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A Widely Applicable Dual Catalytic System for Cross-Electrophile Coupling Enabled by Mechanistic Studies

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Abstract

A dual catalytic system for cross-electrophile coupling reactions between aryl halides and alkyl halides that features a Ni catalyst, a Co cocatalyst, and a mild homogeneous reductant is described. Mechanistic studies indicate that the Ni catalyst activates the aryl halide, while the Co cocatalyst activates the alkyl halide. This allows the system to be rationally optimized for a variety of substrate classes by simply modifying the loadings of the Ni and Co catalysts based on the reaction product profile. For example, the coupling of aryl bromides and aryl iodides with alkyl bromides, alkyl iodides, and benzyl chlorides is demonstrated using the same Ni and Co catalysts under similar reaction conditions but with different optimal catalyst loadings in each case. Our system is tolerant of numerous functional groups and is capable of coupling heteroaryl halides, di-*ortho*-substituted aryl halides, pharmaceutically relevant druglike aryl halides, and a diverse range of alkyl halides. Additionally, the dual catalytic platform facilitates a series of selective one-pot three-component cross-electrophile coupling reactions of bromo(iodo)arenes with two distinct

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Supporting Information

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General methods and instrumentation methods, procedure for cross-electrophile coupling of aryl and alkyl halides, reactivity of (dtbbpy)Ni^{II}(*o*-tol)I with TDAE, varying (dtbbpy)$Ni^{II}Br_2$ loading in dual-catalyzed cross-electrophile coupling of iodobenzene with benzyl chloride, stoichiometric $C(sp^2)$–$C(sp^3)$ bond formation with (dtbbpy)Ni^{II}(*o*-tol)I, radical trapping experiments with TEMPO, optimization of cross-electrophile coupling of phenyl iodide with 1-iodo-3-phenylpropane, optimization of concentration, solvent screen, and temperature, effect of aryl halide *ortho*-substitution on optimization of catalyst loadings, additional reactions for two-component and three-component cross-electrophile couplings, optimization of single-step one-pot three-component coupling, procedure for optimization of two-step one-pot three-component coupling for ^{1}H NMR yields, high-throughput experimentation for optimization of druglike aryl halides, additional reactions for druglike aryl halide cross-electrophile coupling, parallel library synthesis using substrate **5f**, procedure and general information of 3 mmol scale reaction of **5f** with 1-iodo-3-phenylpropane, isolation procedures and characterization of products of two-component cross-electrophile coupling, two-step one-pot three-component coupling, and two-component cross-electrophile coupling with druglike aryl halides, procedure for ^{1}H NMR yields of products, NMR spectra of isolated products, and ultraperformance liquid chromatography traces from HTE experiments (PDF)

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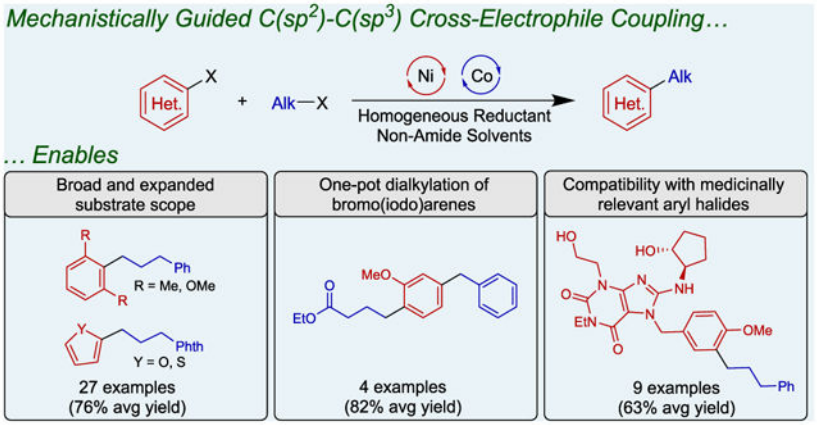
alkyl halides. This demonstrates the unique level of control that the platform provides and enables the rapid generation of molecular complexity. The system can be readily utilized for a wide range of applications as all reaction components are commercially available, the reaction is scalable, and toxic amide-based solvents are not required. It is anticipated that this strategy, as well as the underlying mechanistic framework, will be generalizable to other cross-electrophile coupling reactions.

Graphical Abstract



Keywords

cross-electrophile coupling; nickel; medicinal chemistry; synthetic methods; mechanism

INTRODUCTION

Cross-electrophile coupling in which two electrophiles are coupled in the presence of a reducing agent is a powerful method for C–C bond formation that complements, extends, and provides orthogonal reactivity to traditional cross-coupling reactions.[1] In particular, nickel-catalyzed cross-electrophile coupling reactions that generate new C(sp^2)–C(sp^3) bonds have received significant attention over the last decade due to the prevalence of these linkages in natural products and pharmaceuticals and the limitations of the current synthetic methods to form these bonds (Figure 1a).[2] Despite the widespread interest, there is still only a limited amount of knowledge about key elementary reactions in the proposed mechanism of these reactions (Figure 1b).[3] As a result, reaction development has relied on the empirical screening of a wide range of reaction parameters.[4] Using this strategy, it is often unclear how individual elementary reactions are affected by changes in reaction conditions, which can result in reaction development that is often specific to a limited range of substrates and involves the use of inscrutable additives.[5] This is especially the case when coupling more complex, pharmaceutically relevant substrates.[6] An increased understanding of the mechanism of cross-electrophile coupling reactions could result in the development of more practical systems with broader substrate scopes.

There are two areas where greater understanding of the mechanism of nickel-catalyzed cross-electrophile coupling reactions between alkyl and aryl halides could provide opportunities for improved transformations. The first is related to the pathway by which the alkyl halide is activated to generate a transient radical. In the proposed mechanism, the alkyl halide is proposed to be activated through a radical chain process initiated by an on-cycle Ni^{I} halide complex (Figure 1b), which presents two complications for reaction optimization.[3a] First, it is unclear how Ni^{I} halide species are initially formed as in the current mechanism, an alkyl radical is required to generate the Ni^{I} halide species, which in turn, is needed to generate an alkyl radical.[7,8] Second, the Ni^{I} halide that generates a radical is in the same catalytic cycle as the intermediate that captures the radical, $LNi^{II}(Ar)X$ (Figure 1b). As a result, the rate of radical generation cannot be independently tuned relative to the rate of radical capture, which lowers our ability to control the relative rates of the key steps during catalysis. An appealing solution to circumvent both of these challenges is to employ a cocatalyst that has the sole role of independently generating a radical from the alkyl halide. The use of cocatalysts to generate alkyl radicals has already been implemented by several groups using substrates including epoxides[2i,j,ak] and alkyl (pseudo)halides.[9] However, expanding upon this methodology could enable rational control of catalytic systems, leading to more widely applicable reaction conditions.[10]

The second area where greater mechanistic understanding could provide opportunities for improved transformations is related to the reduction of catalytic intermediates (Figure 1b). Typically, heterogeneous reductants such as Zn^{0} and Mn^{0} are utilized in nickel-catalyzed reductive couplings, but our understanding of the mechanism of electron transfer from a solid-state reductant to a solution-state catalyst is limited.[11] As a result, it is unclear how changes to the solvent and ancillary ligand, as well as the introduction of additives, impact electron transfer events, which makes it difficult to predictably control the rate of reduction in cross-electrophile coupling reactions. Heterogeneous reductants also present practical limitations as reaction success can vary with scale due to mass transfer issues and irreproducible kinetics, and they are often only effective when utilized in highly toxic amide-based solvents.[12] Furthermore, they raise major challenges for the potential application of cross-electrophile coupling reactions in flow chemistry or automated chemical synthesis.[13] To this end, homogeneous organic electron donors (OEDs), which have more well-defined mechanisms of electron transfer, are an attractive alternative to heterogeneous reductants that could help to address these limitations and expand the generalizability of cross-electrophile coupling.[14] To date, a limited number of $C(sp^2)$–$C(sp^3)$ cross-electrophile couplings have been reported that utilize homogeneous OEDs (vide infra);[15,9a,16] however, the utility of these reactions is limited, especially in comparison to systems that utilize heterogeneous reductants. Furthermore, the potential benefits of using OEDs in tandem with a radical generating cocatalyst have not been evaluated.

Here, we leverage the combined effects of a weak homogeneous reductant and a radical generating cocatalyst in Ni-catalyzed cross-electrophile coupling to report one of the most active and operationally simple systems for the coupling of aryl and alkyl halides (Figure 1c). We demonstrate that the product profile encodes mechanistic details about the fate of the $LNi^{II}(Ar)X$ intermediate, and by varying the ratio of the nickel and cobalt catalysts, we can control whether this intermediate traps a radical, which leads to productive catalysis, or

undergoes deleterious off-cycle processes. As a result, a wide range of aryl halides can be coupled with alkyl halides in high yield, including challenging substrates such as di-*ortho*-substituted arenes and heteroarenes. The unique control that our strategy offers is highlighted through a series of novel one-pot three-component couplings of bromo(iodo)arenes with two distinct alkyl electrophiles. Furthermore, we demonstrate the utility of our dual catalytic platform in complex molecule synthesis by performing reactions using medicinally relevant substrates. From a practical perspective, our system allows challenging cross-electrophile coupling reactions to be performed using commercially available starting materials, including a homogeneous reductant, which provides advantages in terms of both scope and practicality compared to reactions with heterogeneous reductants. Additionally, from a mechanistic perspective, we present a dual catalytic strategy that may be broadly translatable to a variety of reductive transformations.

RESULTS AND DISCUSSION

Development of a Dual Catalytic System for Cross-Electrophile Coupling.

Complexes of the type $LNi^{II}(Ar)X$ (X = Cl, Br, or I), which arise from oxidative addition of an aryl halide to a coordinatively unsaturated Ni^0 species, are proposed to be key intermediates in cross-electrophile coupling because they are likely the catalyst resting state and are responsible for capturing alkyl radicals (Figures 1b and 2).[3a] In an ideal cross-electrophile coupling reaction, the $LNi^{II}(Ar)X$ intermediate would be stable and the rate at which reactive radicals are generated would be optimized relative to the concentration of $LNi^{II}(Ar)X$ to facilitate effective radical capture. In current systems for cross-electrophile coupling, the rate of alkyl radical generation by a Ni^I halide cannot be tuned independently of the concentration of $LNi^{II}(Ar)X$ because they are connected (vide supra). Additionally, under the reaction conditions typically utilized, $LNi^{II}(Ar)X$ complexes are unstable and can undergo two deleterious side reactions: (i) bimolecular decomposition via a process involving ligand rearrangement between two molecules of $LNi^{II}(Ar)X$ to form $LNi^{II}X_2$ and $LNi^{II}(Ar)_2$, which in turn undergoes reductive elimination to generate a biaryl and a Ni^0 species (Figure 2)[3d,17] or (ii) direct reduction (depending on the reaction conditions and the reductant) to highly unstable $LNi^{I}(Ar)$ species, which typically decompose to give coordinatively unsaturated Ni^0 species as well as aryl and biaryl products (Figure 2).[3c,d,11b,18] We hypothesized that we could solve these challenges and improve cross-electrophile coupling reactions by developing a strategy in which: (i) a well-defined cocatalyst is used to generate a radical from an alkyl electrophile so that the concentration of $LNi^{II}(Ar)X$ can be controlled relative to the concentration of alkyl radicals, (ii) reactions are performed at low nickel loadings so that radical capture by $LNi^{II}(Ar)X$ is favored over bimolecular decomposition, and (iii) a reductant that is weaker than Zn^0 or Mn^0, but still able to reduce $LNi^{II}X_2$, is used so that the reductive decomposition of $LNi^{II}(Ar)X$ is minimized.

A recent example of a cross-electrophile coupling reaction using a weaker reductant than Zn^0 was described by Weix and co-workers.[15a] They demonstrated that $(dtbbpy)Ni^{II}Br_2$ (dtbbpy = 4,4′-ditertbutyl-2,2′-bipyridine) is an effective precatalyst for the coupling of a limited range of alkyl halide electrophiles, such as benzyl chlorides, with aryl iodides using

tetrakis(dimethylamino)ethylene (TDAE), a homogeneous OED with E° = −0.57 V vs NHE,[11b] as the reductant (Scheme 1).[19] Apart from being a weaker reductant than Mn^0 (E° = −1.19 V vs NHE)[11b] or Zn^0 (E° = −0.86 V vs NHE),[11b] TDAE also has a practical advantage because it can facilitate cross-electrophile coupling reactions in nonamide solvents, which is often not possible with heterogeneous reductants.[15a] In preliminary experiments, we examined the stability of the model catalytic intermediate (dtbbpy)Ni^{II}(*o*-tol)I in a range of solvents both in the presence and absence of TDAE (see Supporting Information). In weakly or nonpolar solvents, such as 1,4-dioxane or toluene, no reaction is observed between TDAE and (dtbbpy)Ni^{II}(*o*-tol)I over days at room temperature. In contrast, a reaction between TDAE and (dtbbpy)Ni^{II}(*o*-tol)I can be observed over minutes to hours in more polar solvents, such as acetonitrile (see Supporting Information for further discussion). These results suggest that a weakly polar solvent, such as 1,4-dioxane, which stabilizes the key LNi^{II}(Ar)X intermediate, could be beneficial for reactions with nonactivated alkyl halides where the rate of radical generation is slower.

Under the conditions reported by Weix et al.,[15a] we explored a cross-electrophile coupling reaction between phenyl iodide and benzyl chloride using 1,4-dioxane as the solvent and TDAE as the reductant. In the absence of a radical generating cocatalyst, the reaction produced diphenylmethane in 40% yield (Table 1, Entry 1). Notably, significant quantities of benzyl chloride were still present at the end of the reaction, suggesting that radical generation is relatively slow. Remarkably, in the presence of 0.1 mol % of the air-stable cobalt cocatalyst, Co^{II}(Pc) (Pc = phthalocyanine), which has been reported by the Weix and Reisman groups to generate radicals from benzyl electrophiles under reductive coupling conditions,[9b,e] the yield increased to 90% (Entry 3). High yields were also obtained when the Co^{II}(Pc) loading was increased to 1 mol % (Entries 4–6), but the yield began to diminish as the Co^{II}(Pc) loading was increased above 2.5 mol % (Entries 7 and 8). The identity of the byproducts and the starting materials that remained at the end of the reaction changed as the loading of Co^{II}(Pc) was varied (Table 1). At low loadings of Co^{II}(Pc), unreacted benzyl chloride was observed and biphenyl was formed in appreciable quantities (Entries 1 and 2). In contrast, at high Co^{II}(Pc) loadings, no unreacted benzyl chloride was detected, only small amounts of biphenyl were formed, and significant amounts of phenyl iodide remained unreacted (Entries 7 and 8). Mechanistically, these observations align with our hypotheses and suggest that the main roles of the cobalt catalyst are to activate the alkyl electrophile and generate an alkyl radical and the main roles of the nickel catalyst are to activate the aryl electrophile, capture the alkyl radical, and facilitate C–C bond formation. We note that nickel is capable of productively engaging benzyl chloride in the absence of Co^{II}(Pc) (Table 1, Entry 1); however, it is likely that the cobalt catalyst more readily activates benzyl chloride compared to nickel alone when efficient catalysis is observed (Entries 3–6). Additionally, more challenging substrates, such as unactivated primary alkyl bromides (vide infra), were not productively engaged by nickel under similar reaction conditions (see Supporting Information).

To explore the proposed interplay between nickel and cobalt in catalysis, we performed a stoichiometric reaction between (dtbbpy)Ni^{II}(*o*-tol)I and two equivalents of benzyl chloride in the presence of excess TDAE and catalytic amounts of Co^{II}(Pc) in 1,4-dioxane (Table 2). This resulted in the generation of the diarylmethane cross-product, (*o*-tolyl)-

(phenyl)methane, in 76% yield (Table 2, Entry 1). No product formation, however, was observed without $Co^{II}(Pc)$ in either the presence or absence of TDAE (Entries 2 and 3), consistent with our hypothesis that cobalt primarily activates the alkyl electrophile. Furthermore, the use of stoichiometric $Co^{II}(Pc)$ without TDAE also yielded no cross-product (Entry 4), suggesting that the activation of alkyl electrophiles occurs at a reduced cobalt center. In agreement with this proposal, the reduction potential of $TDAE^{2+/0}$ is more negative than that of $Co^{II}(Pc)^{0/1-}$.[20] Low-valent cobalt complexes similar to $Co^{I}(Pc)^{-}$ are known to undergo oxidative addition with alkyl halides through an S_N2 mechanism to form $Co^{III}(Pc)(Alk)$ species.[21] In turn, these high valent Co^{III} complexes can undergo homolysis of the Co^{III}–Alk bond, which produces an alkyl radical and regenerates $Co^{II}(Pc)$.[22] Further support for the proposal that $Co^{II}(Pc)$ is capable of generating alkyl radicals in the presence of TDAE was obtained by performing an analogous radical trapping experiment using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical acceptor instead of (dtbbpy)Ni^{II}(*o*-tol)I.[23] In a similar fashion to our experiment with (dtbbpy)Ni^{II}(*o*-tol)I, trapping of the benzyl radical by TEMPO is only observed in the presence of excess TDAE and catalytic amounts of $Co^{II}(Pc)$ (see Supporting Information). Altogether, these experiments provide evidence for the cobalt-mediated generation of free radicals from an alkyl electrophile and subsequent radical capture by LNi^{II}(Ar)X species in catalysis.

On the basis of our experimental results, we propose a mechanism containing two cycles for the coupling of phenyl iodide and benzyl chloride catalyzed by (dtbbpy)$Ni^{II}Br_2$ and $Co^{II}(Pc)$ (Figure 3). Initially, the (dtbbpy)$Ni^{II}Br_2$ precatalyst is reduced by TDAE to generate a catalytically active Ni^0 species and the two-electron oxidized form of TDAE, which likely precipitates out of solution as $[TDAE^{2+}][Br^{-}]_2$. The Ni^0 species undergoes oxidative addition with an aryl halide to form a (dtbbpy)Ni^{II}(Ar)X intermediate. Subsequently, the (dtbbpy)Ni^{II}(Ar)X intermediate captures an alkyl radical, which is liberated upon the homolysis of a $Co^{III}(Pc)(Alk)$ species. The $Co^{III}(Pc)(Alk)$ species is generated in an independent catalytic cycle through initial reduction of $Co^{II}(Pc)$ to form an anionic $[Co^{I}(Pc)]^{-}$ complex, which can react with an alkyl halide via an S_N2 mechanism. Following radical capture by (dtbbpy)Ni^{II}(Ar)X, a putative (dtbbpy)Ni^{III}(Ar)(Alk)X species is produced, which rapidly reductively eliminates at the Ni^{III} center to liberate the product and form a (dtbbpy)Ni^{I}X species. Finally, we propose that the (dtbbpy)Ni^{I}X species is reduced by TDAE to regenerate Ni^0, closing the catalytic cycle. Further mechanistic work to explore all the potential roles of Ni^{I} species is ongoing.

Our mechanism and preliminary catalytic results are consistent with the presence of three distinct regimes, which are related to the relative loadings of (dtbbpy)$Ni^{II}Br_2$ and $Co^{II}(Pc)$. These regimes can be identified by analyzing the byproducts and the identity of any unreacted substrates. Regime 1 occurs when the rate of radical formation is slow relative to the rate of decomposition of (dtbbpy)Ni^{II}(Ar)X. This results in the presence of unreacted alkyl electrophile when all of the aryl electrophile has been consumed. Additionally, a significant amount of biphenyl is generated from the decomposition of (dtbbpy)Ni^{II}(Ar)X.[14d] Regime 2 occurs when the rate of alkyl radical formation is optimal relative to the formation of (dtbbpy)Ni^{II}(Ar)X. High yields of the coupled product are observed when the concentrations of radical and (dtbbpy)Ni^{II}(Ar)X are matched, so neither decomposes before the trapping event. Regime 3 occurs when alkyl radical formation is faster than the

generation of (dtbbpy)Ni^{II}(Ar)X. In this case, the alkyl radical decomposes before it can be trapped by nickel. As a result, after all of the alkyl electrophile is consumed, the aryl electrophile is still present. This proposal is supported by the data in Table 1, which is separated into the three possible regimes using dashed lines as the Co^{II}(Pc) loading is altered with a fixed loading of (dtbbpy)$Ni^{II}Br_2$. The same trends are also obtained when the loading of (dtbbpy)$Ni^{II}Br_2$ is varied at a fixed loading of Co^{II}(Pc) (see Supporting Information). Practically, these observations suggest that reaction yields may be rationally optimized by tuning only two variables, the loadings of (dtbbpy)$Ni^{II}Br_2$ and Co^{II} (Pc), based on the byproducts and recovered starting materials observed.

Using our approach for the cross-electrophile coupling of aryl iodides with benzyl chlorides as a guide, we applied our strategy of using a dual catalytic system with a homogeneous OED to the coupling of unactivated aryl and alkyl bromides. To date, these synthetically important substrates have typically proven incompatible with homogeneous reductants. Remarkably, in an analogous fashion to our results with benzyl chlorides (vide supra), we were able to optimize the coupling of 4-*tert*-butyl-bromobenzene with 1-bromo-3-phenylpropane by fixing the loading of Co^{II}(Pc) at 2.5 mol % and altering the loading of (dtbbpy)$Ni^{II}Br_2$ based on the byproducts (Table 3). Using 1 mol % of (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc), we obtained a yield of 84% in 1,4-dioxane (Table 3, Entry 3). Notably, no product was observed under these conditions in the absence of Co^{II}(Pc), demonstrating the importance of the cobalt cocatalyst (see Supporting Information). Furthermore, we are also able to couple iodobenzene with 1-iodo-3-phenylpropane in 97% yield under similar conditions after optimizing the loadings of nickel and cobalt (Scheme 2 and see Supporting Information). These results demonstrate that we are able to perform cross-electrophile coupling reactions with relatively unactivated bromo-electrophiles under nearly the same conditions we used to couple aryl iodides with benzyl chlorides and alkyl iodides, with the only difference being the loadings of the nickel and cobalt catalysts. This generalizability of reaction conditions across aryl iodides and bromides, benzyl chlorides, and alkyl bromides and iodides is uncommon for cross-electrophile coupling reaction conditions, which are often specific to a more narrow range of substrates (vide supra). Furthermore, in our dual catalytic system, the role of each reagent is understood and there is no need for commonly utilized additives, such as alkali halide salts or pyridines. As a result, our system provides a method for simple, rational optimization through modulation of catalyst loadings, which, as we show in the following sections, can be broadly applied to a wide range of challenging and novel substrates.

Substrate Scope for Cross-Electrophile Coupling of Simple Aryl and Alkyl Bromides.

Given our development of a system for the cross-electrophile coupling of aryl and alkyl bromides using a homogeneous reductant, we optimized the reaction conditions (see Supporting Information) and evaluated the substrate scope of the method (Figure 4). Aryl electrophiles were primarily coupled with 1-bromo-3-phenyl-propane although in some cases, *N*-(3-bromopropyl)-phthalimide was used as the alkyl electrophile because the polar functional group assists with isolation. To show the generality and simplicity of our optimization protocol, we optimized each substrate to a yield greater than 75% by proton nuclear magnetic resonance (^{1}H NMR) spectroscopy by modulating catalyst loadings

according to the observed product profile (see Supporting Information).[24] Notably, the optimized conditions for each substrate deviate only slightly from our standard reaction conditions, indicating the ease by which high yields can be obtained. Furthermore, good yields can be obtained over more than an order of magnitude variation in Co^{II}(Pc) or (dtbbpy)$Ni^{II}Br_2$ loadings (Tables 1 and 3). This suggests that a wide range of substrates may be successfully coupled under a standard set of conditions even without performing the simple catalyst loading optimization. In a similar fashion to conventional cross-electrophile coupling reactions using heterogeneous reductants[2b,4] our homogeneous dual catalytic system has a broad substrate scope and excellent functional group tolerance. For example, using 1 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc), we are able to couple bromobenzene (**4a**) with *N*-(1-bromopropyl)phthalimide as well as electron-rich 4-bromoanisole (**4b**) and electron-deficient 4-bromotriflurobenzene (**4c**) with 1-bromo-3-phenylpropane in good yields. Additionally, under analogous conditions, aryl halides with a variety of different functional groups, such as 4-bromobenzonitrile (**4d**), 4-bromophenyl methyl sulfone (**4e**), 4-bromobenzaldehyde (**4f**), 4-bromoacetophenone (**4g**), methyl 4-bromobenzoate (**4h**), and 4-bromo-*N*-methylbenzamide (**4i**), can also be coupled with 1-bromo-3-phenylpropane, in good yields. While these types of aryl halides are commonly utilized as substrates in cross-electrophile coupling reactions, it is noteworthy that our system requires only a 1 mol % loading of the nickel catalyst, whereas most previously reported reactions require higher loadings.[1e] Interestingly, when 1-bromo-4-chlorobenzene (**4j**) is used as a substrate with 2 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc), our system is selective for coupling the aryl bromide, which offers opportunities for orthogonal reactivity with traditional cross-coupling reactions.[1h] Our dual catalytic system is also able to couple substrates with acidic groups, such as 4-bromophenethyl alcohol (**4k**) and 5-bromoindole (**4l**) using just 1 mol % of (dtbbpy)$Ni^{II}Br_2$. Furthermore, the reaction between 4-iodoaniline (**4m**) and 1-iodo-3-phenylpropane using 2 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc) generated the desired product in 80% yield. However, the coupling of 4-bromoaniline with 1-bromo-3-phenylpropane resulted in a lower yield (44%, see Supporting Information). In this case, we propose that more reactive iodo-substituted substrates are required because the rates of deleterious side reactions between the acidic group and the catalysts are more competitive when bromo-substituted substrates are utilized.

A major advantage of our system for cross-electrophile coupling is its compatibility with sterically bulky aryl halides. For example, the *ortho*-substituted aryl bromides 2-bromotoluene (**4n**), 2-bromoanisole (**4o**), 2-bromocumene (**4p**), and ethyl 2-bromobenzoate (**4q**) can all be coupled with 1-bromo-3-phenylpropane using 2.5–5 mol % of (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % of Co^{II}(Pc). In particular, the coupling of **4q** is significant as Weix et al. previously reported that it was difficult to couple aryl halides with bulky *ortho*-directing groups.[4] Even more significantly, our system is able to couple the 2,6-disubstituted aryl halides 2-iodo-1,3-dimethylbenzene (**4r**) and 2-iodo-1,3-dimethoxybenzene (**4s**) for which there is virtually no precedent in the cross-electrophile coupling literature.[4,25] For these substrates, aryl iodides are required instead of aryl bromides along with a 10 mol % loading of (dtbbpy)$Ni^{II}Br_2$. This is likely due to the difficulty associated with oxidative addition for these sterically bulky systems and tuning of the ancillary ligand on the nickel catalyst may enable these reactions to be performed with aryl bromide congeners at lower

catalyst loadings. Additionally, from a mechanistic perspective, *ortho*-substitution of aryl ligands is known to inhibit the decomposition of $LNi^{II}(Ar)X$ intermediates via bimolecular homocoupling, relative to complexes with aryl ligands that do not have *ortho*-substitution (Figure 2).[26] This should be advantageous for promoting productive radical capture at $LNi^{II}(Ar)X$ intermediates. In agreement with this proposal, catalysis with *ortho*-substituted aryl substrates can be performed with high efficiency (regime 2, above) using a wider relative range of nickel to cobalt loadings compared to analogous reactions without *ortho*-substitution on the aryl substrate (see Supporting Information).

Heteroaryl halides are important substrates because heteroaromatic groups are common structures in medicinal chemistry.[27] Traditionally, it has proven difficult to use 2-halofurans and 2-halothiophenes as substrates in cross-electrophile coupling reactions, especially when there is no substitution in the 5-position.[2l,14j] Our dual catalytic system can couple 2-bromofuran (**4t**) and 2-bromothiophene (**4u**) in high yields using just 0.5 mol % of $(dtbbpy)Ni^{II}Br_2$, although 5 mol % of the $Co^{II}(Pc)$ cocatalyst is required. Pyridyl halides are another highly challenging class of substrates in cross-electrophile coupling reactions. As a result, complex ligands and various additives are commonly required to facilitate their coupling.[4,6a] In contrast, we can couple 3-bromopyridine (**4v**) with 1-bromo-3-phenylpropane in 71% yield simply by modulating the catalyst loadings to 5 mol % $(dtbbpy)Ni^{II}Br_2$ and 2 mol % $Co^{II}(Pc)$, demonstrating the broad generalizability of our dual catalytic system. 2-bromopyridine (**4w**) is a more difficult substrate and only a 41% yield is observed using 10 mol % of $(dtbbpy)Ni^{II}Br_2$ and 10 mol % of $Co^{II}(Pc)$.

Different types of alkyl electrophiles that are compatible with our dual catalytic system were examined using the same optimization strategy that was utilized for exploring the scope of the aryl electrophile. Benzyl chloride can be coupled with phenyl iodide (vide supra) and methyl 4-bromobenzoate in excellent yields (see Supporting Information), but the reaction requires high loadings of $(dtbbpy)Ni^{II}Br_2$ (5–7 mol %) relative to $Co^{II}(Pc)$ (0.5–1 mol %), consistent with the facile radical generation from the highly reactive alkyl electrophile. In addition to unactivated primary alkyl iodides (vide supra) and bromides (**4a–4w**), the primary alkyl mesylate, 3-phenylpropyl methanesulfonate (**4x**), is compatible with our conditions and can be coupled with methyl 4-bromobenzoate in a high yield using 2.5 mol % $(dtbbpy)Ni^{II}Br_2$ and 1 mol % $Co^{II}(Pc)$. This result is notable because alkyl mesylates can be readily generated in situ from the corresponding alcohols,[9b,28] which are abundant and diverse building blocks that are commonly used in pharmaceutical research.[9c] However, our system is limited to substrates that can be activated via an S_N2 mechanism, consistent with the proposed mechanism (Figure 3). Accordingly, substrates with some steric bulk at the α-carbon of alkyl bromides, such as (bromomethyl)cyclohexane (**4y**), can be coupled with methyl 4-bromobenzoate using 0.5 mol % $(dtbbpy)Ni^{II}Br_2$ and 2.5 mol % $Co^{II}(Pc)$, but no product is generated when either neopentyl bromide or iodide is used as a substrate (see Supporting Information). Similarly, branched secondary alkyl halides such as iodides (**4z**) and benzyl chlorides (**4aa**) can be coupled in moderate yields, but branched secondary alkyl bromides and iodocyclohexane are unreactive (see Supporting Information). In a subsequent section, we explore the types of functionalized alkyl bromides and iodides and benzyl chlorides that are compatible with our system.

Cross-electrophile coupling reactions between vinyl and alkyl electrophiles have been reported under related conditions to those reported for reactions between aryl and alkyl electrophiles using a nickel catalyst with a heterogeneous reductant.[2b,q,ai] Our dual catalytic method is also compatible with vinyl electrophiles as demonstrated by the coupling of 1-bromo-2-methyl-1-propene and *N*-(3-bromopropyl)-phthalimide in 74% yield, using 1 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc) (Scheme 3).

Overall, these results demonstrate that our dual catalytic platform can not only enable the cross-electrophile coupling of many substrates using lower catalyst loadings than those typically reported but can also couple a range of challenging substrates, such as heteroaryl halides and di-*ortho*-substituted aryl halides, simply by rationally changing the relative loading of the two catalysts. We show in the next sections the unique control that our system offers, which provides new opportunities for the discovery of novel transformations and the functionalization of complex molecules.

Potential Applications of the Dual Catalytic System for Cross-Electrophile Coupling.

Three-Component Coupling Reactions.—Reactions that enable the modification of simple aryl rings in a modular fashion are valuable for the creation of diverse libraries of compounds, which often facilitate the discovery of lead structures in medicinal chemistry.[29] To this end, readily accessible dihaloarenes are promising starting materials that can be used to directly and efficiently construct widely diverse structures.[30] Although there are currently numerous methods for the sequential introduction of aryl groups into dihaloarenes via standard $C(sp^2)$–$C(sp^2)$ cross-coupling reactions,[29−31] reports that demonstrate the sequential introduction of alkyl groups are limited[32] due, in part, to the difficulties associated with $C(sp^2)$–$C(sp^3)$ bond formation. We hypothesized that our dual catalytic system is uniquely suited for the dialkylation of bromo(iodo)arenes through consecutive cross-electrophile coupling reactions for three reasons: (i) it is able to efficiently couple a range of highly activated and unactivated aryl and alkyl substrates under a general set of conditions; (ii) TDAE is utilized in only stoichiometric quantities, which means that after initial coupling at the more activated iodide site of the bromo-(iodo)arene, the bromide site should remain unreacted for use in a subsequent coupling reaction. This advantage is unique to our system compared to conventional cross-electrophile coupling reactions, which generally use superstoichiometric quantities of heterogeneous Zn^0 or Mn^0 reductants; and (iii) we observed regioselective activation of the aryl bromide in the dihaloarene substrate 1-bromo-4-chlorobenzene (**4j**), indicating that preferential reactivity at one site in a disubstituted aryl halide is possible.

We performed an initial reaction between 1-bromo-4-iodo-2-methoxybenzene and benzyl chloride using 5 mol % (dtbbpy)$Ni^{II}Br_2$, 0.5 mol % Co^{II}(Pc), and 120 mol % TDAE. The reaction was highly selective for the iodide position and produced a monoalkylated bromoarene in 93% yield (see Supporting Information). We then performed the same reaction in the presence of a second alkyl electrophile 1-bromo-3-phenylpropane and 260 mol % TDAE (see Scheme 4 and Supporting Information for full reaction optimization). In this case, a 76% yield of the desired bis-alkylated product was observed, where the aryl iodide had presumably initially coupled with benzyl chloride, and subsequently, the less

reactive aryl and alkyl bromides had coupled. We suggest that there are two requirements for achieving such high selectivity in one step: (i) a highly activated alkyl electrophile, such as a benzyl chloride, must be employed, which reacts preferentially with the Co catalyst over a second, less activated alkyl electrophile, such as a primary alkyl bromide. (ii) The optimal catalyst loading of nickel and cobalt for the initial coupling must overlap with the optimal catalyst loadings for the second coupling. Analysis of the optimized reaction conditions for coupling alkyl electrophiles in single-component cross-electrophile coupling reactions (vide supra) indicates there are only a limited number of substrates that meet the requirements for use in a one-pot single-step reaction.

To overcome the limitations of our single-step three-component coupling reaction, we explored the possibility of a one-pot three-component cross-electrophile coupling reaction involving the sequential addition of two alkyl halides (Table 4). Initially, upon completion of the reaction between 1-bromo-4-iodo-2-methoxybenzene and benzyl chloride using 5 mol % (dtbbpy)$Ni^{II}Br_2$ and 0.5 mol % Co^{II}(Pc) to form a monoalkylated bromoarene product, we added ethyl 4-bromobutyrate and TDAE and continued the reaction for another 24 h at 80 °C. Remarkably, the in situ-generated bromoarene product underwent a second cross-electrophile coupling reaction with the alkyl bromide in the same pot, without the need to add additional amounts of either catalyst (Table 4, Entry 1 and see Supporting Information for optimization). Across the two steps, the isolated yield of the bis-alkylated product was 82%. This result suggests that there is no significant catalyst death either during or upon completion of initial alkylation.

Using the sequential addition strategy, we extended our one-pot three-component coupling reaction beyond combinations of highly activated and weakly activated alkyl halides. For example, a primary alkyl iodide, such as 1-iodo-3-phenylpropane, and a primary alkyl bromide, such as ethyl 4-bromobutyrate, were sequentially coupled with 1-bromo-4-iodo-2-methoxybenzene in 84% yield using 1 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc) for the initial coupling of the organic iodides followed by the addition of 4 mol % (dtbbpy)$Ni^{II}Br_2$, TDAE, and alkyl bromide to accomplish the second coupling (Entry 2). Although the nickel catalyst was shown to remain active after the initial coupling, an additional 4 mol % of (dtbbpy)$Ni^{II}Br_2$ was added for the second coupling because the optimal conditions for this reaction utilize 5 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc). The three-component reaction is also compatible with an *ortho*-substituted bromo(iodo)arene. Specifically, 1-bromo-2-iodo-4-methylbenzene can be coupled with benzyl chloride and ethyl 4-bromobenzoate in 91% yield in a two-step one-pot process (Entry 3). In this case, 5 mol % (dtbbpy)$Ni^{II}Br_2$ and 0.5 mol % Co^{II}(Pc) are the optimal catalyst loadings for both the first reaction and the second reaction. Thus, only ethyl 4-bromobenzoate and TDAE need to be added after the first coupling to facilitate the second coupling. Unsubstituted bromo(iodo)arenes can also be used to perform sequential coupling reactions. For instance, 1-bromo-4-iodobenzene was coupled with benzyl chloride and ethyl 4-bromobenzoate in 70% yield using 2.5 mol % (dtbbpy)$Ni^{II}Br_2$ and 0.1 mol % Co^{II}(Pc) for the initial coupling of the benzyl chloride followed by the introduction of an additional 5 mol % Co^{II}(Pc), TDAE, and alkyl bromide to accomplish the second coupling (Entry 4). The four examples presented here serve as proof-of-principle that our dual catalytic platform can be used for the rapid construction of multiple $C(sp^2)$–$C(sp^3)$ bonds using readily available

bromo(iodo)arene and alkyl halide starting materials. Our method is a significant advancement over the existing methodology for dialkylation of bromo-(iodo)arenes, which cannot be performed in one-pot and requires the use of preformed organometallic nucleophiles that are not commercially available and generally require multistep syntheses.[32b] As we demonstrate in the next section, our findings should be compatible with medicinally relevant systems as our new catalytic system can promote couplings using complex substrates.

Coupling with Medicinally Relevant Substrates.—Despite the significant attention that C(sp^2)–C(sp^3) cross-electrophile coupling has received over the past decade, methods to couple complex, medicinally relevant substrates are limited or only applicable to a narrow set of substrates.[2aa,6b,c,14e] The major challenge associated with using druglike aryl halides in transition metal-catalyzed transformations is that these substrates contain functional groups that can either bind to the catalyst and sequester it in undesired equilibria or directly cause catalyst decomposition. Consequently, the concentration of catalytic intermediates is perturbed in an unpredictable fashion, which complicates reaction optimization. Given the high value of compounds containing alkylated arene groups in the development and study of pharmaceuticals, a robust method to form C(sp^2)–C(sp^3) linkages that is compatible with a range of medicinally relevant substrates would be valuable for drug discovery.[33]

We hypothesized that our dual catalytic platform would be well-suited to overcoming the challenges of working with complex molecules because of its functional group tolerance (Figure 4) and the improved control offered by the ability to independently control the rates of activation of the aryl and alkyl halides. To this end, we tested the compatibility of our reaction conditions with aryl halides from the MSD Aryl Halide Informer Library as these compounds were at one time intermediates in drug discovery programs, and therefore, represent relevant chemical space for medicinal chemisty.[34] For all substrates, we rationally optimized the reaction by varying the loading of (dtbbpy)$Ni^{II}Br_2$ and Co^{II}(Pc) (vide supra) without changing other reaction parameters, such as solvent, temperature, or the identity of the ancillary ligand.[35] We also did not add additives to the reaction. As a result, it was straightforward to perform the reaction optimization using standard high-throughput experimentation (HTE) techniques (see Supporting Information).[36] Aryl halides **5a–5h** were successfully coupled in moderate to high yields (42–84% yield by ^{1}H NMR spectroscopy) with 1-bromo-3-phenylpropane (Figure 5). The range of functional groups present in these aryl halides highlights the power of our method. For example, successful reactions were observed in the presence of esters, amides, sulfones, alcohols, triazoles, thiophenes, pyridines, and both free and protected amines among many other functional groups. Notably, the challenging, di-*ortho* substituted aryl halide, **5i**, was coupled in a lower, but still medicinally useful, yield (22% by ^{1}H NMR spectroscopy) with 1-iodo-3-phenylpropane. Additionally, we isolated the product from the reaction of **5a** with 1-bromo-3-phenylpropane in a good yield (72%) as proof-of-principle that our method will enable the generation of compounds for drug discovery.

To further investigate the potential applicability of our reaction conditions to C(sp^2)–C(sp^3) bond formation in molecules relevant to drug discovery, we performed a parallel library synthesis via late-stage diversification of aryl halide **5f**, a precursor to oxazolidinone

antibacterials, with different alkyl halides (Figure 6).[37] First, we optimized the loadings of (dtbbpy)$Ni^{II}Br_2$ and Co^{II}(Pc) for the reactions of **5f** with benzyl chloride, 1-iodo-3-phenylpropane, and 1-bromo-3-phenylpropane (see Supporting Information). We then used the optimized conditions for each class of alkyl halide to evaluate the ability of our system to couple a series of functionalized benzyl chlorides and alkyl bromides and iodides with **5f** using HTE techniques (see Supporting Information). For example, all primary alkyl bromides used in the experiment were coupled under the optimal conditions determined for the coupling of **5f** with 1-bromo-3-phenylpropane (**6r**). For each reaction, the amount of **5f** transformed to the product is reported as a ratio of desired product to all other known byproducts, as determined by UV–vis spectroscopy (see Supporting Information). We validated this method by determining the ^{1}H NMR yields for the reactions of **6a**, **6i**, and **6m** with **5f** and showing that they agreed within 10% of the conversion values obtained using UV–vis spectroscopy (Figure 6).

Using our strategy, we observed that 25 out of 32 products were formed in greater than 10% conversion, an overall 78% success rate. A range of functionalized primary benzyl chloride electrophiles could be coupled using 5 mol % (dtbbpy)$Ni^{II}Br_2$ and 0.5 mol % Co^{II}(Pc). Notably, substrates containing a tetrazole (**6b**) or thiophene (**6d**) ring, or a protic amide substituent (**6f**) were all successfully coupled. Furthermore, various primary alkyl iodide and bromide electrophiles could be coupled using 2.5 mol % (dtbbpy)$Ni^{II}Br_2$ and 2.5 mol % Co^{II}(Pc). Notably, challenging substrates containing an unprotected indole (**6o**) and terminal alkenes (**6x**), which are susceptible to Giese-type additions in related reactions,[16c,d] generated product. Additionally, heterocyclic rings, which are prevalent in medicinal chemistry, such as azetidine (**6k**), piperidine (**6n**), and cyclic ethers (**6j**, **6u**, and **6aa**) are compatible with our method.[38] Overall, this experiment demonstrates that our reaction conditions can be generally applied across a series of alkyl halide substrates for parallel library synthesis using a complex aryl halide and HTE methods. It also shows that in an analogous fashion to the aryl halide substrate, our methodology can tolerate a large number of functional groups on the alkyl halide substrate.

Finally, to assess if our method is amenable to scale up, we coupled **5f** with 1-iodo-3-phenylpropane on a 3.0 mmol scale using the linearly scaled conditions from the reaction on a 0.03 mmol scale. In the 0.03 mmol scale reaction, a 96:4 ratio of product to starting material was observed by analysis of the crude reaction mixture by ^{19}F NMR spectroscopy. In the 3 mmol scale reaction, a 95:5 ratio of product to starting material was observed by analysis of the crude reaction mixture by ^{19}F NMR spectroscopy, demonstrating high reproducibility of the reaction on a large scale (see Supporting Information). From this mixture, we were able to isolate the product in 64% yield (Scheme 5). Our system presents two advantages over conventional C(sp^2)–C(sp^3) cross-electrophile coupling reactions that are specific to large-scale reactions: (i) it is compatible with a wide range of nontoxic solvents, including several green solvents such as 2-methyltetrahydrofuran, isopropyl acetate, and methyl ethyl ketone (see Supporting Information), which assists in finding conditions where substrates are fully soluble and reduces environmental impact, and (ii) it utilizes a homogeneous reductant as opposed to a heterogeneous reductant, which should provide more reproducible kinetic profiles.

CONCLUSIONS

We have developed a novel system for C(sp^2)–C(sp^3) cross-electrophile coupling reactions between aryl halides and alkyl halides. Our system uses a nickel and cobalt dual catalytic platform in tandem with a relatively weak homogenous reductant, TDAE, to provide a high level of control over cross-electrophile coupling reactions. Mechanistic studies suggest that the cobalt catalyst selectively activates the alkyl electrophile to generate an alkyl radical, while the nickel catalyst primarily activates the aryl electrophile and captures the alkyl radical, ultimately leading to the formation of a new C(sp^2)–C(sp^3) bond. The method allows for reactions to be rationally optimized by modulating the relative loadings of the two catalysts based on the reaction byproducts. Our dual catalyst platform is able to efficiently couple a wide range of substrates with excellent functional group tolerance. Notably, we can couple heteroaryl substrates, such as 2-bromothiophene, 2-bromofuran, and 2-bromopyridine, and di-*ortho*-substituted aryl iodides, which are rarely compatible with methods for C(sp^2)–C(sp^3) cross-electrophile coupling. We further demonstrate the unique control that our methodology provides through a series of novel one-pot three-component dialkylations of bromo(iodo)arenes. Finally, we show the utility of our strategy to medicinal chemistry in two ways: (i) through the successful coupling of a range of druglike aryl halides and functionally diverse alkyl halides using HTE and (ii) through a larger scale reaction involving a druglike aryl halide. Overall, our mechanistic work has enabled the discovery of a system for C(sp^2)–C(sp^3) cross-electrophile coupling that has a broad scope and is applicable to both synthetic and medicinal chemistry. Furthermore, the underlying principles behind our dual catalytic strategy can likely be used to improve a number of existing transformations and facilitate the discovery of new reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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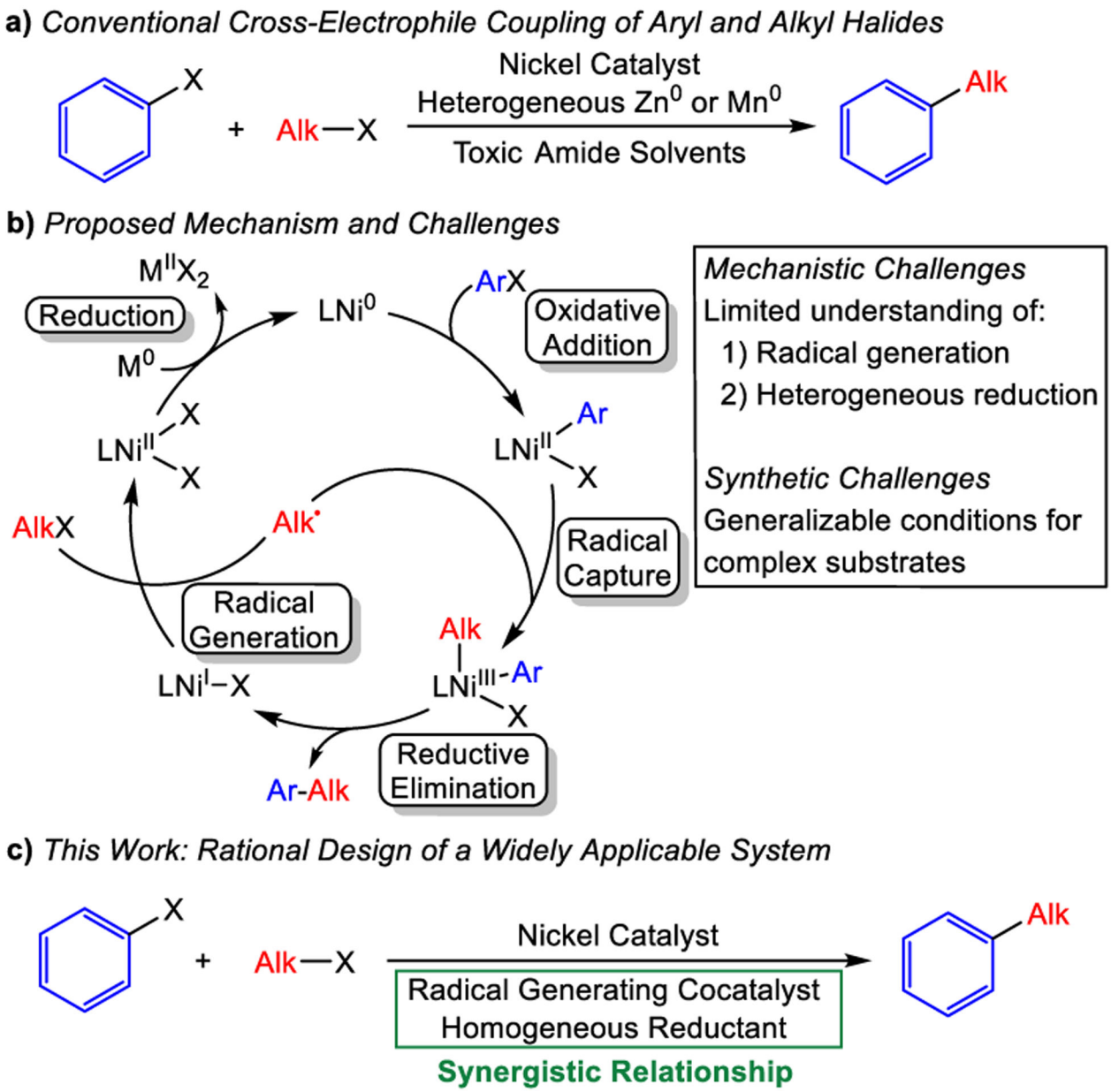


Figure 1.

(a) General depiction and (b) mechanism of conventional nickel-catalyzed cross-electrophile coupling reactions using a heterogeneous reductant.[3a] (c) Cross-electrophile coupling reactions described in this work with a dual catalyst system and a homogeneous reductant.

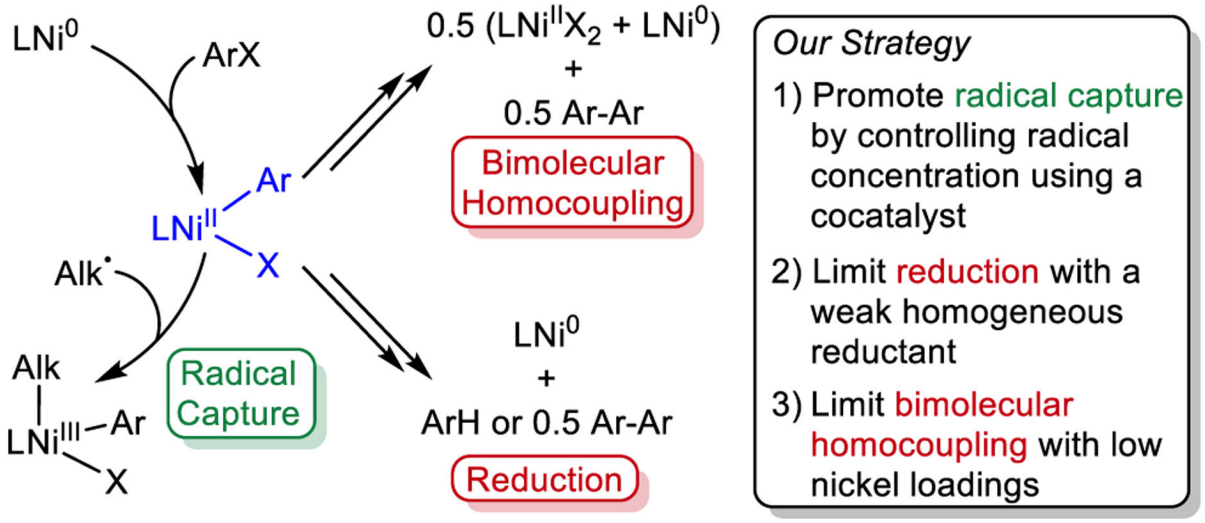


Figure 2.
Potential reactions of $LNi^{II}(Ar)X$ in catalysis and an envisioned strategy for system development.

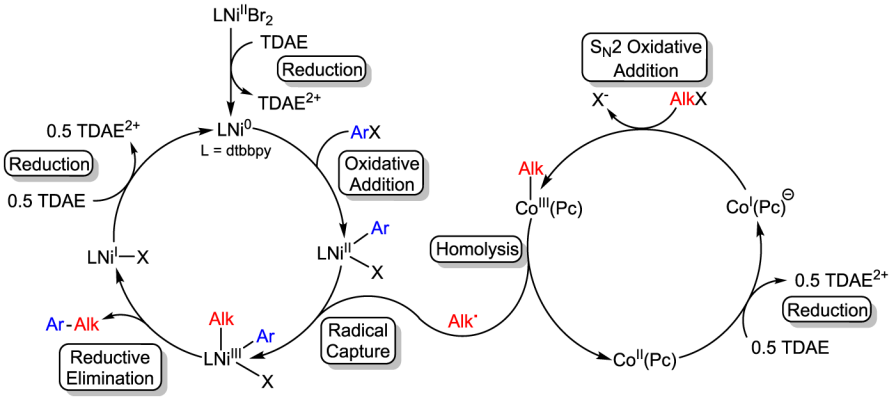


Figure 3.

Proposed mechanism for the cross-electrophile coupling of aryl and alkyl halides in the presence of $Co^{II}(Pc)$.

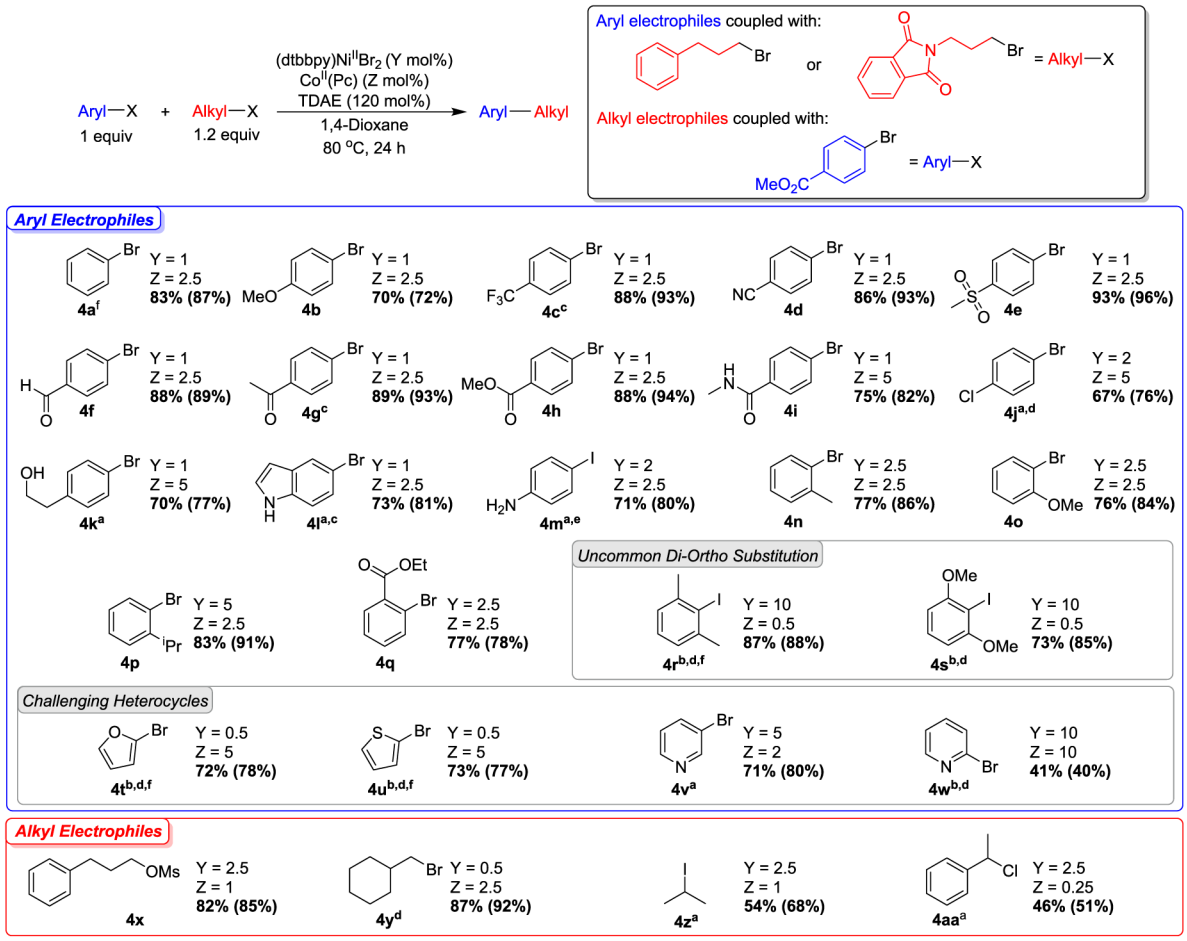


Figure 4.

Substrate scope for dual-catalyzed cross-electrophile coupling between aryl halides and alkyl halides or pseudohalides. Values outside of parentheses are isolated yields and values inside of parentheses are NMR yields, which were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard. [a]1.6 equiv. of alkyl substrate, 140 mol % TDAE. [b]2.0 equiv. of alkyl substrate, 160 mol % TDAE. [c]36 h. [d]48 h. [e]1-iodo-3-phenylpropane used as an alkyl substrate. [f]*N*-(3-bromopropyl)phthalimide used as an alkyl substrate instead of 1-bromo-3-phenylpropane.

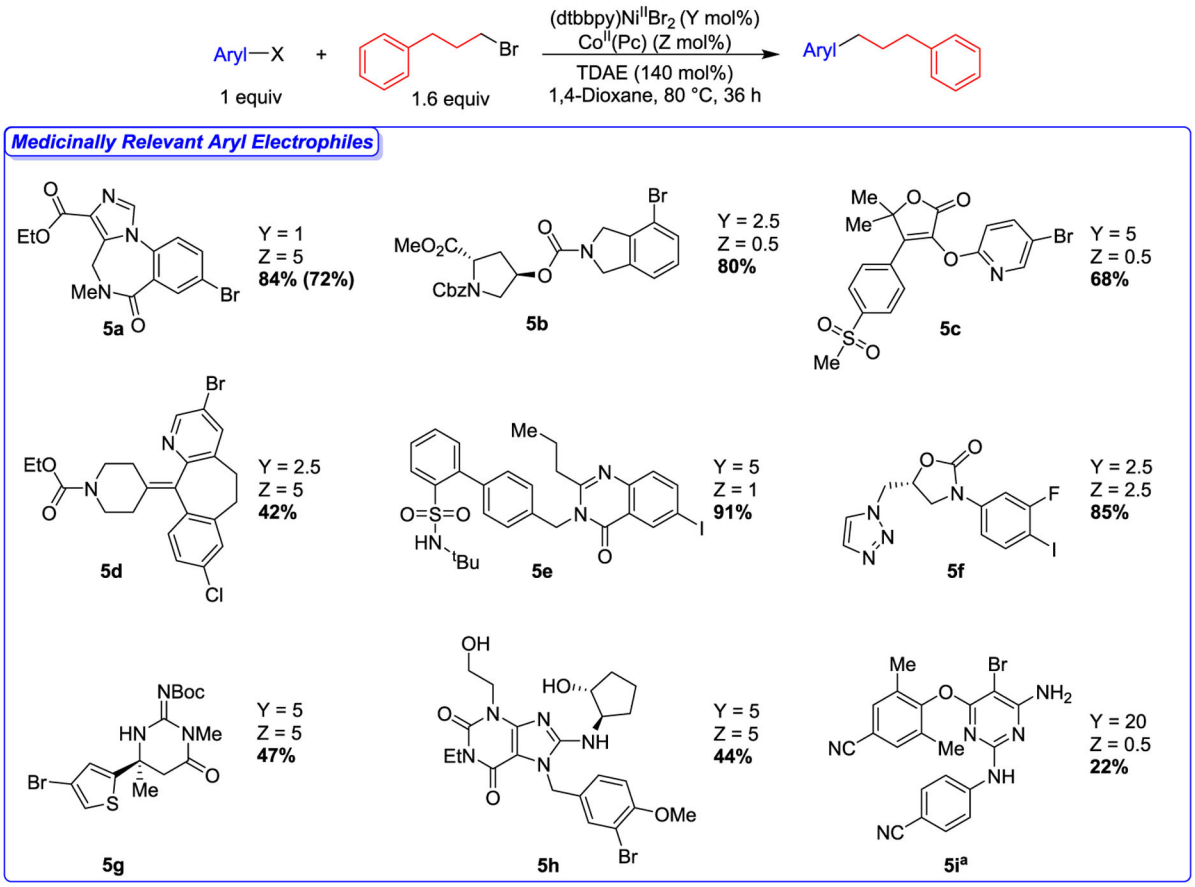


Figure 5.

Substrate scope for dual-catalyzed cross-electrophile coupling between MSD Aryl Halide Informer Library and 1-bromo-3-phenylpropane. Values outside of parentheses are NMR yields, which were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard, and values inside of parentheses are isolated yields on 0.10 mmol scale. [a]2 equivalents of 1-iodo-3-phenylpropane alkyl substrate, 160 mol % TDAE, 48 h.

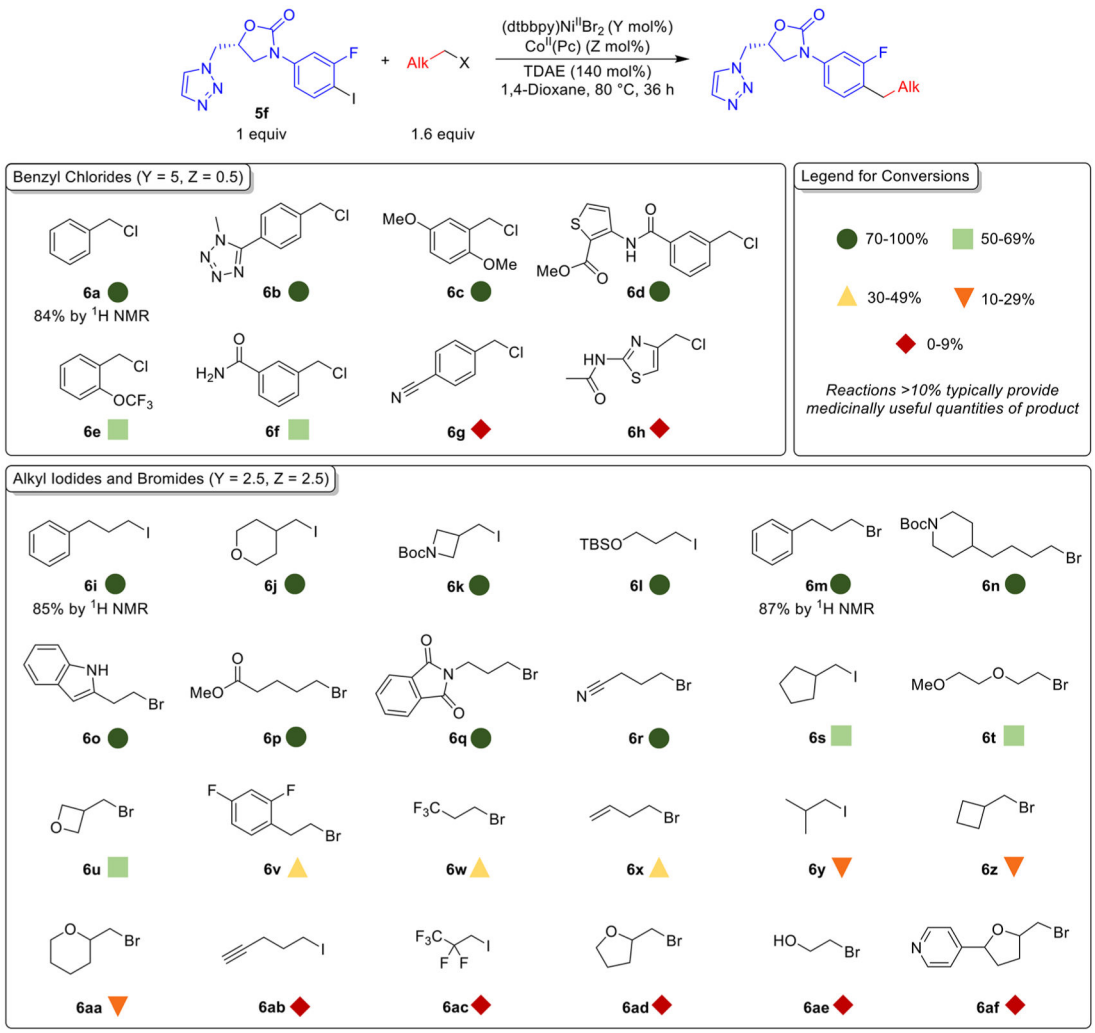
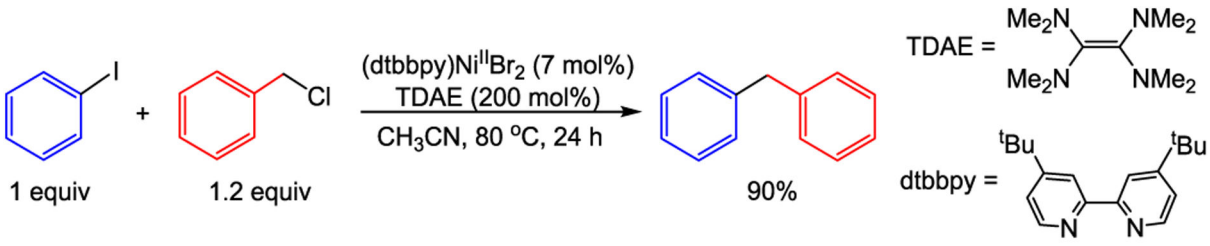


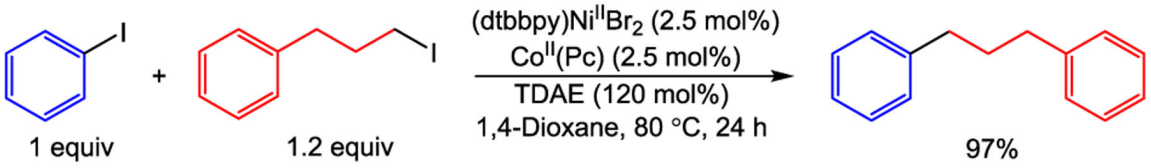
Figure 6.

Dual-catalyzed cross-electrophile coupling reactions between **5f** and a series of benzyl chlorides, alkyl iodides, and alkyl bromides. Values are reported as the conversion to product relative to all known species derived from **5f** determined by UV–vis spectroscopy (see Supporting Information for details). NMR yields were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

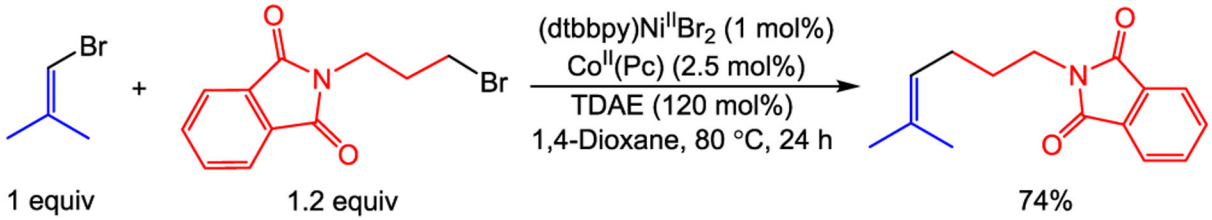


Scheme 1.

Cross-Electrophile Coupling of Aryl Iodides with Benzyl Chlorides Using TDAE Reported by Weix et al[15a]

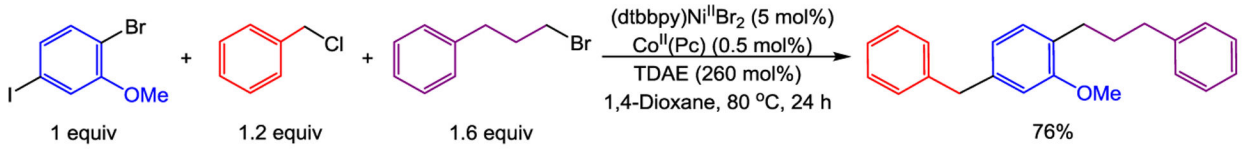


Scheme 2.
Cross-Electrophile Coupling of Iodobenzene with 1-Iodo-3-Phenylpropane



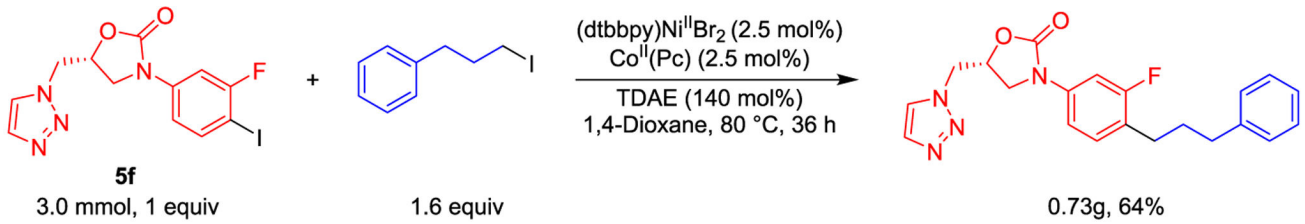
Scheme 3.

Cross-Electrophile Coupling of 1-Bromo-2-Methyl-1-Propene with *N*-(3-bromopropyl)Phthalimide



Scheme 4.

Single-Step Three-Component Cross-Electrophile Coupling of 1-Bromo-4-Iodo-2-Methoxybenzene with Benzyl Chloride and 1-Bromo-3-Phenylpropane

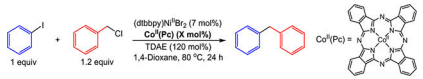


Scheme 5.

3.0 mmol Scale Cross-Electrophile Coupling of 5f with 1-Iodo-3-Phenylpropane

Table 1.

Cross-Electrophile Coupling of Iodobenzene and Benzyl Chloride with Varying Amounts of $Co^{II}(Pc)$[ab]



entry	$Co^{II}(Pc)$ (X mol %)	product (%)	unreacted ArI (%)	biphenyl (%)	unreacted BnCl (%)[c]	catalytic regime
1	0	40	3	21	28	1
2	0.01	77	<1	6	16	1
3	0.1	90	5	2	4	2
4	0.25	87	4	2	<1	2
5	0.5	96	3	1	<1	2
6	1	90	4	2	<1	2
7	2.5	75	14	1	<1	3
8	5	62	21	1	<1	3

[a]Reaction conditions: iodobenzene (0.0625 mmol), benzyl chloride (0.075 mmol), (dtbbpy)$Ni^{II}Br_2$(0.0044 mmol), and TDAE (0.075 mmol) in 1,4-dioxane (0.5 mL) at 80 °C for 24 h.

[b]Yields are reported as the average of two trials and were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

[c]Yield of recovered benzyl chloride reported relative to iodobenzene loading.

Table 2.

Stoichiometric Reaction of (dtbbpy)Ni^{II}(*o*-tol)I with Benzyl Chloride under Various Reaction Conditions[ab]

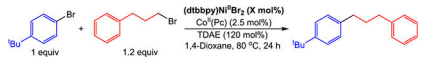
entry	deviation from conditions	yield (%)
1	none	76
2	No Co^{II}(Pc)	<1
3	No Co^{II}(Pc) & no TDAE	<1
4	100 mol % Co^{II}(Pc) & no TDAE	<1

[a]Reaction conditions: (dtbbpy)Ni^{II}(*o*-tol)I (0.0132 mmol), benzyl chloride (0.0264 mmol), Co^{II}(Pc) (0.00185 mmol), and TDAE (0.0264 mmol) in 1,4-dioxane (1.5 mL) at room temperature for 1 h.

[b]Yields are reported as the average of two trials and were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

Table 3.

Cross-Electrophile Coupling of 4-*tert*-Butyl-Bromobenzene with 1-Bromo-3-Phenylpropane with Varying Amounts of (dtbbpy)$Ni^{II}Br_2$ [a,b]



entry	(dtbbpy)$Ni^{II}Br_2$ (X mol %)	product (%)	unreacted ArBr (%)	biphenyl (%)	unreacted AlkBr (%)[c]	catalytic regime
1[d]	0.1	55	29	<1	3	3
2[d]	0.5	68	22	<1	6	3
3	1	84	6	<1	<1	2
4[e]	2.5	66	4	9	10	1
5[f]	5	53	<1	12	30	1

[a] Reaction conditions: 1-bromo-4-tertbutylbenzene (0.0625 mmol), 1-bromo-3-phenylpropane (0.075 mmol), Co^{II}(Pc) (0.0016 mmol), and TDAE (0.075 mmol) in 1,4-dioxane (0.5 mL) at 80 °C for 24 h.

[b] Yields are reported as the average of two trials and were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

[c] Yield of recovered 1-bromo-3-phenylpropane reported relative to 4-*tert*-butyl-bromobenzene loading.

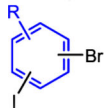
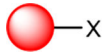
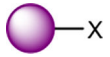
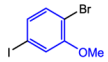
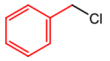
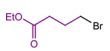
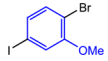
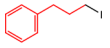
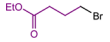
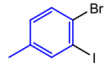
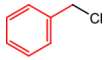
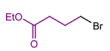
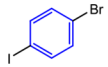
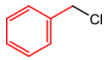
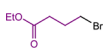
[d] Reaction run for 48 h.

[e] Reaction run for 12 h.

[f] Reaction run for 4 h.

Table 4.

One-Pot Three-Component Cross-Electrophile Coupling of Bromo(Iodo)Arenes with Alkyl Halides[ab]

Entry				Y_1, Z_1 (mol%)	Y_2, Z_2 (mol%)	Yield (%)
1				5, 0.5	0, 0	**82 (88)**
2[b]				1, 2.5	4, 0	**84 (91)**
3				5, 0.5	0, 0	**91 (95)**
4				2.5, 0.1	0, 5	**70 (78)**

[a]Yields outside of parentheses are isolated yields and yields inside of parentheses are NMR yields, which were determined by integration of ^{1}H NMR spectra against a hexamethylbenzene external standard.

[b]1.1 equivalents of 1-iodo-3-phenylpropane and 110 mol % TDAE were used in initial coupling.