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Nickel-Catalyzed C-O Cross-Coupling Reaction at Low Catalytic Loading and Weak Base Participation

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Abstract: Herein, we report a nickel-catalyzed crossing-coupling reaction for the synthesis of diaryl ethers. The desired products are achieved by coupling heterocyclic alcohols with aryl bromides bearing strong electron withdrawing nitro group under the catalyst system of $NiCl_2(PPh_3)_2$ and weak base $KHCO_3$. This mild reaction exhibits a broad functional group tolerance. Compound **4** as an important intermediate is suitable for further structural modification of MALT1 inhibitor MI-2.

Introduction

Diaryl ethers are an important class of organic compounds throughout the pharmaceuticals and agricultural chemicals.[1] The development of useful methods for preparing diaryl ethers has received continuous attention from the synthetic community.[2] Among the existing methods, metal-catalyzed cross-coupling reactions as the most important transformations have been intensively applied in both academia and industry fields.[2b,3] For example, Cu-[3d,4] and Pd-catalyzed[5] C-O bond-forming reactions have become fast and economical methods to synthesize aryl ethers,[3a,6] and those methods are often used in the reactions between aryl halides with phenols or alcohols.[7]

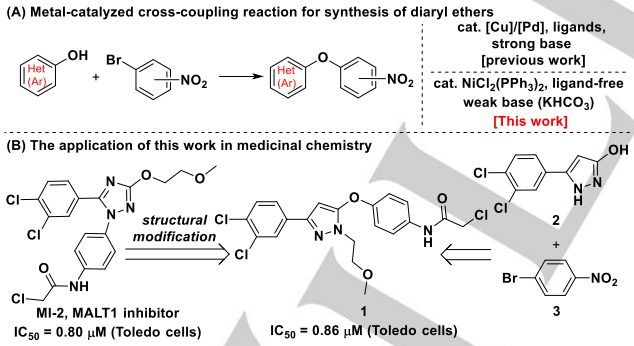
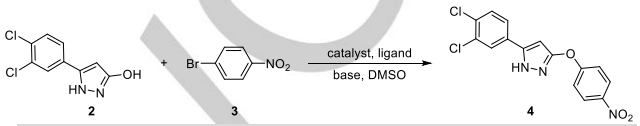


Figure 1. Recent work for the synthesis of diaryl ethers and the application of this work.

At current stage, with the emergence of various catalytic systems,[5h,8] some significant improvements have been made for the both reaction conditions. A dramatic increase of reaction yields have been realized using strong bases,[2f,9] novel ligands,[10] and high reaction temperature (Figure 1A).[4b,11]

MI-2 is an irreversible MALT1 inhibitor featuring direct binding to MALT1 and suppression of its protease function.[12] As a new skeleton, compound **1** is a structural modification of MI-2 and exhibits a nearly equipotent antiproliferative effect with MI-2 in Toledo cells (Figure 1B).[12b] During the synthesis of **1**, the key intermediate **4** was obtained by coupling **2** and **3** with the above modified reaction condition (Table1, entry 2). However, when we conducted a large-scale production with same reaction condition, the desired product **4** was observed with a significant decrease in efficiency. In this case, we decided to explore the one more optimal reaction conditions.

Table 1. Optimization of the reaction conditions.[a]



2 3 4

entry	catalyst	ligand	base	yield(%)[b]
1	CuI	L-proline	K_3PO_4	<5
2[c]	CuI	L-proline	Cs_2CO_3	49(45)
3	CuI	L-proline	K_2CO_3	58
4	$CuSO_4$	EDTA	K_2CO_3	63
5	$NiCl_2·6H_2O$	EDTA	K_2CO_3	69
6[d]	$NiCl_2(PPh_3)_2$	EDTA	K_2CO_3	79
7	$NiCl_2(PPh_3)_2$	-	K_2CO_3	81
8[e]	$NiCl_2(PPh_3)_2$	-	$KHCO_3$	91
9[e,f]	$NiCl_2(PPh_3)_2$	-	$KHCO_3$	97(85)
10	-	-	$KHCO_3$	0

[a] Reaction condition: **2** (0.05 mmol), **3** (1.0 equiv), base (1.0 equiv), DMSO (1 mL), catalyst (10 mol%), ligand (20 mol%), 90 °C for 16 h under argon atmosphere. [b] Determined by 1H NMR analysis of the crude products. The isolated yield is given in parentheses. [c] The reaction time was 2.5 h. [d] The reaction time was 7 h. [e] **2** (0.3 mmol), **3** (1.2 equiv), base (1.5 equiv). [f] $NiCl_2(PPh_3)_2$ (1 mol%).

Results and Discussion

We began our studies by using 5-(3,4-dichlorophenyl)-1H-pyrazol-3-ol **2** and 1-bromo-4-nitrobenzene **3** as the model substrates. After considerable efforts, the optimized reaction conditions were found to furnish the desired product efficiently. Initially, we chose K_3PO_4 as the base in the presence of CuI and L-proline, but no significant reaction was observed (entry 1). K_2CO_3 showed higher reactivity, providing the product in 58% yield (entry 3). On this basis, we screened different catalysts and found that the $NiCl_2(PPh_3)_2$ provided the optimal result (entry 4-6). The product was afforded in 79% yield when EDTA as ligand. Interestingly, there was a significant increase in yield without ligand involvement (entry 7). The capability of $KHCO_3$ was better

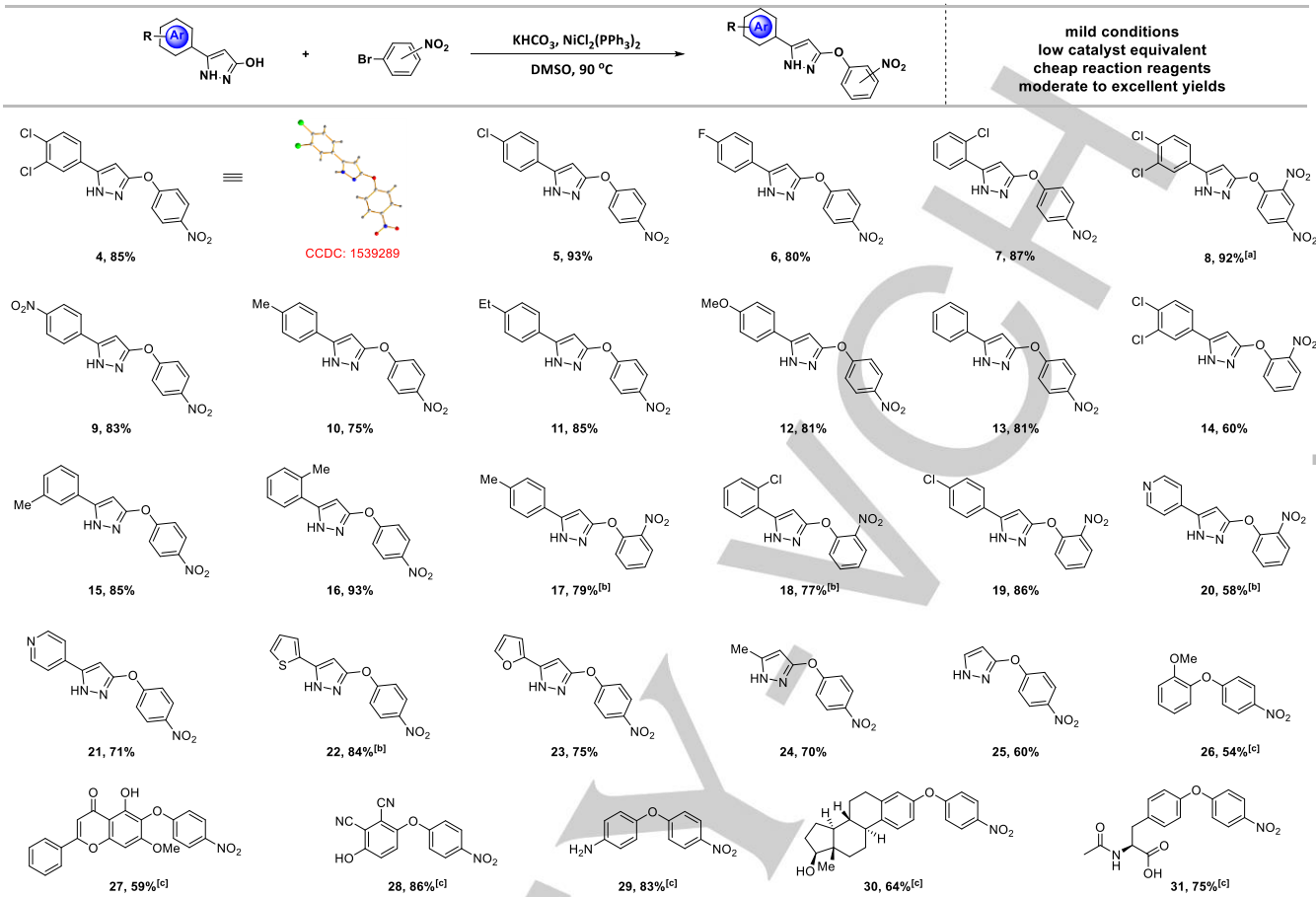


Figure 2. Reaction conditions: Heterocyclic alcohols (0.3 mmol), aryl bromides (1.2 equiv), $KHCO_3$ (1.5 equiv), $NiCl_2(PPh_3)_2$ (1 mol%), 90 °C, 16 h, Ar, isolated yield. [a] The reaction was carried out at r.t. for 1 h. [b] The reaction was carried out at 95 °C. [c] Please see supporting information for detailed reaction conditions.

than K_2CO_3, providing **4** in the yield of 91% (entry 8). Weak base participation is more suitable for this reaction to avoid the undesired products. Further optimization showed that 1 mol% of $NiCl_2(PPh_3)_2$ is optimal (entry 9).

Having established the optimal reaction conditions, the substrate scope was then investigated to examine the generality of this protocol. As shown in Figure 2, the reaction conditions could be applied to various of substrates, to provide the corresponding products in moderate to excellent yields. Notably, the fluoro, chloro, and nitro in heterocyclic alcohols were all tolerated in our catalytic system, and the corresponding products (**4-9**, **14**, **18**, **19**) were obtained in good yields. The chemical structure of **4** was further established by X-ray crystallographic. Certainly, different electron-donating groups, such as methyl, methoxy and ethyl were satisfactory substrates giving the corresponding arylated products (**10-12**, **15-17**) in high yields. The optimized reaction conditions could be applied to various heterocycle or groups affording the desired products **20-25** in 58-84% yields. Finally, when the standard reaction conditions are changed, the method is also suitable for the synthesis of complex compounds no containing pyrazole ring, leading to the formation of **26-31** in 54-86% yields.

Gram-scale synthesis of compound **1** was started from compound **4** via three-step reactions (Figure 3A). The predicted conformation of compounds **1** and MI-2 with MALT1 was evaluated by using the AutoDock Vina algorithm (Figure 3B).[13] The molecular docking results suggest that compound **1** and MI-2 have excellent binding affinity to MALT1.

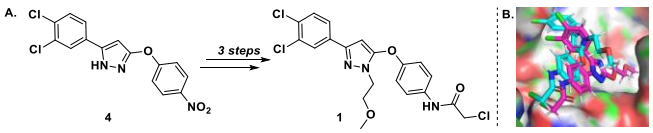


Figure 3. (A) Three-step synthesis of compound **1** (gram- scale). (B) Predicted binding mode of **MI-2** (magenta) and **1** (light blue) to MALT1**.**

According to the previous literature,[8f,14] the possible reaction pathway is proposed in Figure 4. The active Ni(0) species **I** which may be generated in situ in the presence of $KHCO_3$ under the reaction conditions. Ni(II) species **II** is formed via the oxidative addition of active Ni(0) with substrate. Coordination of the heterocyclic alcohol to key species **II**, followed by deprotonation, would form complex IV. Reductive elimination of IV delivered diaryl ether and regenerate the catalytic species **I**.

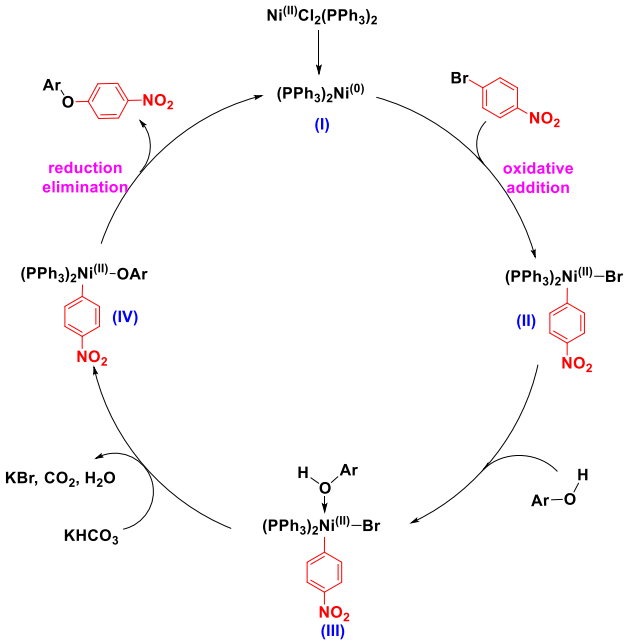


Figure 4. Proposed mechanism for C-O cross-coupling reaction.

Conclusions

In conclusion, a low dosage $NiCl_2(PPh_3)_2$ and weak base $KHCO_3$ catalytic system has been developed for the aromatic C-O coupling reaction. This reaction proceeds under mild reaction conditions and is applicable to a wide variety of substrates with strong electron-withdrawing nitro group. This new protocol can complement existing reaction methods.

Experimental Section

General Procedure for the formation of diaryl ethers. To a vial equipped with a magnetic stirrer bar were added heterocyclic alcohols (0.3 mmol), aryl bromides (0.36 mmol), DMSO (1 mL), $KHCO_3$ (0.45 mmol) and $NiCl_2(PPh_3)_2$ (1 mol%). The reaction mixture was stirred at 90 °C under argon atmosphere. After the reaction was completed (monitored by TLC analysis), the mixture was poured into 0.5 N HCl solution and the aqueous phase was extracted with EtOAc. The organic layer was washed sequentially with H_2O and brine, then dried over Na_2SO_4. The solvent was removed under vacuo and the crude product was purified by chromatography on silica gel to give the desired product.

CCDC 1539289 (for 4) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Acknowledgements

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Keywords: Nickel-catalyzed • low catalytic loadings • weak base • MALT1 inhibitor • MI-2

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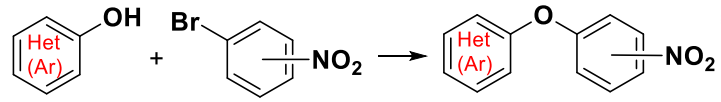
Entry for the Table of Contents

Key Topic: Cross Coupling



$NiCl_2(PPh_3)_2$, ligand-free, weak base ($KHCO_3$) [This work]

Nickel-Catalyzed C-O Cross-Coupling Reaction at Low Catalytic Loading and Weak Base Participation

A series of diaryl ethers have been synthesized through nickel-catalyzed C-O cross coupling by using a low dosage $NiCl_2(PPh_3)_2$ and weak base $KHCO_3$ under mild conditions.

F. Wu, K. Zhu, G. Wu, Y. Gao, H. Chen*