**Screening of a Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides**

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**Background:**

The development of cross-electrophile coupling (XEC) methods has rapidly advanced in response to the limitations of conventional cross-coupling reactions. This project aimed to evaluate how different substrates and conditions affect an XEC reaction and to incorporate this analysis into a practical laboratory exercise for a future CHEM 346 course.

Conventional cross-coupling reactions construct C-C bonds between an electrophile and a nucleophile. Yet, there exist a few limitations. First, the commercial availability of nucleophiles is less than their corresponding electrophiles, restricting the diversity of potential coupling partners.1 Second, special conditions are needed for certain nucleophiles due to their reactive and unstable nature. Third, the inherent reactivity of nucleophiles can interfere with other electrophilic function groups, which lowers the function group compatibility. These limitations stem from the use of nucleophilic reagents, and an alternative approach, such as cross-electrophile coupling reactions without nucleophilic reagents, would be desirable.

The cross-electrophile coupling reaction in this research constructs a C-C bond between two electrophilic halides (**Scheme 1**).2,3 A Ni(II) catalyst was used to facilitate this reaction. Five aryl halides and five alkyl halides, each with different stereoelectronic properties, were used to assess their effect on reaction yield and side reaction pathways.



**Scheme 1**. General reaction scheme for the cross-electrophile coupling of aryl halides with alkyl halides.

**Results:**

Initial replication of the literature procedure yielded no product with NiI2 and NiBr2· xH2O as the metal salt. Low conversion (21 %) was achieved with NiBr2· dme, which was better dissolved in solvents. These results indicated metal salts' solubilities are crucial in promoting reactivity. Further screenings were conducted using DMA, NMP, and DMPU solvent, with NMP yielding the highest. Timepoints between 1 and 24 hours showed no increase in yield, likely indicating the mixture extraction process introduced air that degraded the active catalysts.

Another screening was conducted between an N2-purged solvent condition and an Ar atmosphere condition. Results showed a significant increase in yield to an average of 60. Yet, there was no difference between the two tested conditions, indicating that purged solvent was the key contributing factor. This result was likely due to the small scale of the reaction (0.025 mmol), allowing unpurged solvent oxygen to oxidize the active catalyst completely.

Based on the previous results, the following screenings used N2-purged NMP solvents. Smaller vials were used to decrease the empty headspace. These measures led to successful substrate screenings of the reaction, with all reactions exhibiting reasonable reactivity.

The experimental data revealed several trends in the reactivity (**Scheme 2**). First, primary alkyl halides (**A1**-**A3**) exhibited good reactivity, suggesting that less hindered alkyl substrates favor product formation. Second, secondary and tertiary halides (**A4**, **A5**) were associated with diminished yield, potentially due to increased steric hindrance during oxidative addition. Third, the α-ester group in **A5** enhanced reactivity despite worse steric hindrance than **A4**. This result was likely due to more stabilized intermediate radicals with the electron-withdrawing ester group, supporting the proposed radial chain theory in the mechanism.3

For aryl halides, there was a clear preference for more electron-poor substrates. Ortho-substituted substrates **E4** led to much lower yields than para **E1**, likely due to increased steric hindrance. Comparable high yields were observed with smaller ortho substituents like nitrile (**E5**), reaffirming the impact of aryl halides steric hindrance on the reaction.



**Scheme 2.** Screening data for the cross-electrophile coupling of aryl halides with alkyl halides.

**Significance:**

This study underscores the critical role of metal solubility and solvent preparation in cross-electrophile coupling reactions between aryl halides with alkyl halides, with NMP solvent and N2-purged conditions significantly increased yields. Less sterically hindered primary alkyl halides and electron-poor aryl halides were the more reactive. Steric hindered second and tertiary alkyl substrates also exhibited reactivity albeit with lower yield. These data can provide helpful information regarding substrate selection in future synthesis using this reaction.

**References:**

1. Everson, D. A.; Weix, D. J. Cross-Electrophile Coupling: Principles of Reactivity and Selectivity. *J. Org. Chem.* **2014**, *79* (11), 4793–4798.

This paper provides helpful information as to the reason behind the development of XEC reactions.

1. Johnson, K. A.; Biswas, S.; Weix, D. J. Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chemistry – A European Journal* **2016**, *22* (22), 7399–7402.

The benchtop experimental procedure in this paper was initially followed and later modified.

1. Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc. Chem. Res.* **2015**, *48* (6), 1767–1775.

The proposed mechanism in this paper was used to justify the tertiary alkyl substrate result.

1. Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135* (43), 16192–16197.

This paper provides helpful insight into the mechanism and selectivity of the Nickel-Catalyzed XEC reactions.

1. Aguirre, A. L.; Loud, N. L.; Johnson, K. A.; Weix, D. J.; Wang, Y. ChemBead Enabled High-Throughput Cross-Electrophile Coupling Reveals a New Complementary Ligand. *Chemistry – A European Journal* **2021**, *27* (51), 12981–12986.