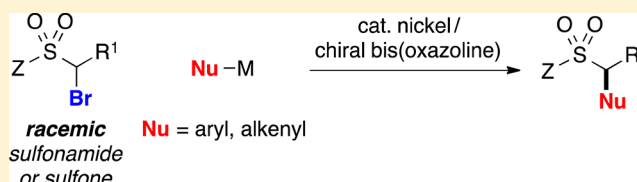
■ INTRODUCTION

Sulfonamides and sulfones serve both as useful intermediates in organic synthesis[1] and as important target molecules in their own right.[2,3] For example, enantioenriched secondary benzylic sulfonamides and sulfones display a range of biological activity (e.g., protein tyrosine phosphatase inhibitor,[4] antisepsis agent,[5] and γ-secretase inhibitor[6]).[7] However, to the best of our knowledge, there are no methods for the direct catalytic asymmetric synthesis of such sulfonamides, and just a few for such sulfones.[8]

One potential route to these compounds is the stereo-convergent coupling of a racemic α-halosulfonamide/sulfone with an appropriate nucleophile (eq 1). During the past several
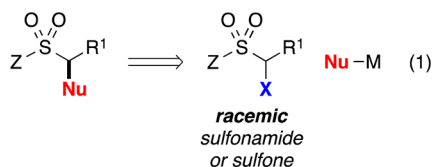
years, we have described an array of nickel-catalyzed enantioselective cross-couplings of secondary alkyl electrophiles. Whereas couplings of *activated* electrophiles (a leaving group α to a carbonyl, aryl, alkenyl, alkynyl, or cyano group) proceed in good ee with a variety of nucleophiles (alkyl-, aryl-, and alkenylmetal),[9,10] reactions of *unactivated* electrophiles have been limited, with three exceptions,[11] to *alkyl*metals, specifically alkyl-(9-BBN) reagents.[12]

Because α-halosulfonyl compounds are generally poor substrates for S$_N$2 reactions, and the sulfonyl group does not effectively stabilize an adjacent radical (bond dissociation

energy for a C–H bond of dimethylsulfone: 99 kcal/mol),[13] we view them as unactivated alkyl electrophiles. Herein, we report the first examples of the stereoconvergent cross-coupling of unactivated alkyl electrophiles with nucleophiles other than organoboranes, as well as the first general method for their coupling with aryl- or alkenylmetal reagents; in particular, we describe nickel/bis(oxazoline)-catalyzed cross-couplings of racemic α-bromosulfonamides and -sulfones with organozinc and organozirconium reagents, thereby furnishing secondary benzylic and allylic sulfonamides and sulfones in good enantiomeric excess (eq 2).[14]
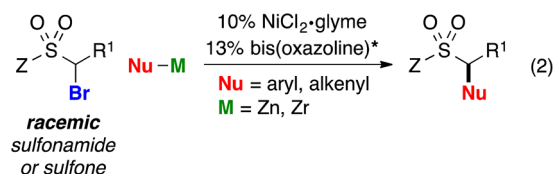
■ RESULTS AND DISCUSSION

Upon investigating a variety of reaction parameters, we determined that a nickel/bis(oxazoline)[15] catalyst can achieve the cross-coupling of an α-bromosulfonamide with an arylzinc reagent in very good ee and yield at −20 °C (Table 1, entry 1); NiCl$_2$·glyme and bis(oxazoline) **L1** ((*R,R*) and (*S,S*)) are commercially available. All previous reports of stereoconvergent Negishi reactions of racemic electrophiles have employed activated coupling partners.[9a–c,e–g]

**Table 1. Stereoconvergent Negishi Phenylation of a Racemic α-Bromosulfonamide: Effect of Reaction Parameters[a]**

entry	change from the "standard conditions"	ee (%)	yield (%)[b]
1	none	96	88
2	no NiCl₂·glyme	–	<2
3	no L1	–	16
4	r.t., instead of −20 °C	93	39
5	L2, instead of L1	93	84
6	L3, instead of L1	78	28
7	L4, instead of L1	56	6
8	L5, instead of L1	70	44
9	PhMgBr, instead of PhZnI	89	44
10	5% NiCl₂·glyme, 6.5% L1	96	72
11	under air, rather than under N₂ (capped vial)	96	52
12	0.1 equiv of water added	97	84

[a]All data are the average of two experiments. [b]The yield was determined through GC analysis with the aid of a calibrated internal standard.
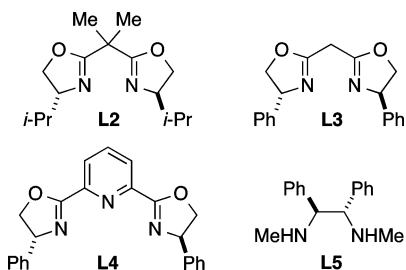
Essentially no cross-coupling is observed in the absence of NiCl₂·glyme (Table 1, entry 2), and a low yield of the desired product is obtained if ligand **L1** is omitted (entry 3). At room temperature, the coupling proceeds in good ee, but hydrodebromination predominates over C—C bond formation. The corresponding valine-derived bis(oxazoline) (**L2**) is nearly as effective as phenylglycine-derived **L1** (entries 1 and 5), whereas removal of the gem-dimethyl substituents on the linker between the oxazolines of **L1** leads to a substantial drop in efficiency (entry 6). Although pybox ligands are often the ligand of choice for nickel-catalyzed stereoconvergent Negishi reactions,[9a−c,e] pybox **L4** is not effective for this particular cross-coupling, nor is a 1,2-diamine ligand[9d,12] (entries 7 and 8). The use of PhMgBr in place of PhZnI leads to a small loss in ee and a substantial loss in yield (entry 9). When the catalyst loading is reduced in half, no erosion in enantioselectivity is observed, although the yield falls by a modest amount (entry 10). The process is somewhat oxygen-sensitive (entry 11; 66% conversion) but not particularly moisture-sensitive (entry 12).

Under these conditions, we can achieve stereoconvergent Negishi cross-couplings of a variety of racemic α-bromosulfonamides with PhZnI to generate highly enantioenriched benzylic sulfonamides (Table 2).[16] The nitrogen of the sulfonamide can bear either an alkyl or an aryl substituent, with little impact on ee or yield (entries 1−5). Furthermore, the R¹ side chain can

Table 2. Stereoconvergent Negishi Phenylations of Racemic α-Bromosulfonamides: Scope with Respect to the Sulfonamide[a]

entry	R₂N	R¹	ee (%)	yield (%)[b]
1	Me–N(Me)–	n-Bu	96	90
2	Ph–N(Me)–	n-Bu	94	95
3	Bn–N(Me)–	n-Bu	94	94
4	pyrrolidin-1-yl	n-Bu	96	85
5	morpholin-4-yl	n-Bu	96	92
6	Me₂N	–(CH₂)₆–CH=CH₂	95	88
7	Me₂N	–(CH₂)₄–OTBS	98	92
8[c]	Me₂N	–(CH₂)₄–(thiophen-2-yl)	90	54
9[c]	Me₂N	cyclopentyl	99	44

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Amount of PhZnI: 1.5 equiv.

include functional groups and can be either primary (entries 6−8) or secondary (entry 9), although in the case of the latter a diminished yield is observed. On a gram scale, the cross-coupling illustrated in entry 2 proceeds in 92% ee and 98% yield.

The conditions that we developed for stereoconvergent Negishi reactions of α-bromosulfonamides (Table 2) can be applied without modification to the corresponding sulfones (Table 3).[17] The scope with respect to the sulfone is broad. Thus, the R substituent can range in steric demand from methyl to t-butyl (entries 1−4), and it can be aromatic (entry 5). With respect to the R¹ group, it may be linear or branched (entries 1−5).

Table 3. Stereoconvergent Negishi Phenylations of Racemic α-Bromosulfones: Scope with Respect to the Sulfone[a]

entry	R	R¹	ee (%)	yield (%)[b]
1	Me	n-Bu	94	96
2[c]	Me	Cy	99	83
3	Me	(CH₂)₆NBnCbz	90	74
4	t-Bu	n-Bu	98	96
5	Ph	n-Bu	84	96

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Amount of PhZnI: 1.5 equiv.

We have examined the scope of arylzinc nucleophiles that participate in this method for the catalytic asymmetric synthesis of benzylic sulfonamides and sulfones (Table 4). Electron-rich

Table 4. Stereoconvergent Negishi Arylations of α-Bromosulfonamides and -Sulfones: Scope with Respect to the Arylzinc Reagent[a]

entry	R	Ar		ee (%)	yield (%)[b]
1	Me₂N	X = Me		**96**	89
2	Me₂N	X—C₆H₄— CF₃		**98**	94
3	Me₂N	CO₂Et		**97**	>99
4	Me₂N	MeO-phenyl		**96**	88
5	Me₂N	X = OMe		**96**	64
6	Me₂N	Me		**97**	78
7[c]	Me₂N	Et		**97**	86
8	Me₂N	BocN-indole		**89**	68
9	Me	X = OMe		**96**	84
10	Me	Me		**97**	80
11[c]	Me	Et		**98**	82

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Amount of ArZnI: 2.0 equiv; amount of catalyst: 20% NiCl₂·glyme, 26% (R,R)-**L1**.

and electron-poor arylzinc reagents are suitable partners, as is a heteroarylzinc reagent, furnishing the desired product in very good ee. Especially noteworthy is our observation that o-substituted phenylzinc reagents can be employed with both sulfonamide- and sulfone-based electrophiles (entries 5–7 and 9–11); in our previous studies of nickel-catalyzed enantioselective arylations, o-substituted nucleophiles have generally been poor coupling partners.[18,19]

Next, we sought to expand the scope of stereoconvergent cross-couplings of α-bromosulfonamides and -sulfones to include a second family of nucleophiles, specifically, alkenyl-metal reagents. We determined that, whereas reactions of alkenylzinc reagents proceed in poor yield using the method described above, alkenylzirconium reagents serve as suitable nucleophiles under modified conditions (Table 5).[20,21] Thus, an array of allylic sulfonamides and sulfones[22] can be synthesized with good enantioselectivity in the presence of functional groups such as a thiophene and a primary alkyl chloride.

We have suggested that, for at least some nickel-catalyzed cross-couplings of alkyl electrophiles, an alkyl radical may be generated during the oxidative-addition step of the catalytic cycle.[23,24] In the case of electrophiles that bear an appropriately positioned pendant olefin, we have observed complete cyclization of the putative radical onto the olefin in some instances,[25] and no cyclization in another.[9f]

In order to gain insight into the mechanism of the stereoconvergent arylations described herein, we investigated the Negishi reaction of an α-bromosulfonamide bearing a

Table 5. Stereoconvergent Negishi Cross-Couplings of α-Bromosulfonamides and -Sulfones: Alkenylzirconium Reagents as Nucleophiles[a]

entry	electrophile	R²	ee (%)	yield (%)[b]
1	Me(Me)N–SO₂–CH(n-Bu)Br	CH₂Ph	**90**	81
2	Cy(Cy)N–SO₂–CH(n-Bu)Br	CH₂Ph	**94**	83
3		(CH₂)₂OTBDPS	**94**	82
4	Ph(Bn)N–SO₂–CH((CH₂)₃-thienyl)Br	(CH₂)₄Cl	**80**	62
5	morpholino–SO₂–CH(n-Bu)Br	Ph	**96**	68
6[c]	Me–SO₂–CH(Cy)Br	CH₂Ph	**93**	50

[a]All data are the average of two experiments. [b]Yield of purified product. [c]Ligand used: (R,R)-**L1**.

pendant olefin (eq 3).[26] At 70% conversion of the electrophile, we observe a 38% yield of the direct (uncyclized) cross-

$$Me_2N\text{-}SO_2\text{-}CH(Br)(CH_2)_3CH=CHD \xrightarrow[\text{stopped at 70\% conversion}]{\substack{PhZnI \\ \text{see Table 2}}} Me_2N\text{-}SO_2\text{-}CH(Ph)(CH_2)_3CH=CHD \quad (3)$$

7   recovered alkyl bromide: **only E**

8   **38% yield**   **96% ee (only E)**

via [**10** radical intermediate] ?

cis–9   **8% yield**

trans–9   **9% yield**

coupling product (**8**) and a 17% combined yield of cyclized cross-coupling products (**9**).

Cyclopentane derivatives *cis*-**9** and *trans*-**9** are each an ~1:1 mixture of diastereomers (differing in the relative stereochemistry at the deuterium-bearing carbon), consistent with the expectation for cyclization of radical intermediate **10** (but not for a simple organometallic pathway involving only β-migratory insertion and then reductive elimination). Our observation that uncyclized cross-coupling product **8** has deuterium only in the trans position suggests that, when intermediate **10** does cyclize, the process is irreversible.

Simple 5-hexenyl radical cyclizations proceed with first-order rate constants of ~10^5 s^{-1}.[27] Although, to the best of our knowledge, the rate of cyclization of sulfonamide-substituted radical **10** has not been determined, it is very likely to be significantly slower than diffusion (~10^9 s^{-1}).[13a] Our

observation of cyclized, cross-coupled products (**9**) therefore represents evidence that a nickel-catalyzed asymmetric cross-coupling process may include a noncage radical pathway. Consistent with this suggestion, the ratio of uncyclized (**D**)/cyclized (**C**) product changes as the concentration of catalyst changes (Figure 1).[28]
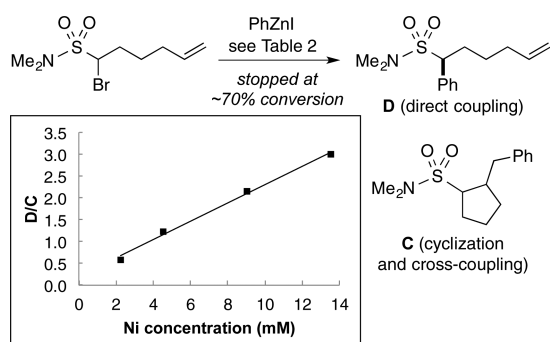
Figure 1. Dependence of the ratio of uncyclized (D)/cyclized (C) product on the concentration of nickel.

CONCLUSIONS

We have developed methods for the enantioselective synthesis of secondary sulfonamides and sulfones, specifically, nickel-catalyzed Negishi arylations and alkenylations of racemic α-bromosulfonamides and -sulfones with readily available organozinc and organozirconium reagents; with regard to stereoconvergent couplings of *un*activated alkyl electrophiles, previous examples had been limited to organoboron nucleophiles and, with the exception of three isolated examples, to *alkyl*ation reactions. In terms of mechanism, a cyclization/stereochemical probe has provided evidence for a radical intermediate that has a sufficient lifetime to escape the solvent cage and cyclize irreversibly under the coupling conditions. Additional studies directed at elucidating the mechanisms of cross-coupling reactions of alkyl electrophiles, as well as expanding the scope of such processes, are underway.

ASSOCIATED CONTENT

S **Supporting Information**
Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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(17) Under our standard conditions, an α-chlorosulfone was not a suitable cross-coupling partner.

(18) For recent examples, see refs 9g and 15d.

(19) Under our standard conditions, doubly ortho-substituted arylzinc reagents are not suitable coupling partners.

(20) For a report of the use of alkenylzirconium reagents in nickel-catalyzed stereoconvergent cross-couplings of α-haloketones, see ref 15b.

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