Nickel-Catalyzed Structural Rearrangement of Sulfonamides: Intramolecular Cross-Electrophile Coupling Reaction of Sulfonamides with Alkyl Chlorides

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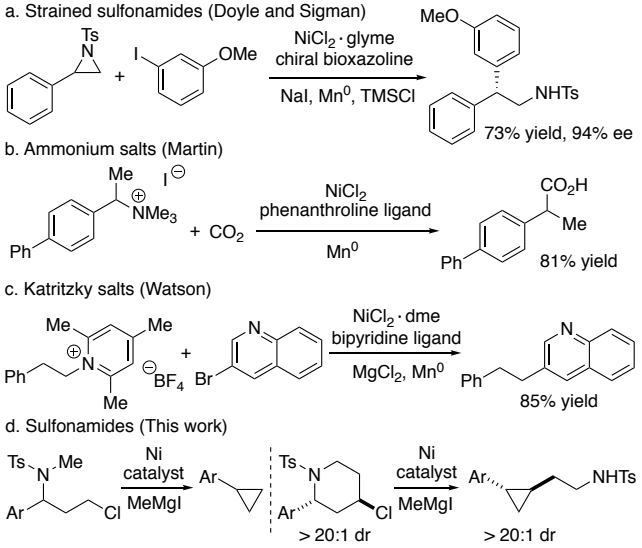
ABSTRACT: The application of amine derivatives as coupling partners is rare due to the inherent strength of the C–N bond. Herein we report the first cross-electrophile coupling reaction of unstrained benzylic sulfonamides. Nickel-catalyzed intramolecular cross-electrophile coupling reactions of acyclic and cyclic benzylic sulfonamides with pendant alkyl chlorides generate cyclopropane products. Mechanistic experiments and DFT calculations are consistent with initiation of the reaction by magnesium iodide-accelerated oxidative addition of the benzylic sulfonamide. This work establishes neutral and unstrained amine derivatives as XEC partners, furnishes structural rearrangement of benzylic sulfonamides, and provides valuable information regarding catalyst design for the development of new cross-electrophile coupling reactions of carbon-heteroatom bonds.

INTRODUCTION

Amines are ubiquitous across biomolecules, natural products, and pharmaceutical agents.[1] However, despite their abundance, it is often challenging to engage amines in reactions that allow for the cleavage of C–N bonds.[2] This hurdle lies in the inherent strength of carbon-nitrogen bonds compared to the carbon-heteroatom bonds present in more reactive and commonly utilized electrophiles, such as alkyl halides. Furthermore, the amido leaving groups generated can serve as strong ligands, resulting in catalyst deactivation.[3] The discovery of new catalysts capable of engaging C–N bonds would improve our ability to design reactions that exploit reticent electrophiles, as well as inform future catalyst design.

Cross-electrophile coupling (XEC) reactions[4] of amine derivatives are rare, and current examples require substrates where the C–N bond has been activated,[5,6,7,8] either by incorporation into a strained ring or by formation of an ammonium salt.[9,10,11,12] For example, the Doyle and Sigman laboratories reported the nickel-catalyzed cross-electrophile coupling reaction of strained, benzylic sulfonyl aziridines with aryl iodides to generate enantioenriched 2-arylphenethylsulfonamides (Scheme 1a).[9] Martin and coworkers developed the nickel-catalyzed cross-electrophile coupling reaction of benzylic ammonium salts with carbon dioxide to afford benzylic carboxylic acids (Scheme 1b).[10] Recently, the Watson laboratory reported the nickel-catalyzed cross-electrophile coupling reaction of Katritzky salts with aryl bromides (Scheme 1c).[12] These important developments have demonstrated the feasibility of applying amine derivatives as electrophiles in cross-electrophile coupling reactions, but expansion to less activated C–N bonds is a necessary challenge to overcome in order to further advance the field.

Scheme 1. Cross-Electrophile Coupling Reactions of Amine Derivatives



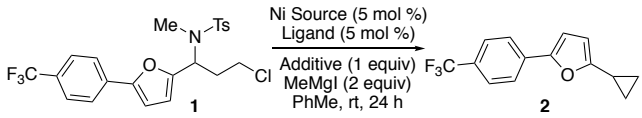
In this manuscript, we describe the first cross-electrophile coupling reaction of benzylic sulfonamides (Scheme 1d).[13] Alkyl chlorides and benzylic sulfonamides are engaged in an intramolecular nickel-catalyzed XEC reaction to afford monosubstituted cyclopropanes. Additionally, *N*-tosyl-4-chloropiperidines undergo a stereose-

lective ring contraction to afford trans-substituted cyclopropanes with high diastereoselectivity. These results are noteworthy because the ability to manipulate the structures of sulfonamides is valuable due to their prevalence in the pharmaceutical industry.[14] For example, sulfonamide-containing compounds are known to possess a wide variety of biological properties, including anti-inflammatory, anti-hypertensive and anti-convulsant activity. Recent studies have demonstrated that sulfonamides can mediate protein-protein interactions involved in cancer progression and inhibit neurotransmitter biosynthesis.[15] In this manuscript, we report the structural rearrangement of sulfonamides—the transformation of *N*-tosylpiperidines to *N*-tosyl(aminoethyl)cyclopropanes—as well as setting the foundation for further development of nickel-catalyzed XEC reactions of unstrained and neutral amine derivatives.

RESULTS AND DISCUSSION

Development of Sulfonamide Cross-Electrophile Coupling Reaction. We began by evaluating the intramolecular cross-electrophile coupling reaction of sulfonamide **1**. The optimal XEC reaction conditions employed air-stable ((*R*)-BINAP)$NiCl_2$ as the catalyst, MeMgI as the reductant, and MgI_2 as a Lewis acid additive to afford cyclopropane **2** in 77% yield (Table 1, entry 1).[16] Omission of MgI_2 or higher reaction temperatures resulted in decreased yields (entries 2–3), and increased loading of the nickel catalyst was unable to further improve the yield of **2** (entry 4). When $Ni(cod)_2$ was employed as a precatalyst with *rac*-BINAP as the ligand, the yield was severely diminished (entry 5). We attribute this outcome to the strong coordination of 1,5-cyclooctadiene to the nickel catalyst, which we hypothesize prevents the nickel catalyst from engaging the substrate and entering the catalytic cycle (entry 6). In order to determine whether ligands other than BINAP could generate a more effective catalyst for the reaction, we selected $NiCl_2$(dme) as a precatalyst and performed the XEC with monodentate phosphines, nitrogen-based ligands, and NHCs (entries 7–13). None of these experiments provided improved yields of cyclopropane **2**. Finally, control experiments demonstrated that the XEC reaction does not proceed without the nickel catalyst or MeMgI (entries 15–16).

Table 1. Optimization of Cross-Electrophile Coupling Reaction Conditions

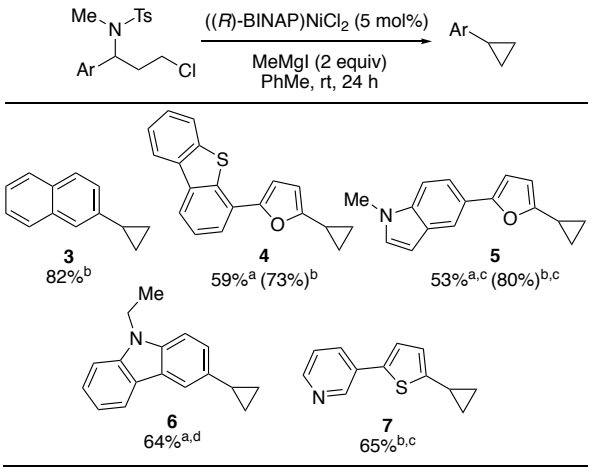


Entry	Ni Source	Ligand	Additive	Yield (%)[a]
1	((*R*)-BINAP)$NiCl_2$	none	MgI_2	77
2	((*R*)-BINAP)$NiCl_2$	none	none	63
3[b]	((*R*)-BINAP)$NiCl_2$	none	MgI_2	40
4[c]	((*R*)-BINAP)$NiCl_2$	none	MgI_2	77
5	$Ni(cod)_2$	*rac*-BINAP	MgI_2	27
6[d]	$Ni(cod)_2$	*rac*-BINAP	MgI_2	23
7	$NiCl_2$(dme)	*rac*-BINAP	MgI_2	29
8	$NiCl_2$(dme)	*rac*-BINAP	none	8
9	$NiCl_2$(dme)	XantPhos	none	0
10	$NiCl_2$(dme)	DPEPhos	none	16
11	$NiCl_2$(dme)	BPhen	none	11
12	$NiCl_2$(dme)	SiMes · HBF_4	none	15
13	$NiCl_2$(dme)	PCy_3	none	28
14	$NiCl_2(PCy_3)_2$	none	none	7
15	none	none	none	0
16[e]	((*R*)-BINAP)$NiCl_2$	none	MgI_2	0

[a]Yield determined by ^1H NMR based on comparison to PhTMS as internal standard. [b]50 ºC instead of rt. [c]15 mol % nickel catalyst loading. [d]10 mol% cod added. [e]MeMgI added.

After determining the optimal cross-electrophile coupling reaction conditions, we evaluated the scope of the reaction to include a variety of substrates containing pendant aromatic and heterocyclic functionalities (Table 2). Naphthyl-substituted cyclopropane **3** was readily synthesized in 82% yield. Shifting our attention to more challenging substrates, we were gratified to observe that cyclopropanes **4** and **5** were generated in 73% and 80% yield, respectively, demonstrating the feasibility of applying the XEC reaction to substrates containing furan, dibenzothiophene, and indole moieties. We were pleased to find that a carbazole was also tolerated in the XEC reaction, affording cyclopropane **6** in 64% yield. Finally, our XEC reaction was successfully employed in the synthesis of pyridyl-substituted cyclopropane **7**. The robust scope of this reaction demonstrates the ability of the XEC reaction to tolerate an array of medicinally relevant heterocyclic functionalities.

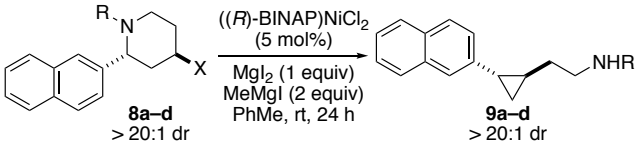
Table 2. Scope of XEC Reaction for Monosubstituted Cyclopropane Synthesis



[a]Isolated Yield. [b]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [c]1 equiv MgI_2 added. [d]1.5 equiv MgI_2 added.

Development of Piperidine Ring Contraction. We next aimed to develop an intramolecular stereoselective cross-electrophile coupling reaction of 4-halopiperidines, which would allow for the synthesis of cyclopropanes containing pendant sulfonamides.[17] *N*-Tosyl-4-chloropiperidines were conveniently synthesized in a single step by the aza-Prins reaction of aldehydes and homoallylic sulfonamides.[18,19] The allylic strain imparted by the sulfonyl group drives the aryl or vinyl group to the axial position, therefore most of these aza-Prins reactions are highly diastereoselective to afford trans-disubstituted piperidines.[20] We were delighted to observe that when subjected to our optimized XEC reaction conditions, tosylpiperidine **8a** afforded cyclopropane **9a** in 96% yield and excellent stereoselectivity (Table 3, entry 1). The analogous ring contraction of nosylpiperidines would be desirable due to the facile removal of the nosyl group, but unfortunately subjection of substrate **8b** to the reaction conditions resulted in a complex mixture of products (entry 2). Triflamide **8c** was engaged in the XEC reaction with high efficiency, resulting in quantitative yield of cyclopropane **9c** with excellent diastereoselectivity (entry 3). Finally, we hypothesized that 4-(trifluoromethyl)benzenesulfonamide **8d** would possess intermediate reactivity between tosylamine **8a** and triflamide **8c**. Surprisingly, however, the XEC reaction of **8d** afforded only 34% yield of **9d**, albeit with excellent stereoselectivity (entry 4). In the interest of thoroughly evaluating the boundaries of the XEC reaction, we also evaluated the ring contractions of 4-fluoro and 4-bromo-*N*-tosylpiperidines (entries 5–6). These experiments afforded little or none of the desired cyclopropane product, confirming that alkyl chlorides were ideal XEC partners with sulfonamides.

Table 3. Evaluation of Sulfonamides and Halides for Piperidine Ring Contraction

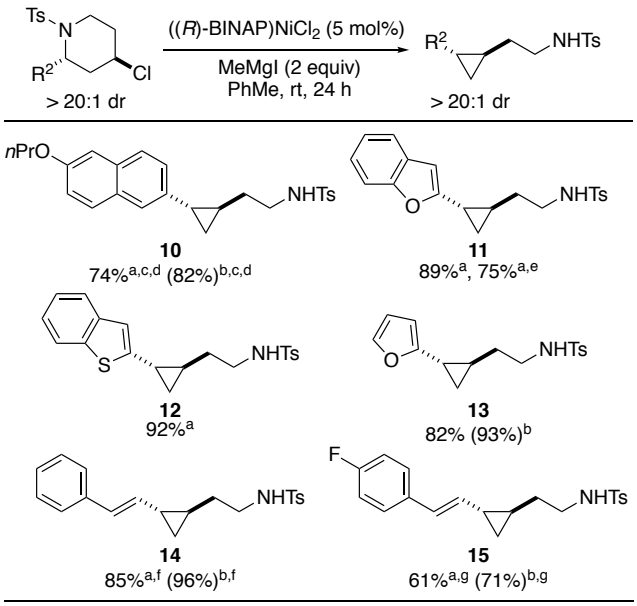


Entry	R	X	SM	Yield 9 (%)[a]	Recovered 8 (%)[a]
1	Ts	Cl	**8a**	96	< 2
2	Ns	Cl	**8b**	< 5	< 5
3	Tf	Cl	**8c**	> 99	< 2
4[b]	Ts^F	Cl	**8d**	32	34
5	Ts	F	**8e**	< 2	< 2
6	Ts	Br	**8f**	< 12	< 2

[a]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [b]Ts^F = 4-(trifluoromethyl)benzenesulfonyl.

With *N*-tosyl and *N*-triflylpiperidines successfully engaging in the intramolecular cross-electrophile coupling reaction, we proceeded to evaluate the scope of the reaction (Table 4). We chose to focus on *N*-tosylpiperidines due to their ease of synthesis and because the C–N bonds are less activated than the corresponding triflamides. First, we demonstrated that aryl ethers were tolerated in the XEC through the synthesis of cyclopropane **10** in 82% yield. Benzofuran-, benzothiophene-, and furan-substituted piperidines could be employed in the XEC, affording cyclopropanes **11**, **12**, and **13** in 89%, 92%, and 93% yield, respectively.[21] Notably, the XEC reaction can be performed outside of the glovebox to provide a similar yield of cyclopropane **11**. Additionally, we applied the XEC reaction to vinylpiperidines in order to furnish vinylcyclopropanes **14** and **15** in high yields.[22] Vinyl piperidines performed best in the XEC reaction with $Ni(cod)_2$ as the precatalyst, contrary to all other acyclic sulfonamides and *N*-tosylpiperidines evaluated.[23] We hypothesize that the allylic sulfonamide is capable of competing with 1,5-cyclooctadiene for binding to the nickel catalyst. Importantly, all cyclopropane products in Table 4 were synthesized with excellent diastereoselectivity (>20:1 dr).

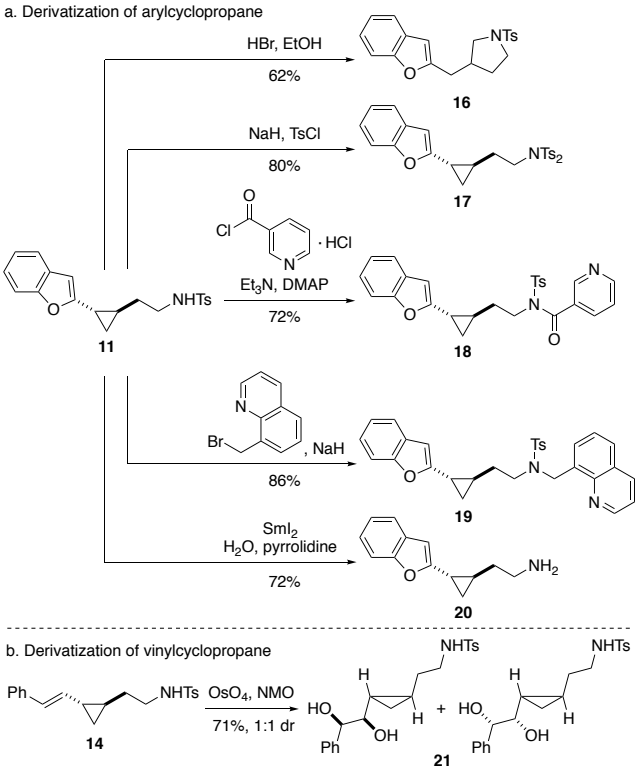
Table 4. Scope of Piperidine Ring Contraction



[a]Isolated yield. [b]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard. [c]1 equiv MgI_2 added. [d]Starting material 7:1 dr trans:cis. [e]Reaction performed on the benchtop with 3 equiv of MeMgI for 48 h. [f]Used $Ni(cod)_2$ (5 mol %) and BPhen (5 mol %) instead of ((*R*)-BINAP)$NiCl_2$. [g]Used $Ni(cod)_2$ (5 mol %) and SIMes·HCl (5 mol %) instead of ((*R*)-BINAP)$NiCl_2$.

Synthetic Applications of Cyclopropane Products. In order to demonstrate the synthetic utility of the cyclopropane products, we performed an array of derivatization reactions to afford valuable functionalities (Scheme 2). We were delighted to observe that when subjected to hydrobromic acid and heat, cyclopropane **11** underwent an unusual ring expansion to *N*-tosylpyrrolidine **16**.[24,25] We envision that under acidic conditions, the cyclopropane is activated for nucleophilic attack to form an intermediate alkyl bromide that leads to the observed pyrrolidine.[26] This transformation broadens our ability to manipulate the backbone of sulfonamides. Additionally, sulfonamide **11** smoothly underwent tosylation to afford sulfonimide **17**. Acylation and alkylation reactions were also facile to generate nicotinamide derivative **18** and substituted quinoline **19**. The tosyl group was efficiently deprotected with samarium(II) iodide to afford primary amine **20**.[27] Finally, vinylcyclopropane underwent dihydroxylation to afford diol **21**.

Scheme 2. Derivatization of Cyclopropane Products

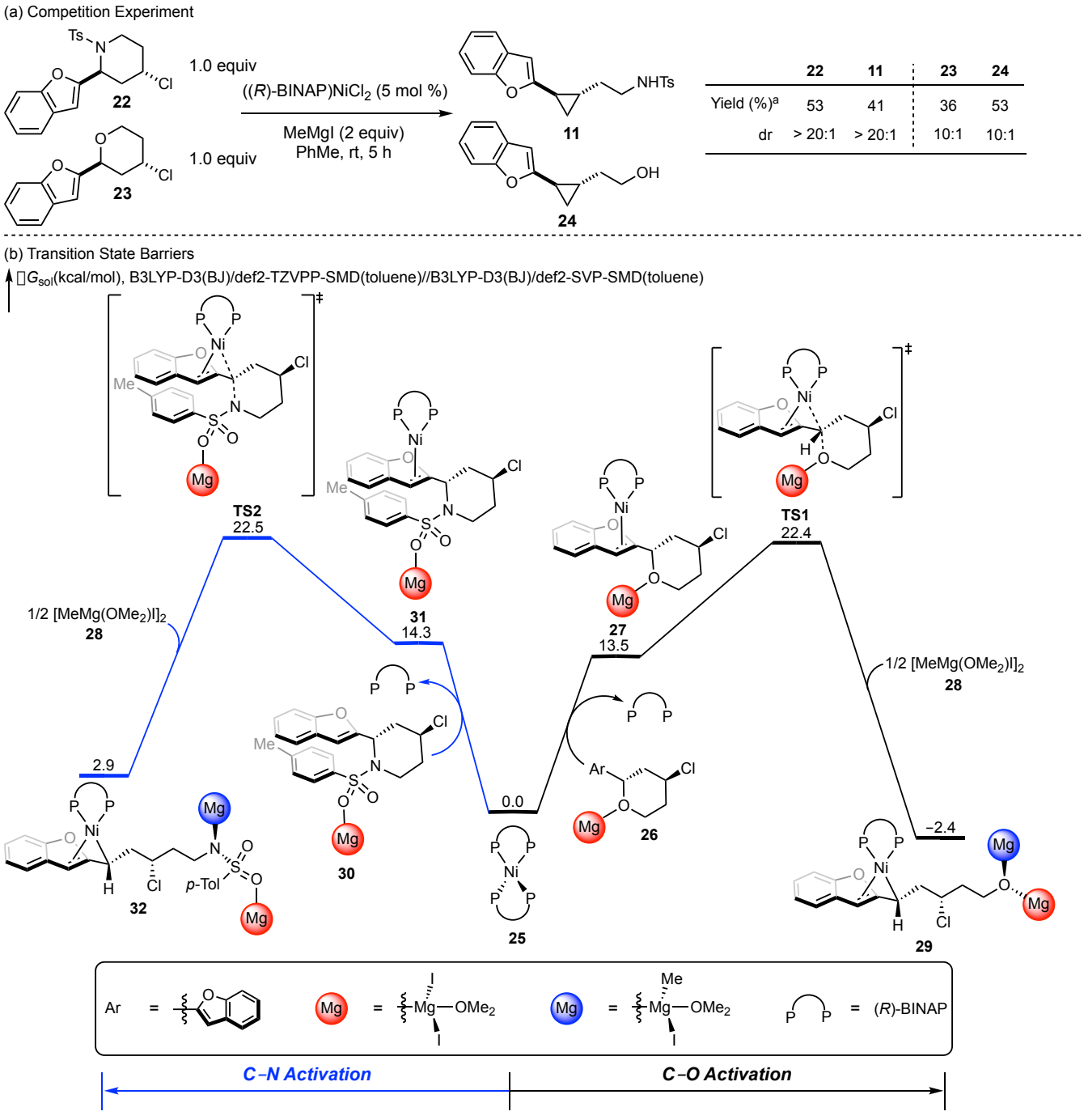


Competition Experiments and Proposed Mechanism. We next sought to decipher the key mechanistic aspects that drive the reaction. The XEC reactions of sulfonamides share many similar features with XEC reactions of ethers (e.g., **23**) that one of our laboratories has previously developed.[17a,17b,28] For example, the XEC reactions of sulfonamide **22** and ether **23** are both facilitated by addition of MgI_2, the optimal catalyst for both reactions is a BINAP-ligated nickel complex, and MeMgI is employed as a reductant in both cases.[29] Therefore, we hypothesized that both reactions should share fundamental mechanistic details. We expected that a competition experiment between *N*-tosyl-4-chloropiperidines and 4-chlorotetrahydropyrans in a ring contraction would provide further insight. Piperidine **22** and tetrahydropyran **23** were subjected to XEC reaction conditions and afforded a mixture of both XEC products in a 1.2:1 ratio, slightly favoring alcohol **24** over sulfonamide **11** (Scheme 3a). These results demonstrate that the XEC reaction of the benzylic sulfonamide and ether have similar barrier heights for the rate-determining step for cyclopropane formation. We hypothesize that this elementary step is the oxidative addition reaction at the benzylic carbon-heteroatom bond.[28]

To gain mechanistic insights into the oxidative addition step for each XEC reaction (Scheme 3b), we have conducted a density functional theory (DFT) study[30] of this process with the B3LYP[31] level of theory with def2-SVP[32] basis set, including solvation energy corrections and Grimme's D3 (BJ-damping) dispersion corrections.[33] The barriers for oxidative addition at the benzylic sulfonamide and benzylic ether are 22.5 and 22.4 kcal/mol, respectively. These barrier heights are similar, in agreement with the results of the competition experiment. Notably, in both oxidative addition reactions MgI_2 plays a key role as a Lewis acid catalyst to activate the carbon-heteroatom bond.[34,28] The

calculated transition state structures also revealed that the geometrical requirements are similar for both elementary steps.

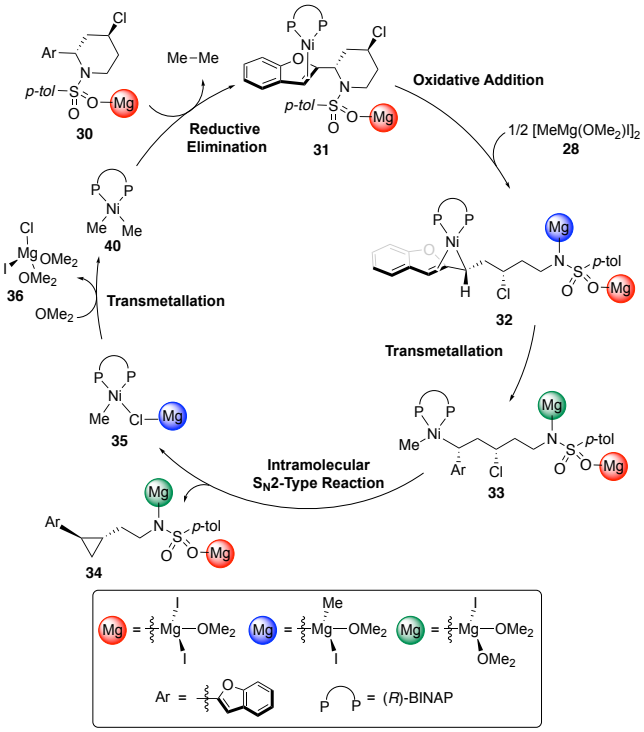
Scheme 3. Competition Experiment and Comparison of Oxidative Addition Barriers



[a]Yield determined by ^{1}H NMR based on comparison to PhTMS as internal standard.

A plausible mechanism for the sulfonamide XEC reaction is shown in Scheme 4. The elementary steps mirror those that we have previously proposed for XEC of benzylic ethers.[28] First, Lewis-acidic MgI_2 binds to the sulfonamide oxygen, activating the sulfonamide for oxidative addition. The nickel catalyst binds to the arene, followed by rate-determining oxidative addition of the C–N bond. Next, transmetallation with methylmagnesium iodide affords Ni(II) species **33**. This key intermediate undergoes an intramolecular reaction between the benzylnickel moiety and the alkyl chloride, inverting both stereocenters and releasing cyclopropane product **34**. From the perspective of the benzylnickel moiety, the cyclopropane-forming step can be envisioned as an intramolecular, invertive S_E2-type reaction.[35,36] In the context of the alkyl chloride center, the cyclopropane-generating step is visualized as an intramolecular, invertive S_N2-type reaction.[37] A second transmetallation followed by reductive elimination of ethane regenerates the active nickel catalyst. Although further experiments are necessary to fully elucidate the mechanism of the sulfonamide XEC reaction, the above competition experiment data, DFT calculations, and analogies to related ring contractions offer a substantial foundation. This mechanistic understanding will aid in the future development of innovative XEC reactions of amine derivatives.

Scheme 4. Proposed Mechanism for Sulfonamide XEC



CONCLUSION

This work represents the first cross-electrophile coupling reaction of benzylic sulfonamides. The reaction employs an air-stable nickel(II) catalyst to affect the intramolecular XEC of sulfonamides to generate arylcyclopropanes, as well as the ring contraction of *N*-tosylpiperidines to afford aryl and vinylcyclopropanes with pendant sulfonamides. The ring contractions proceed in excellent diastereoselectivity, and represents a new sulfonamide skeletal rearrangement with potential applications in medicinal chemistry. The synthetic utility of the products is further exemplified by derivatization of sulfonamide **11** to afford valuable functionalities such as pyrrolidines and sulfonimides. Finally, competition experiments and computational studies are consistent with initiation of the reaction by oxidative addition of the C–N bond. This work establishes precedent for the cross-electrophile coupling reaction of unstrained and neutral sulfonamides, and provides a framework that will be beneficial to guide development of new catalysts for the activation of other strong C–N bonds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, NMR spectra, computational details, energies and Cartesian coordinates of calculated structures. (PDF).

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Notes

The authors declare no competing financial interest.

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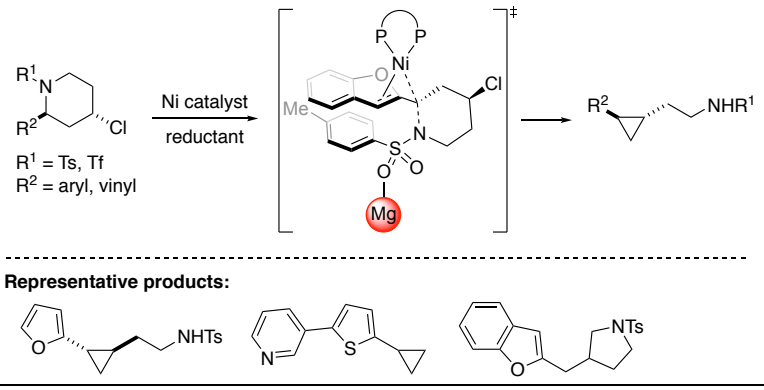

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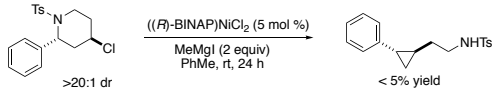
[21] A simple benzylic substrate was subjected to the XEC reaction and provided the desired product in < 5% yield.



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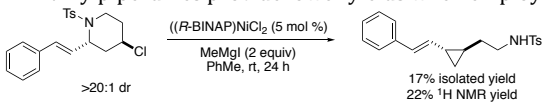

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