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

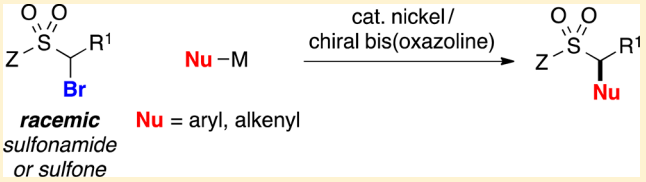
Junwon Choi,[‡,†] Pablo Martín-Gago,[‡] and Gregory C. Fu*[,‡]

[‡]Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

[†]Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States

Supporting Information

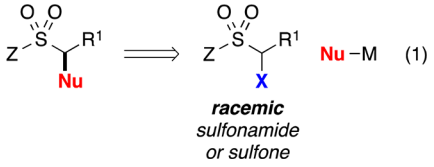
ABSTRACT: The development of efficient methods for the generation of enantioenriched sulfonamides and sulfones is an important objective for fields such as organic synthesis and medicinal chemistry; however, there have been relatively few reports of direct catalytic asymmetric approaches to controlling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

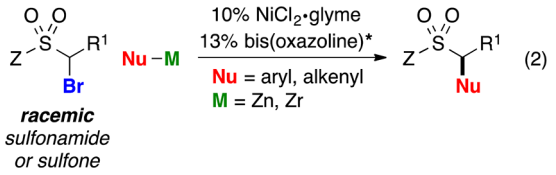
Sulfonamides and sulfones serve both as useful intermediates in organic synthesis[1] and as important target molecules in their own right.[2,3] For example, enantioenriched secondary benzylic sulfonamides and sulfones display a range of biological activity (e.g., protein tyrosine phosphatase inhibitor,[4] 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 stereoconvergent 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_N2 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]

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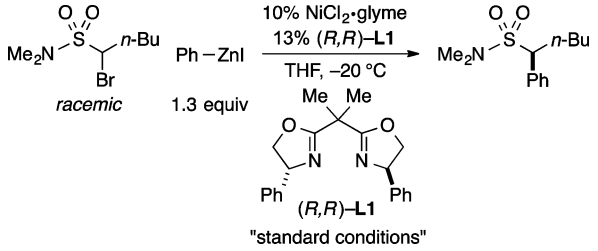
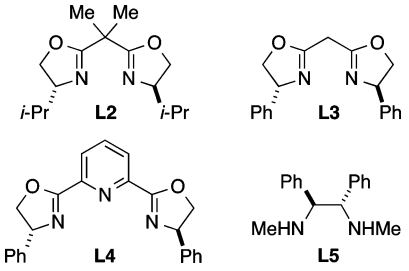
Table 1. Stereoconvergent Negishi Phenylation of a Racemic α-Bromosulfonamide: Effect of Reaction Parameters[a]



entry	change from the "standard conditions"	ee (%)	yield (%)[b]
1	none	96	88
2	no $NiCl_2$·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% $NiCl_2$·glyme, 6.5% **L1**	96	72
11	under air, rather than under N_2 (capped vial)	96	52
12	0.1 equiv of water added	97	84

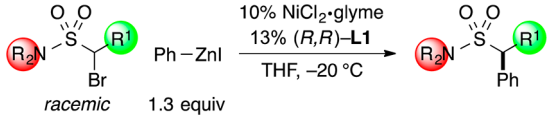
[a]All data are the average of two experiments. [b]The yield was determined through GC analysis with the aid of a calibrated internal standard.

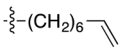
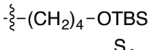
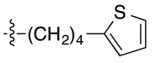


Essentially no cross-coupling is observed in the absence of $NiCl_2$·glyme (Table 1, entry 2), and a low yield of the desired product is obtained if ligand **L1** is omitted (entry 3). At room temperature, the coupling proceeds in good ee, but hydrodebromination predominates over C–C bond formation. 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 R^1 side chain can 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.

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

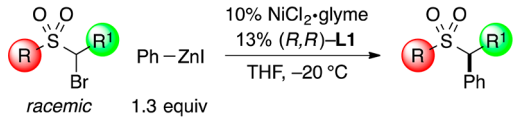


entry	R_2N	R^1	ee (%)	yield (%)[b]
1		*n*-Bu	96	90
2		*n*-Bu	94	95
3		*n*-Bu	94	94
4		*n*-Bu	96	85
5		*n*-Bu	96	92
6	Me_2N		95	88
7	Me_2N		98	92
8[c]	Me_2N		90	54
9[c]	Me_2N		99	44

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

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 R^1 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	R^1	ee (%)	yield (%)[b]
1	Me	*n*-Bu	94	96
2[c]	Me	Cy	99	83
3	Me	$(CH_2)_6NBnCbz$	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.

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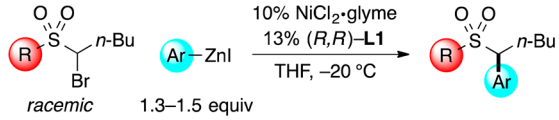
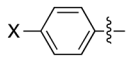
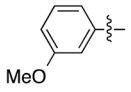
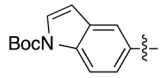
We have examined the scope of arylzinc nucleophiles that participate in this method for the catalytic asymmetric synthesis of benzylic sulfonamides and sulfones (Table 4). Electron-rich and electron-poor arylzinc reagents are suitable partners, as is a heteroarylzinc reagent, furnishing the desired product 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]

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	Me_2N		X = Me	96	89
2	Me_2N		CF_3	98	94
3	Me_2N		CO_2Et	97	>99
4	Me_2N			96	88
5	Me_2N		X = OMe	96	64
6	Me_2N		Me	97	78
7[c]	Me_2N		Et	97	86
8	Me_2N			89	68
9	Me		X = OMe	96	84
10	Me		Me	97	80
11[c]	Me		Et	98	82

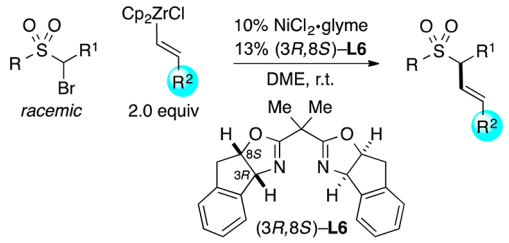
[a]All data are the average of two experiments. [b]Yield of purified product. [c]Amount of ArZnI: 2.0 equiv; amount of catalyst: 20% $NiCl_2$·glyme, 26% (*R*,*R*)-**L1**.

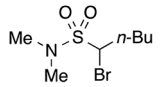
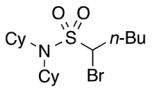
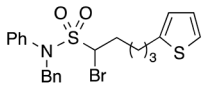
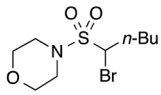
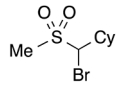
Next, we sought to expand the scope of stereoconvergent cross-couplings of α-bromosulfonamides and -sulfones to include a second family of nucleophiles, specifically, alkenylmetal reagents. We determined that, whereas reactions of alkenyl*zinc* reagents proceed in poor yield using the method described above, alkenyl*zirconium* 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]

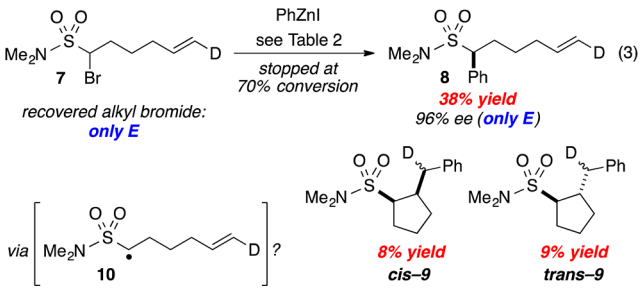
In order to gain insight into the mechanism of the stereoconvergent arylations described herein, we investigated the Negishi reaction of an α-bromosulfonamide bearing a pendant olefin (eq 3).[26] At 70% conversion of the electrophile, we observe a 38% yield of the direct (uncyclized) cross-coupling product (**8**) and a 17% combined yield of cyclized cross-coupling products (**9**).

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



entry	electrophile	R^2	ee (%)	yield (%)[b]
1		CH_2Ph	90	81
2		CH_2Ph	94	83
3		$(CH_2)_2OTBDPS$	94	82
4		$(CH_2)_4Cl$	80	62
5		Ph	96	68
6[c]		CH_2Ph	93	50

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



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 $\sim 10^5$ 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 ($\sim 10^9$ s^{-1}).[13a] Our

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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]

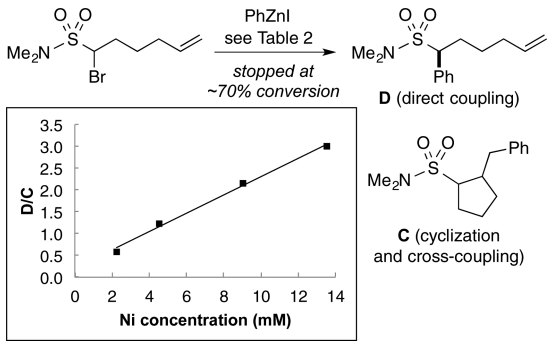

Figure 1. Dependence of the ratio of uncyclized (D)/cyclized (C) product on the concentration of nickel.

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

Supporting Information

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

AUTHOR INFORMATION

Corresponding Author

gcfu@caltech.edu.

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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