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Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Ethers: Enantioselective Synthesis of Diarylethanes

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Abstract: Secondary benzylic ethers undergo stereospecific substitution reactions with Grignard reagents in the presence of nickel catalysts. Reactions proceed with inversion of configuration and high stereochemical fidelity. This reaction allows for facile enantioselective synthesis of biologically active diarylethanes from readily available optically enriched carbinols.

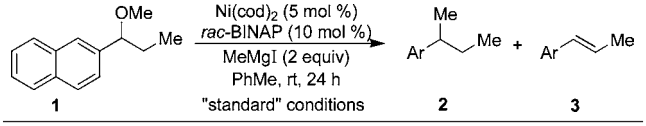
Despite the historical and pedagogical importance of the S_N2 reaction in organic chemistry, reaction of a carbon nucleophile with a secondary electrophile to generate a tertiary carbon stereocenter with inversion of configuration remains an atypical disconnection in complex molecule synthesis. While organocuprate displacement reactions achieve such transformations,[1] these reactions are generally substrate dependent.[2] Cross-coupling reactions utilizing nickel catalysts could provide an alternative strategy; however, during reactions of alkyl halides stereochemical information is lost.[3,4] Stereospecific nickel-catalyzed alkyl−alkyl cross-coupling reactions, where stereochemical information from the alkyl halide or pseudohalide is conserved with an achiral catalyst, have not been reported.[5,6]

We hypothesized that alkyl ethers would be suitable electrophilic partners for stereospecific alkyl−alkyl cross-coupling reactions because C−O bonds are likely to undergo heterolytic cleavage and, therefore, stereospecific oxidative addition reactions. The rich literature of nickel-catalyzed substitution reactions of allylic ethers is consistent with this hypothesis.[7] We chose reaction conditions inspired by recent studies aimed to accelerate oxidative addition of nickel catalysts with unactivated sp^3 C−O bonds.[8] At the outset, we recognized that reaction conditions would need to be modified because reported reactions of secondary alcohol derivatives require elevated temperatures and often provide low yields of products due to competitive β-hydride elimination.[8a]

Our studies began with an examination of reaction conditions to accelerate the desired cross-coupling reaction of substrate **1a**, while minimizing β-hydride elimination (Table 1). Our investigations began by utilizing benzylic ethers, with the goal of developing enantioselective syntheses of diarylethanes (vide infra). We hypothesized that ligands that facilitate formation of an η^3-arylalkyl complex would accelerate the reaction by lowering the transition state energy that leads to oxidative addition. To identify such ligands, we examined a series of bidentate phosphines[9] and found that BINAP provided the optimal product distribution. Control experiments illustrate the importance of suppressing the formation of alkene **3** from β-hydride elimination (entries 5 and 6). In addition to diminishing the yield of the desired cross-coupled product, styrenes have a detrimental effect on the reaction; addition of only 20 mol % of styrene effectively inhibits the desired cross-coupling reaction.[10]

We next examined the cross-coupling of enantioenriched ether **1** under the optimized reaction conditions (Table 2, entry 1). In the presence of a nickel catalyst and *racemic* BINAP, stereospecific cross-coupling of enantioenriched ether **1** provides enantioenriched **2**. The reaction proceeds with inversion of configuration and high stereochemical fidelity.[11]

Table 1. Variation of Reaction Conditions

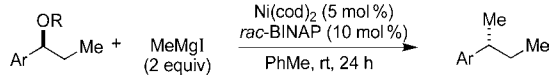


1 2 3

entry	variation from standard conditions	yield **2** (%)[a]	yield **3** (%)[a]
1	none	77	19
2	dppf instead of *rac*-BINAP	8	80
3	DPEphos instead of *rac*-BINAP	52	48
4	Xantphos instead of *rac*-BINAP	46	42
5	20 mol % **3** added	58	7
6	20 mol % styrene added	12	6

[a] Yield determined by ^{1}H NMR spectroscopy by comparison to an internal standard ($PhMe_3Si$).

Table 2. Stereospecific Cross-Coupling Reactions



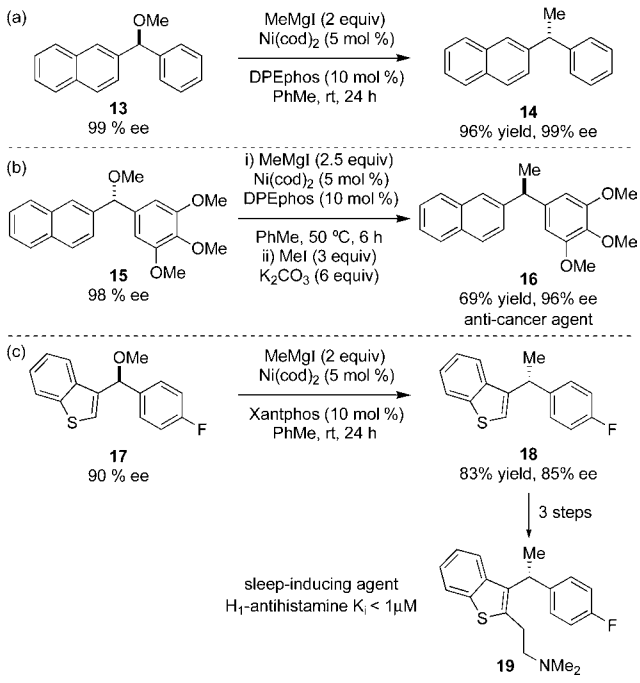
entry	substrate, (ee (%))[a]	product	yield (%)[b]	ee (%)[a]
1	**1** R = Me (96)	**2**	72	94
2[c]	**4** R = Bn (95)	**2**	72	96
3	**5** (89)	**6**	70	85
4[d]	**7** (90)	**8**	71	90
5[d]	**9** (86)	**10**	82	87
6[d]	**11** (95)	**12**	87	95

[a] %ee determined by SFC. [b] Isolated yield after column chromatography. [c] Reaction run at 35 °C instead of rt. [d] DPEphos used instead of *rac*-BINAP.

Stereospecific cross-coupling proceeds smoothly with a series of enantioenriched benzylic ethers (Table 2). We examined three ligands, *rac*-BINAP, Xantphos, and DPEphos, with each substrate.[12] In general, the highest yields were obtained by using *rac*-BINAP for substituted naphthalenes and DPEphos for substituted heterocycles. Benzyl ether **4** reacted similarly to the methyl ether **1** (entry 2).[13,14] In all cases, the reaction was stereospecific and provided product in enantiomeric excesses similar to those of the starting ether. This method accomplishes smooth translation of stereochemical information from a secondary carbinol to a tertiary stereocenter. This strategy is particularly practical since there are many outstanding methods for the enantioselective synthesis of secondary carbinols.[15,16]

We sought to apply this reaction in the synthesis of enantioenriched diarylethanes, a structural motif which exhibits a diverse range of biological properties, including anticancer, antidepressant, and antiviral activity.[17] While creative approaches to the enantioselective synthesis of this moiety exist,[18] most require inclusion of functional group handles that are later removed. Classical resolution by crystallization of diastereomeric salts is frequently the most practical method for the preparation of enantioenriched diarylmethanes. We envisioned a direct synthesis of enantioenriched diarylethanes from readily available diarylmethanols.[19] Under our standard reaction conditions, nickel-catalyzed cross-coupling of diarylmethanol **13** proceeded with high stereochemical integrity and in good yield to afford **14** (Scheme 1).

Scheme 1. Synthesis of Enantioenriched Diarylethanes



To highlight the potential applications of this method, we examined cross-couplings of ethers **15** and **17**. Benzylic ether **15** underwent cross-coupling with high stereochemical fidelity to provide enantioenriched diarylethane **16**. Racemic **16** is a potent inhibitor of tubulin polymerization.[20] During the course of the reaction, a portion of the material underwent deprotection of the *para*-methoxy group.[21] Therefore, the unpurified reaction mixture was treated with methyl iodide to reinstall the ether and obtain a high yield of **16**. Benzothiophene **19**, an anti-insomnia agent, was also prepared in enantioenriched form.[22] Cross-coupling of diarylmethanol **17** provided the requisite tertiary stereogenic center; subsequent functionalization of the benzothiophene ring was accomplished using literature methods.[23b]

In summary, selective formation of tertiary stereogenic centers has been achieved using a stereospecific nickel-catalyzed cross-coupling reaction. This strategy provides a new synthesis of enantioenriched 1,1-diarylalkanes, important pharmacophores in medicinal chemistry. Efforts to expand the scope of this transformation and elucidate the mechanistic details are underway.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Absolute configurations of **1** and **2** were assigned based on comparison of optical rotations to literature values. See Supporting Information for details.

(12) See Supporting Information for details.

(13) Notably, substitution occurs α to the naphthalene ring, not the phenyl ring. Consistent with this observation, simple benzylic ethers do not undergo cross-coupling under these reaction conditions (see Supporting Information for details). These observations are consistent with the greater stability of arylalkylmetal complexes containing extended aromatic systems.

(14) Substitution of methylmagnesium iodide with *n*-propylmagnesium iodide in cross-coupling reactions with ether **5** provided cross-coupled product, albeit in variable yield (between 14−65%).

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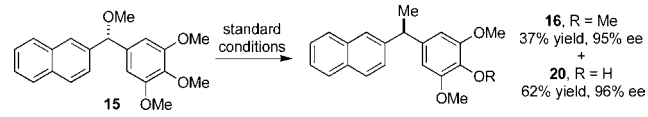
(21) ^{1}H NMR analysis of the unpurified reaction mixture showed that a mixture of **16** and phenol **20** was formed. These compounds could be separated; however, for convenience we treated the mixture with methyl iodide to reinstall the *p*-methoxy group. See Supporting Information for full details.



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