ACCOUNTS
of chemical research

Direct Functionalization Processes: A Journey from Palladium to Copper to Iron to Nickel to Metal-Free Coupling Reactions

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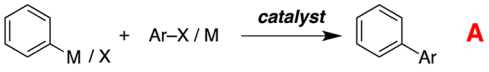
RECEIVED ON JUNE 22, 2012

CONSPECTUS

The possibility of finding novel disconnections for the efficient synthesis of organic molecules has driven the interest in developing technologies to directly functionalize C−H bonds. The ubiquity of these bonds makes such transformations attractive, while also posing several challenges. The first, and perhaps most important, is the selective functionalization of one C−H bond over another. Another key problem is inducing reactivity at sites that have been historically unreactive and difficult to access without prior inefficient prefunctionalization.

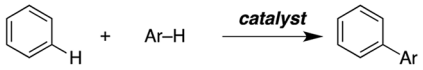
Although remarkable advances have been made over the past decade toward solving these and other problems, several difficult tasks remain as researchers attempt to bring C−H functionalization reactions into common use. The functionalization of sp^3 centers continues to be challenging relative to their sp and sp^2 counterparts. Directing groups are often needed to increase the effective concentration of the catalyst at the targeted reaction site, forming thermodynamically stable coordination complexes. As such, the development of removable or convertible directing groups is desirable. Finally, the replacement of expensive rare earth reagents with less expensive and more sustainable catalysts or abandoning the use of catalysts entirely is essential for future practicality.

Traditional Cross-Coupling



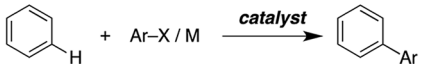
A

Oxidative Coupling of C–H Bonds



B

Direct Arylation



C

This Account describes our efforts toward solving some of these quandaries. We began our work in this area with the direct arylation of *N*-iminopyridinium ylides as a universal means to derivatize the germane six-membered heterocycle. We found that the Lewis basic benzoyl group of the pyridinium ylide could direct a palladium catalyst toward insertion at the 2-position of the pyridinium ring, forming a thermodynamically stable six-membered metallocycle. Subsequently we discovered the arylation of the benzylic site of 2-picolonium ylides. The same *N*-benzoyl group could direct a number of inexpensive copper salts to the 2-position of the pyridinium ylide, which led to the first description of a direct copper-catalyzed alkenylation onto an electron-deficient arene. This particular directing group offers two advantages: (1) it can be easily appended and removed to reveal the desired pyridine target, and (2) it can be incorporated in a cascade process in the preparation of pharmacologically relevant 2-pyrazolo[1,5-*a*]pyridines.

This work has solved some of the challenges in the direct arylation of nonheterocyclic arenes, including reversing the reactivity often observed with such transformations. Readily convertible directing groups were applied to facilitate the transformation. We also demonstrated that iron can promote intermolecular arylations effectively and that the omission of any metal still permits intramolecular arylation reactions. Lastly, we recently discovered a nickel-catalyzed intramolecular arylation of sp^3 C−H bonds. Our mechanistic investigations of these processes have elucidated radical pathways, opening new avenues in future direct C−H functionalization reactions.

Introduction

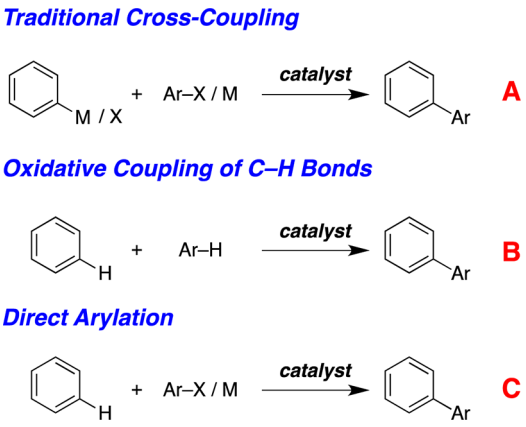
Background. Since the discovery of the Ullmann reaction over 100 years ago,[1] metal-catalyzed coupling reactions have provided powerful methods for the formation of C−C bonds en route to molecules of relevance in many chemical, biological, and material domains (Scheme 1A).[2,3] Moreover,

Published on the Web 10/26/2012 www.pubs.acs.org/accounts
10.1021/ar300185z

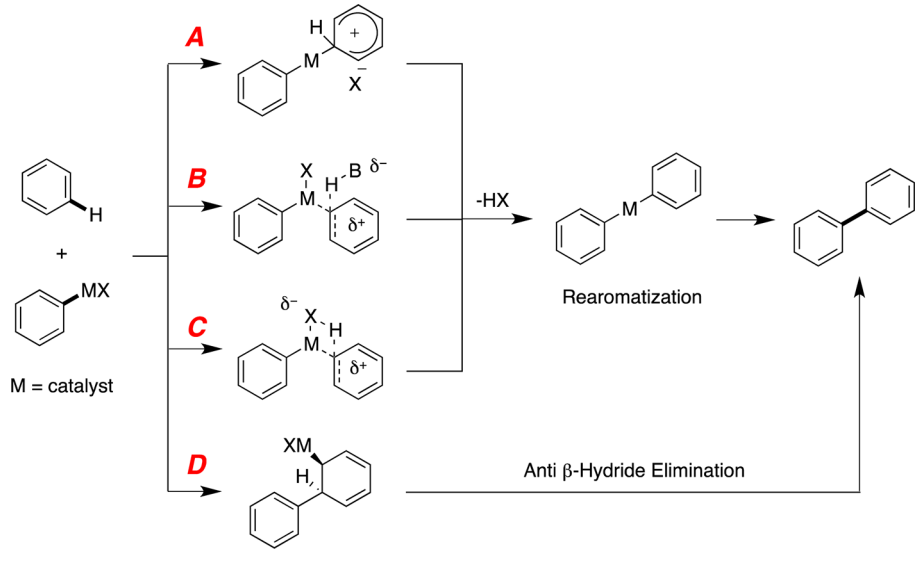
spectacular advancements in the area of direct C–H functionalization have given chemists powerful tools to take advantage of the ubiquity of these bonds in chemical feedstocks.[4−6] The direct transformation of C–H bonds provides a streamlined and more efficient synthesis of desired compounds. Eliminating the need for preactivation of coupling partners increases the economy of the functionalization, avoiding the generation of stoichiometric quantities of sometimes toxic salts yielded in more traditional cross-coupling methods.[4−6] Despite advances in the field, the activation of C–H bonds is a conspicuous challenge due to their high energy and relative inertness.[4] The ideal coupling situation would involve the coupling of two C–H groups (Scheme 1B). Though impressive efforts have been made in this domain, there are issues with reactivity and, perhaps more importantly, with selectivity.[7] As a compromise, some efforts over the past decade have been directed toward *direct* arylation reactions whereby one of the two preactivating groups is replaced by a C–H bond (Scheme 1C).[8] One challenge in such a reaction lies in breaking the strong C–H bond in a chemoselective manner. A way this has been overcome is though the use of directing groups. In this approach a metal catalyst can be guided to a desired reaction site, increasing the effective molarity of the reagent at the target C–H bond, and ultimately favoring the formation of thermodynamically stable metallocycles.[7] Through this strategy numerous catalytic systems have been reported describing intra- and intermolecular arylation reactions, as well as numerous other direct transformations.[4,5,7] A corollary however is that many of these directing groups may be undesired in the target compound, and as such more flexible methods are needed.

While direct arylation reactions have been largely successful on arenes and electron-rich heteroarenes, electron-poor arenes such as pyridine have presented a significant quandary.[4,9,10] Several mechanisms for direct arylations have been proposed (Scheme 2), each of which are difficult to apply to electron-deficient species.[4] The S_EAr pathway (path A) requires an electron-rich arene to bind the transition metal center. This route would be difficult to obtain with pyridine adducts due to insufficient electron density. Similarly, concerted S_E3 sequences have been reported (path B), though such a mechanism would lead to a partial build up of positive charge in the arene, which again would be disfavored in electron-poor substrates. The same can be said for a

SCHEME 1. Various Arylation Strategies



SCHEME 2. Various Proposed Mechanisms for Direct Arylation Reactions



σ-bond metathesis pathway (path C). Heck-like mechanisms are often not considered due to the unlikelihood of *anti*-β-hydride elimination (path D).[2] Given these studies, the difficulties in performing the direct arylation, and other C–H activation, of pyridine become clear.

In parallel, classical cross coupling at the 2-position of pyridine has been problematic.[6,11] Catalyst poisoning by the Lewis basic nitrogen must be considered, though can be overridden with the judicious choice of ligand.[12] 2-Halopyridines are viable pseudoelectrophiles, though their commercial availability is limited and synthesis often nonselective. 2-Metallopyridines are largely limited to environmentally challenging Stille cross-coupling reactions.[13] In light of these realities, the development of transition-metal catalyzed activation α to the nitrogen atom not only would provide an efficient route to synthesize more complex pyridine derivatives but also would solve the two aforementioned outstanding problems in the elaboration of this azine.

Inspiration. Part of our research program has revolved around developing stereoselective methods in the synthesis of stereoenriched six-membered azacycles. To accomplish this, we set about activativing the pyridine core via the use of *N*-imidate pyridinium salts[9] and *N*-iminobenzoyl pyridinium ylides[14−18] (Figure 1). Given the challenges mentioned, *vide supra*, we hypothesized that these activated pyridiniums may prove amenable to direct functionalization and, due to the presence of a *removable* directing group, that this would occur at the 2-position of the heterocyclic ring. Our inspiration was the elegant work by Prof. Fagnou who built on the pioneering work of Bercaw,[19] Jordan,[20] and Bergman[21] demonstrating that pyridine *N*-oxides could be readily arylated at the 2-position in presence of $Pd(OAc)_2$.[22,23] Further consideration of our own pyridinium species eliminated the application of imidate salts due to their poor stability above 0 °C. However, *N*-iminopyridinium ylides are extremely stable, accessible on scale through a two-step, one-pot sequence from pyridine.[14] Electronically they are similar to the pyridine *N*-oxides, and the *N*-iminobenzoyl group appeared to be analogous to the anilide directing groups developed by Tremont and Daugulis (Figure 2).[24,25] Indeed our work delineated the directing group ability of the *N*-iminobenzoyl group of the ylide in the diastereoselective Grignard addition to the 2-position of the pyridinium (Scheme 3),[15] as well as in the asymmetric hydrogenation of 2-susbtituted pyridinium ylides to afford piperidines.[16,17] The stability toward main group transition metals was also demonstrated in the Ni-catalyzed cycloaddition of *gem*-diacceptor cyclopropanes onto quinolonium ylides.[18]

The remainder of this Account will discuss our progress in the direct functionalization of *N*-iminopyridinium ylides in an effort to improve the tools available in the direct functionalization of electron-deficient arenes while offering a universal scaffold for pyridine elaboration. We will also describe how this led into the development of other novel direct arylation reactions using more sustainable transition metal catalysts, even eliminating the need for such metals.

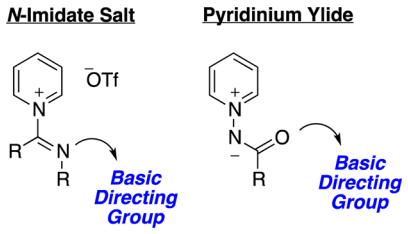


FIGURE 1. *N*-Imidate pyridinium salts and *N*-iminopyridinium ylides.

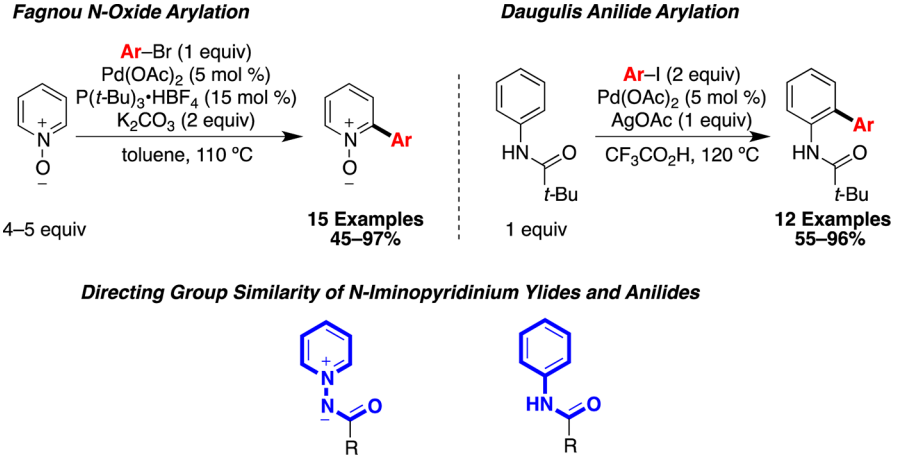
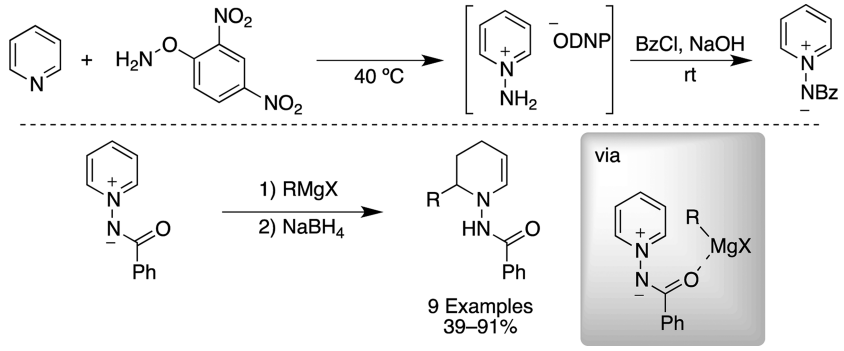
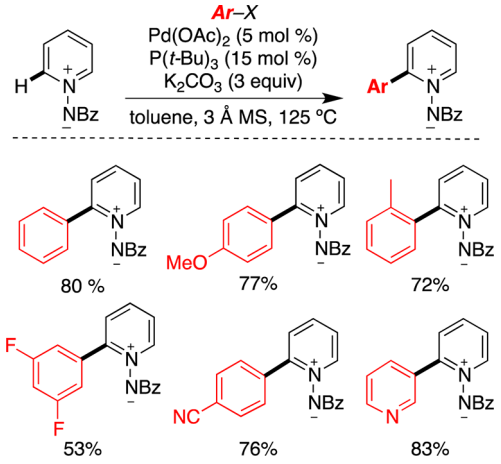


FIGURE 2. Comparison of pyridinium and anilide arylation.

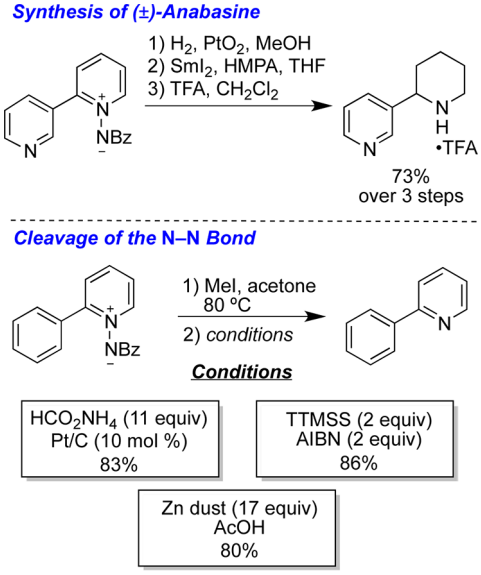
SCHEME 3. Directed Addition of Grignard Reagents to *N*-Iminopyridinium Ylides



SCHEME 4. Selected Scope for the Directed Arylation of *N*-Iminopyridinium Ylides



SCHEME 5. Synthesis of (±)-Anabasine and Cleavage of the N–N Bond



Discussion

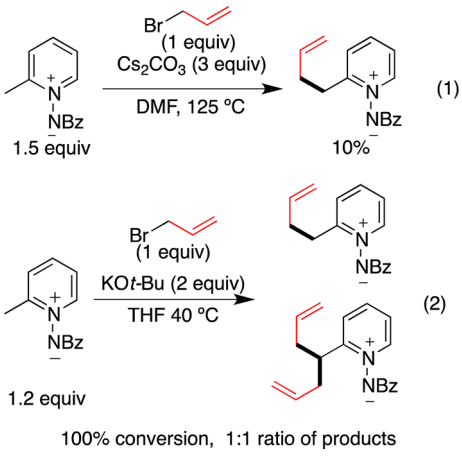
***N*-Iminopyridinium Ylides. Pd-Catalyzed Direct Arylation.** The disclosure of the direct arylation of pyridine *N*-oxides has no doubt inspired much of the work of direct functionalization of a plethora of electron-deficient azines because it provided a solution to two important problems.[22] It offered the first general scope of direct arylation onto pyridine, and it provided an answer to the aforementioned 2-pyridyl cross-coupling problem. However, there were some drawbacks, namely, the requirement of a large excess of the pyridine *N*-oxide to suppress the formation of a 2,6-bisarylated product.[22] We believed that our pyridinium ylides could overcome this drawback due to the presence of a Lewis basic directing group helping to limit the reaction to one site. The fact that these ylides tend to be easily manipulated, bench-stable powders also increases their attractiveness.

Reaction optimization revealed that in presence of $Pd(OAc)_2$ and P(*t*-Bu)$_3$ a wide range of aryl iodides could be readily coupled to the pyridinium ylide in moderate to excellent yields with only 1.5 equiv of the pyridinium (Scheme 4).[26] Furthermore, a range of pyridinium ylide analogues were also viable coupling partners. This methodology was applied to the synthesis of (±)-anabasine whereby 3-iodopyridine was reacted with *N*-iminobenzoyl pyridinium ylide to furnish the corresponding bispyridyl adduct. The activated pyridinium ylide could be chemoselectively reduced to piperidine, leaving the unactivated pyridine ring intact (Scheme 5).[26] Cognizant that the *N*-activating/directing group may be undesired in the synthesis of more complex molecules, we demonstrated that it could be removed under a variety of conditions, through a two-step, one-pot *N*-methylation/reduction sequence (Scheme 5).[26]

Benzylic Functionalization. During the course of our direct arylation studies, it was noted that the 2-picolonium ylide gave a marked decrease in the yield for the expected 2-aryl product.[27] Investigation revealed that arylation of the benzylic position was indeed preferred. These results added to the few examples of direct arylation of sp^3-sites at the

time.[28–30] Reaction optimization demonstrated that when DavePhos was used as the source of phosphine a wide range of electron-poor, -rich, and -neutral aryl chlorides could be coupled in good to excellent yields (Scheme 6). This was one of the few accounts of aryl chlorides being applied in mild direct functionalization processes, an advantage due to their low cost and wide availability relative to their corresponding aryl bromide and iodide analogues.[27] Pyridine derivatives were operative, and only methyl groups at the 2-position demonstrated reactivity as alkyl groups at the 3- and 5- positions remained intact, indicating the need for *N*-iminobenzoyl group to direct the reaction (Scheme 6). 2-Ethyl pyridine also coupled with aryl chlorides selectively at the benzylic site.

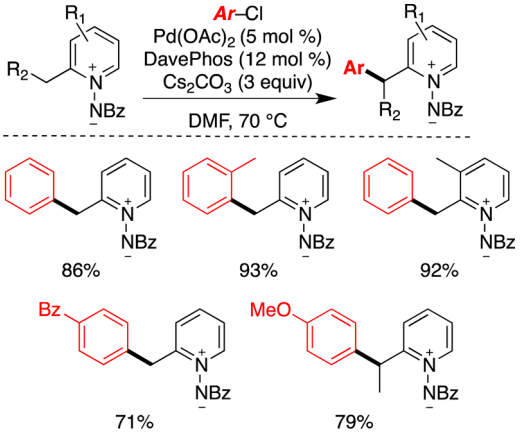
Given the mild conditions, we were curious about the mechanism of reaction. The application of aryl chlorides was reasoned to be the consequence of the bulky, electron-rich phosphine employed. The question remained how the benzylic site underwent carbopalladation. Enamines are known to undergo arylation reactions.[31] Given this similarity in the pK_a of the benzylic site, deprotonation of the methylene site would lower the energy of the endocyclic nitrogen atom, and the negative charge on the adjacent nitrogen can be delocalized into the more electronegative oxygen atom (Scheme 7). Previous infrared studies indicated a stretching vibration for the carbonyl group to be 1560 cm^{-1}, suggesting a preference for this tautomer.[15] To probe the viability of the deprotonation of the benzylic site, the 2-picolinium ylide was reacted with Cs_2CO_3 in DMF in presence of allyl bromide (eq 1). The corresponding allylated pyridinium was isolated in 10% yield, suggesting this manifold was indeed viable. We could improve on this yield through the use of KO*t*-Bu as a base; however the allylation became unselective with a mixture of both mono- and bisallylated adducts formed (eq 2).



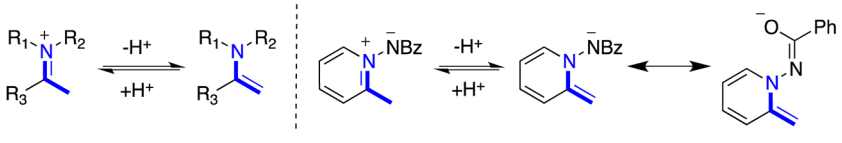
The reaction mechanism for the arylation is believed to proceed as follows (Scheme 8). Palladium undergoes oxidative addition into the aryl chloride (A). Simultaneously the 2-alkyl pyridinium ylide is deprotonated and converted into an enamine-like species (B). Presumably there exists an excess of this carbon nucleophile in solution because the Cs_2CO_3 is largely soluble under the reaction conditions. The Lewis basic *N*-imino group directs carbopalladation of the exocyclic olefin (C). Cis/trans isomerization (D) followed by reductive elimination (E) provides the arylated product while regenerating the active Pd^0 catalyst.

Copper-Catalyzed Alkenylation. Derivatives of 2-alkenyl pyridine are relevant pharmacophores. Given our success in the arylation of pyridinium ylides, an alkenylation process would increase the versatility of the motif, further approaching our goal of a universal template for making libraries of six-membered nitrogen-containining molecules. At the onset of these studies, there, surprisingly, had been

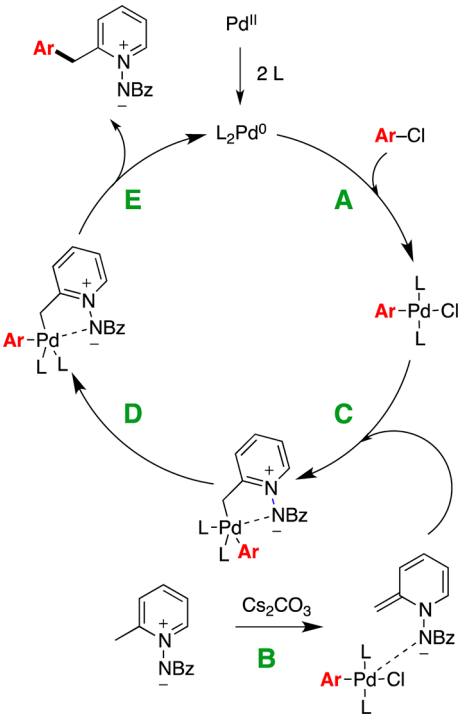
SCHEME 6. Selected Scope for the Benzylic Arylation of *N*-Iminopyridinium Ylides



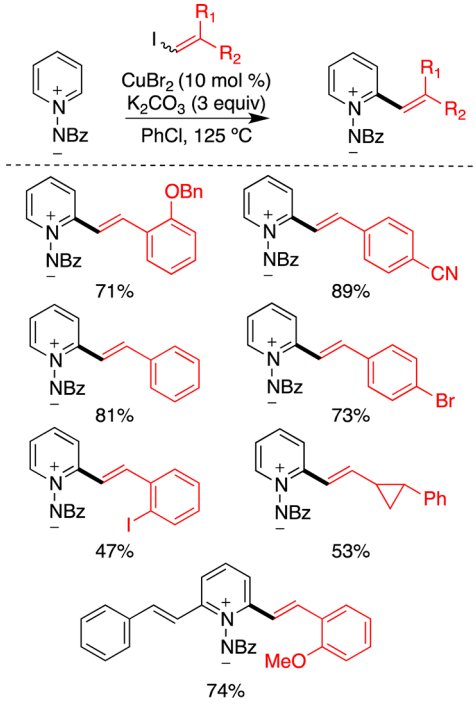
SCHEME 7. Comparison of Enamines to 2-Alkyl *N*-Iminopyridinium Ylides



SCHEME 8. Proposed Catalytic Cycle for the Benzylic Arylation of *N*-Iminopyridinium Ylides



SCHEME 9. Selected Scope for the Direct Alkenylation



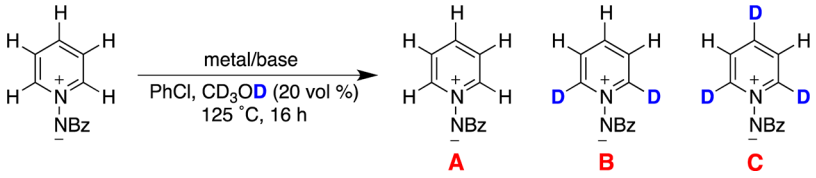
only a single reported study on the direct alkenylation of electron-deficient heterocyclic arenes,[32] and very few of direct alkenylations of any sort.[33,34] Given the often harsh conditions or high step count needed to access the 2-alkenyl pyridine motif, we reasoned that this proposed methodology would offer an efficient means to access this privileged architecture.

We began our optimization with (*E*)-β-phenyl vinyl iodide[35] under palladium catalysis. Systematic screening failed to improve the yield above 55%. The inclusion of additives proved detrimental save two exceptions. DMSO was added in 10 vol % to help stabilize Pd-black observed in the reaction mixture, improving the yield to 60%.[36] Copper salts had been used to mask nonproductive Lewis basic sites.[37] Concerned that the ylide group, while activating the α-position, may in this case result in catalyst poisoning, we added 0.5 equiv of CuBr, noting a 63% yield of the 2-vinyl pyridine. Gratifyingly, we subsequently found that CuBr itself catalyzed the process in very good yield without any exogenous ligand. In fact, the alkenylation proved insensitive to the copper source employed as most Cu^0, Cu^I, and Cu^{II} salts furnished similar results.[36]

Under the optimal conditions, we coupled a range of electron-rich, electron-poor, and sterically congested styryl iodides in good to excellent yields.[36] A feature was the chemoselectivity as halogen atoms present on the aryl component of the (*E*)-β-aryl vinyl iodide were tolerated with no competing arylation noted (Scheme 9). As with the Pd-catalyzed processes, substitution on the pyridinium was tolerated. In contrast, alkenes bearing sp^3 subsitution, such as 1-iodohexene, furnished the targets in moderate to poor yield, likely due to increased difficulty of oxidative insertion into the C–I bond. An exception was an iodoalkene bearing a cyclopropane, though this is attributed to the high s-character of the carbocycle.[36] Given the strongly reducing nature of the N–N scission described above, there was concern whether the free 2-vinyl pyridine could be liberated with the double bond intact. Ultimately, this was achieved through methylation of the ylide followed by reduction with Zn dust in presence of AcOH.[36]

A KIE of 1.45 suggested that the C–H bond breaking event was not rate limiting. To ascertain the directing group effect of the *N*-imino benzoyl group, we undertook labeling studies in presence of CD_3OD (Table 1). Stirring the ylide in PhCl with 20 vol % CD_3OD at 125 °C failed to provide any deuterium incorporation into the pyridinium. Performing the same process in presence of K_2CO_3 expectedly gave 90% D incorporation at the 2, 4, and 6 positions.[36] The inclusion of $CuBr_2$, in the absence of any base, still gave deuterium incorporation at the 2- and 6-sites of the pyridinium exclusively, suggesting that the copper readily inserts in a directed fashion without the aid of the base. Curiously, under the

TABLE 1. Deuterium Labeling Study in the Direct Alkenylation of *N*-Iminopyridinium Ylides



entry	metal/base	% D incorporation[a]	LCMS [M + 1]	product
1	none	0	199.2	A
2	$CuBr_2$ (10 mol %)	n/a[b]	201.2	B
3[c]	K_2CO_3 (2 equiv)	90	202.2	C
4	$CuBr_2$ (10 mol %), K_2CO_3 (2 equiv)	92	201.2	B

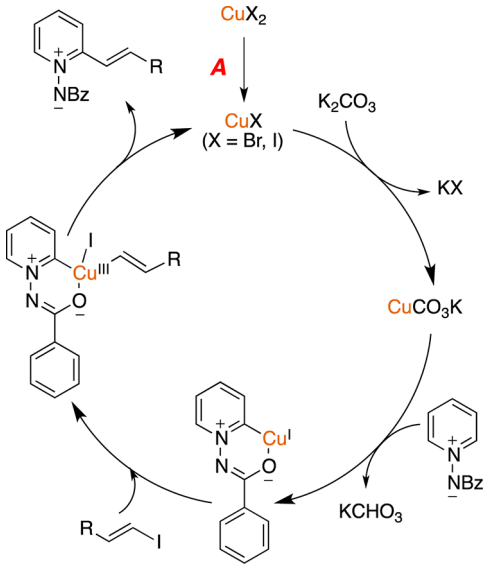
[a]Incorporation determined by ^{1}H NMR. [b]%D incorporation could not be determined by ^{1}H NMR due to peak broadening. [c]Equal D incorporation in 2,4,6-positions.

complete reaction conditions with both $CuBr_2$ and K_2CO_3, again selective deuterium incorporation only at the 2- and 6-sites was observed, despite the large excess of carbonate relative to the copper catalyst. Furthermore, unlike when $CuBr_2$ was used in absence of base, the level of deuterium could be determined, implying the possible presence of a different catalytic reagent.[36]

With this data in hand, the following catalytic cycle was proposed (Scheme 10). Given that a wide range of active catalysts were equally operative and the result obtained in the labeling study, it is believed that a single active copper species is responsible for the alkenylation. We believe that the active copper species is a Cu^I intermediate. Copper(II) can be reduced to Cu^I via the pyridinium ylide as evidenced by the red-brown color of the solution (A).[36] In the case of Cu^0, the ylide can add into the copper, generating a Cu^{II} intermediate that is again converted to the active Cu^I catalyst. Once Cu^I is available, it may undergo a known ligand exchange with K_2CO_3 (B) to generate $CuCO_3K$, which undergoes a directed insertion into the 2-position of the pyridinium ring (C).[36] As noted, the carbonate, though not needed to effect the insertion, is required for the reaction to proceed and may ultimately act in controlling the pH of the reaction through the formation of potassium bicarbonate. The metalated pyridinium can oxidatively add into the alkenyl iodide (D), forming a high energy Cu^{III} intermediate that undergoes reductive elimination to liberate the product (E) and CuI.

Discovery of a New Route to Pyrazolo[1,5-*a*]pyridines. During the course of the direct vinylation optimization, we observed that when the pyridinium ylide is reacted with a styryl iodide in presence of a Pd catalyst and silver salt, a 2-substituted pyrazolo[1,5-*a*]pyridine (from here on shortened to pyrazolopyridine) was obtained in a moderate 45% yield (Scheme 11).[38,39] We were keen to study this

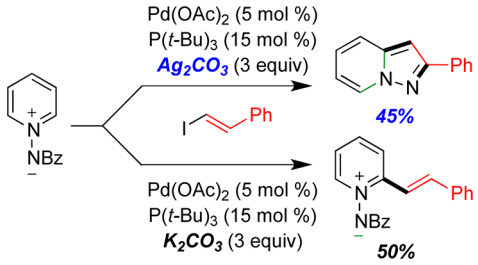
SCHEME 10. Proposed Catalytic Cycle for the Cu-Catalyzed Direct Alkenylation of *N*-Iminopyridinium Ylides



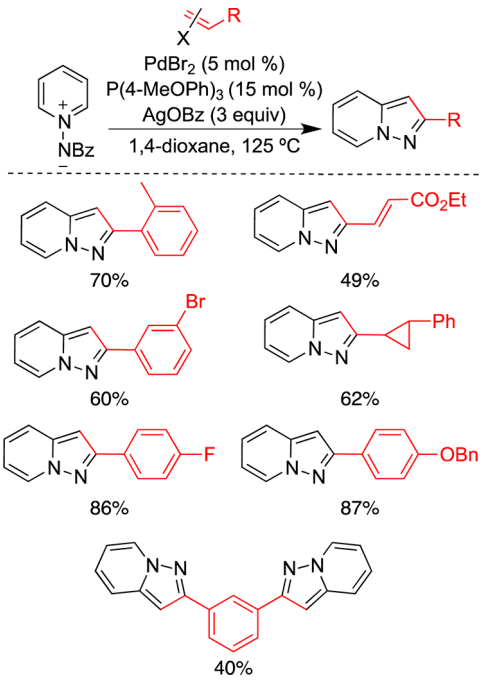
for several reasons. First, these molecules are pharmacologically relevant, serving as DAC inhibitors in oncological studies, applicable in the treatement of psychostimulant addictions, and showing promise in the treatment of Parkinson's disease and schizophrenia.[38,39] Second, previous to these studies, access to this privileged motif often required five to seven synthetic steps, where we may access the scaffold via a two-step sequence from pyridine. Third, where the methodology described above highlights the use of a readily removable directing group, this method would include a portion of the directing group into the target molecule, providing an economical process, further expanding the scope of the ylide.

Reaction optimization determined that AgOBz was optimal for the reaction. Under the most advantageous conditions, a range of (*E*)-β-aryl vinyl iodides and bromides were

SCHEME 11. Initial Observation of Pyrazolopyridines

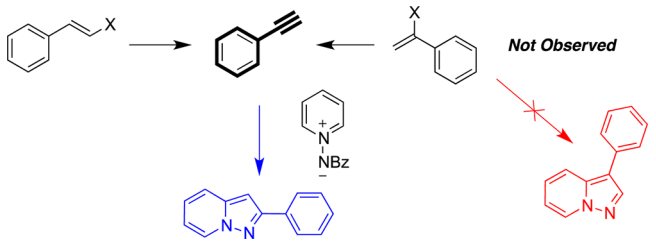


SCHEME 12. Selected Scope of Vinyl Halides in the Preparation of 2-Substituted Pyrazolopyridines

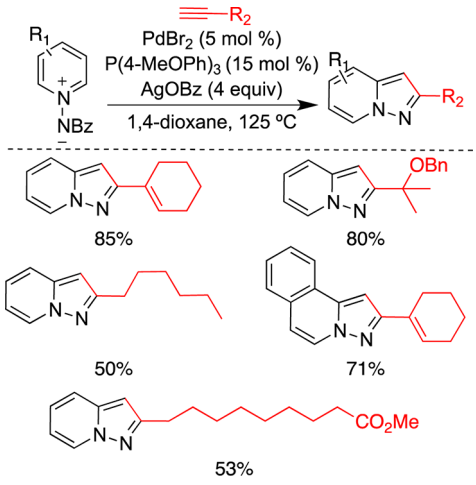


reacted with a range of substituted of pyridinium ylides, furnishing a library of some 50 2-substituted pyrazolopyridines in good to excellent yields (Scheme 12). As with the Cu-catalyzed vinylation, the reaction was chemoselective; halides present on the aryl groups did not undergo arylation.[38,39] However, with the limitation of alkenes bearing alkyl groups, in addition to the observation that *E* and *Z* alkenes as well as α-bromostyrene all furnished the same product, we were curious to the exact nature of the reacting partner (Scheme 13).[39] When the styryl iodide was introduced to the reaction conditions, it was readily converted to phenyl acetylene, revealing the potential reactive species. Gratifyingly we found that a range of terminal alkynes were viable reaction partners, furnishing comparable yields to those observed with the iodoalkenes (Scheme 14). Most

SCHEME 13. Proposed Reactive Intermediate



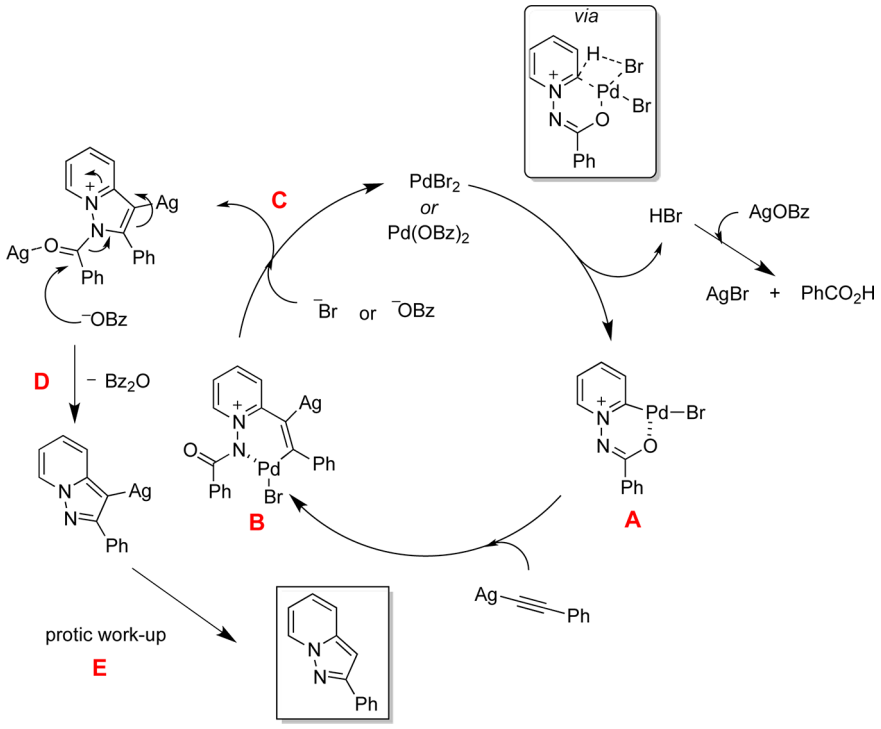
SCHEME 14. Selected Scope of Alkynes in the Preparation of 2-Substituted Pyrazolopyridines



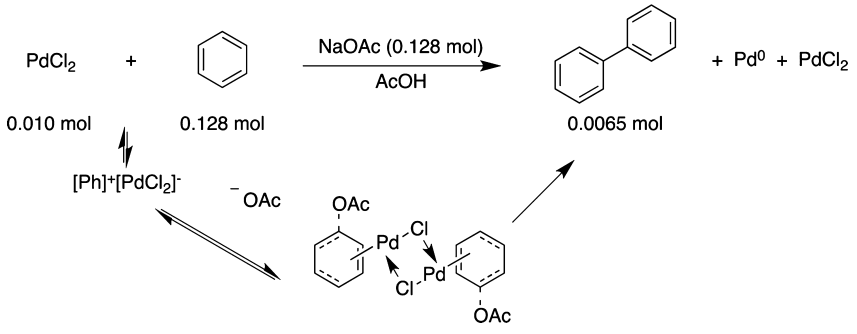
interestingly alkyl-substituted alkynes were viable reaction partners, expanding the scope of pyrazolopyridines. It is likely that the acidity of haloalkenes with sp^3 substitution is not sufficient to permit facile elimination to the corresponding alkyne.[39]

We were intrigued by the effect of the benzoyl directing group on the reaction. We prepared an array of electron-rich and -poor variants, and in all cases the more electon-rich *N*-iminobenzoyl groups gave the best results. This indicated that increased Lewis basicity is more important in directing the palladium to the reactive site than increasing the acidity of the 2-position of the pyridinium ring.[39] The low KIE of 1.5 appears to agree with this. The proposed catalytic cycle is as follows (Scheme 15). Palladium undergoes directed insertion into the 2-position of the pyridinium ring (A). The palladated ylide may then add into the silver acetylide giving the metallocycle B. The role of the silver may be to activate the sp-bond, and the fact that this species is needed may explain why internal alkynes are not viable partners. Similar Pd-complexes had been reported, as has Pd-catalyzed conjugate addition of amines. Reductive elimination (C) then

SCHEME 15. Proposed Catalytic Cycle for the Synthesis of Pyrazolopyridines



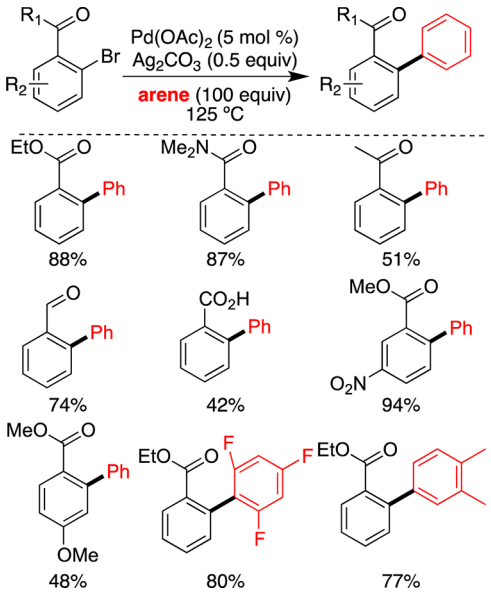
SCHEME 16. Van Helden's Pd-Mediated Benzene Dimerization



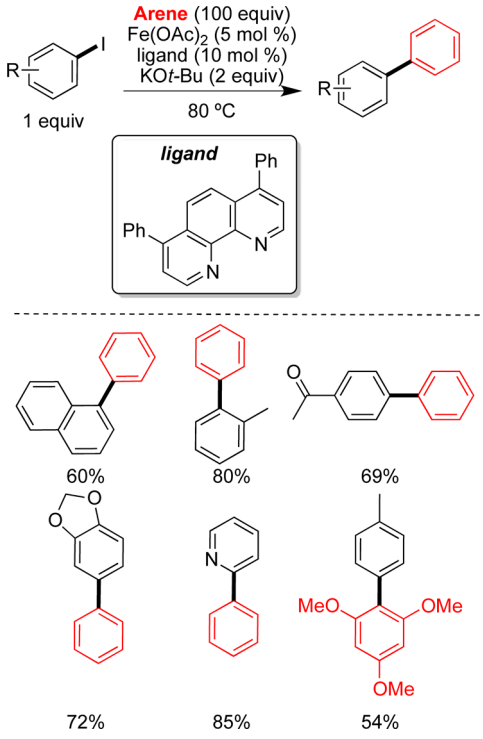
gives the cyclic intermediate that rearomatizes through the expulsion of the benzoyl moiety (D); which may be assisted by Lewis acidic Ag reagent. Protonolysis of the C–Ag bond at C3 upon work up gives the observed product, explaining the lack of deuterium incorporation in the labeling studies (E).

Arylation of Non-heterocyclic Arenes . Umpolung Arylation. In 1965, van Helden described a Pd-mediated homocoupling of benzene using a stoichiometric amount of $PdCl_2$.[40] The reaction is believed to proceed by a σ–π coordination between the Pd and benzene, followed by rapid attack of the acetate ion to generate the $C_6H_6 \cdot PdCl_2$ Wheland pair. Dimerization of the system and disproportionation afforded biphenyl, $PdCl_2$, and Pd^0 (Scheme 16). We reasoned that this could be rendered catalytic through the stabilization offered by directing groups in addition to the inclusion of an external oxidant.[41] We envisioned that an aryl halide with an *ortho*-directing group would provide a thermodynamically stable palladacycle following oxidative insertion. The metal could coordinate to the π system of a benzene ring, insert into an arene C–H bond and reductively eliminate. The oxidant would then regenerate the catalytically active species. This proposed reactivity is opposite of what is typically observed in direct arylation processes whereby a directing group is used to stabilize a metallocycle following insertion into the C–H bond. It also presents advantages in that the desired pseudoelectrophile could

SCHEME 17. Selected Scope for the Umpolung Arylation of Various Arenes



SCHEME 18. Selected Scope for the Fe-Catalyzed Arylation



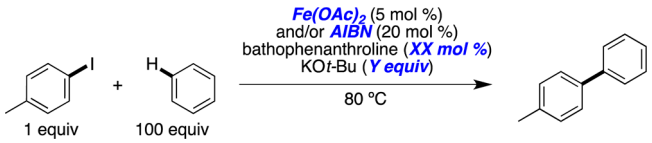
be synthesized using well-established strategies and the arene coupling partner could be used as the reaction medium.

Our optimal conditions required only 5 mol % $Pd(OAc)_2$ and 0.5 equiv of Ag_2CO_3 to proceed.[41] We reported the use of 100 equiv of benzene for ease of manipulation, though this could be lowered to 10 equiv and furnish acceptable results. A range of directing groups were compatible, including esters, amides, carboxylic acids, ketones with and without enolizable centers, and aldehydes (Scheme 17). Electron-withdrawing groups on the haloarene proved beneficial, likely due to increased ease of oxidative insertion, though electron-rich substrates were also well behaved. Arene partners other than benzene were also demonstrated to be suitable.[41]

Direct Arylation through Radical Processes. Iron-Catalyzed Arylation. As mentioned earlier in this Account, one of the persistent challenges in direct functionalization reactions is the application of more sustainable and environmentally benign catalysts. Iron reagents can solve this problem. Reaction optimization determined that the optimal reaction conditions consisting of 5 mol % $Fe(OAc)_2$, 10 mol % bathophenanthroline, and 2 equiv of KO*t*-Bu could couple various aryl iodides with benzene.[42] Of note was the absence of a directing group to stabilize the organometallic intermediate formed in the process. Furthermore, the inclusion of a stoichiometric amount of metal additive previously reported with Fe-catalyzed arylation processes was not needed.[42] As with the umpolung arylation, the arene loading could be lowered to <20 equiv without detriment. The scope again proved to be general, tolerating neutral, electron-rich, and electron-deficient aryl halides (Scheme 18).[42] Electron-sufficient aryl iodides furnished the best results, operating even at room temperature. Enolizable centers in addition to other functional groups such as esters were well behaved despite the presence of a strong base. Arenes other than benzene were also viable reaction partners.

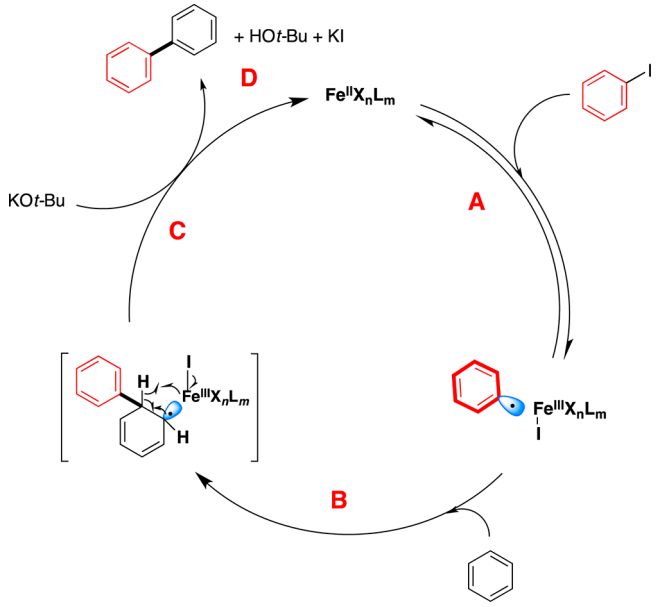
Control studies determined that this was indeed an Fe-catalyzed process unlike some evidence shown in other Fe-mediated processes.[43] The inclusion of Cu impurities proved dentrimental and yields improved with increased purity of the $Fe(OAc)_2$. Radical inhibitor and KIE studies led to the conclusion of a radical pathway. This was corroborated with the fact the 20 mol % AIBN in the absence of an Fe source furnished the arylated product in 17% yield (Table 2), and the observation that arylation often favors the formation of more hindered *ortho*-substituted products stabilized through hyperconjugation.[42] Given these results, we believe that the reaction proceeds through a mechanistic pathway akin to a metal-catalyzed living radical polymerization (Scheme 19).[42] The first step of the process involves activation of the C–I bond by a one-electron oxidation of the metal center, reversibly forming the initiating radical species

TABLE 2. Arylation in the Presence of Iron and AIBN



entry	catalyst	ligand loading (mol %)	KO*t*Bu loading	yield (%)
1	$Fe(OAc)_2$	10	2 equiv	91
2	none	10	2 equiv	<1
3	AIBN	none	2 equiv	17
4	$Fe(OAc)_2$ + AIBN	10	none	<1

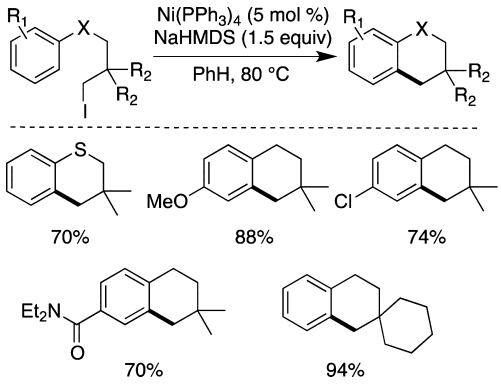
SCHEME 19. Proposed Mechanism for the Iron-Catalyzed Homolytic Arylation of Arenes



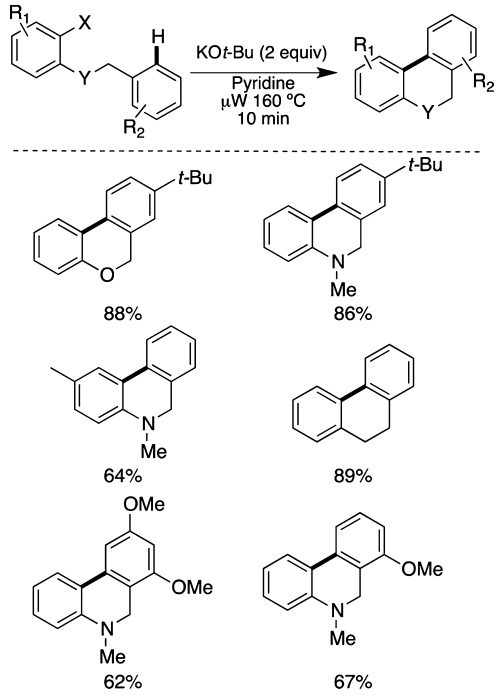
associated with an oxidized metallo-intermediate (A). This intermediate is then transformed into the desired biaryl product by addition onto the unactivated arene, which is possibly precoordinated to the iron catalyst (B). Proximal abstraction of the iodine permits rearomatization while regenerating the active Fe^{II} catalyst (C). At this stage, the radical is no longer bound to the iron reagent, but instead the duo forms a tight pair, generating HI that can be quenched by the presence of KO*t*-Bu (D). Such a pathway would explain the increased effectiveness of electron-rich iodides, because radical intermediates would be better stabilized.

Nickel-Catalyzed Arylation. We wished to pursue radical activation without the inclusion of harsh or toxic initiators, in particular, a homolytic arylation process to include functionalization of sp^3 centers. Optimization determined that a system of $Ni(PPh_3)_4$ in conjunction with NaHMDS effectively

SCHEME 20. Selected Scope for Ni-Catalyzed Intramolecular Homolytic Arylation

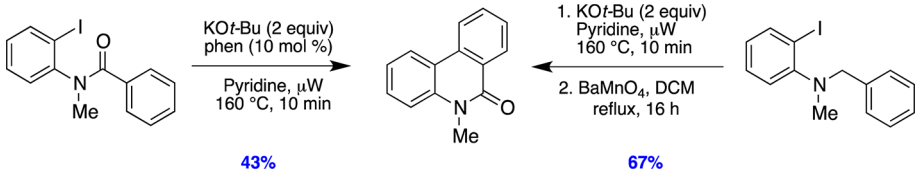


SCHEME 21. Selected Scope for Metal-Free Intramolecular Arylation



catalyzed an intramolecular arylation of thiol ethers in good to excellent yield (Scheme 20).[44] Substrate scope delineated that the sulfur could be replaced with carbon without detriment. The formation of five-membered cycles was possible in moderate yield, suggesting the importance of a thermodynamically favored adduct over a kinetically relevant pathway. Radical inhibitor studies ruled out the possibility of the Friedel–Crafts mechanism, helping confirm the existence of a radical manifold. DOSY experiments enabled the determination of the diffusion coefficients of the reagents in solution and determined that a complex comprising Ni, the base, and

SCHEME 22. Alternate Means To Prepare Phenanthridines



the aryl halide must be formed in order for the reaction to proceed in a productive fashion.[44] Ni^0 was found to be a catalyst in the reaction and not simply a radical initiator. The exact nature of this complex is the subject of ongoing investigation within our group.

Toward Metal-Free Processes. During the course of our iron studies, we observed that electron-rich arenes would undergo arylation under forcing conditions (>150 °C) in the absence of the iron catalyst. Though admittedly electronically biasing the system to stabilize hypothetical radical intermediates, we recognized that this laid the groundwork for the development of a completely metal-free arylation process. We reasoned that including a tether for an intramolecular arylation would increase the effective concentration of the radical generated efficiently to enable a homolytic arylation to occur.[45] This proved to be correct as a system of KHMDS/pyridine or KO*t*-Bu/pyridine/phenantroline allowed the intramolecular arylation en route to the synthesis of a range of cyclic alkanes, ethers, and amines in moderate to excellent yields (Scheme 21). This methodology permitted access to biologically relevant phenanthridones via two means: (i) oxidation of the cyclic amine following cyclization or (ii) subjecting an amide to the reaction conditions (Scheme 22). The fact that electron-deficient anilines, in conjunction with reaction inhibition in presence of TEMPO or galvinoxyl, confirmed again that a radical pathway was indeed operative. The generation of the radical is thought to arise from the complexation of the base to pyridine of phenantroline, as demonstrated by Itami and others.[45]

Summary and Outlook

Direct functionalization strategies have offered the unique opportunity to take advantage of the ubiquity of C–H bonds en route to the preparation of small and, in some cases, complex molecules. Our contribution to the field started through demonstrating that *N*-iminopyridinium ylides can be a versatile scaffold on which to effect several transformations, direct and otherwise. As a solution to the site-selectivity problem of many direct transformations, we demonstrated the use of powerful, yet readily removable, directing groups that under specific conditions can even be incorporated into a target molecule. Through the use of a stabilizing group, we could invert the reactivity typically reported with arylation reaction. Perhaps most importantly, we demonstrated that inexpensive, sustainable catalysts could be employed. We discovered that many of these proceed via radical pathways, opening alternative avenues to toxic tin initiators, or the use of AIBN. Needless to say work is continuing in this field, and we wish to continue our contributions to the field by enabling the functionalization of other classes of small molcules and increase the mechanistic knowledge involved such that we and others can continue to grow the field.

This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), the Canada Research Chair Program, the Canada Foundation for Innovation, the Centre for Green Chemistry and Catalysis of FRQNT, and Université de Montréal. J.J.M. is grateful to FQRNT and NSERC for postgraduate and postdoctoral scholarships. Prof. Timothy F. Jamison. Dr. Andy Kleinke, and Dr. Yuan Zhang are thanked for proofreading of this manuscript.

BIOGRAPHICAL INFORMATION

James J. Mousseau was born in Montréal, Quebec, in 1981. Upon completing his B.Sc. in Biochemistry in 2004 at Concordia University, he continued his M.Sc. studies at Concordia under the supervision of Prof. Louis A. Cuccia and was involved in the synthesis of novel crescent-shaped urea-linked heterocyclic foldamers. In 2011, he completed his Ph.D. studies under Prof. André B. Charette at Université de Montréal studying arene direct functionalization processes. He currently is a Postdoctoral Fellow at the Massachusetts Institute of Technology under Prof. Timothy F. Jamison where his current research investigates epoxide ring-opening cascade reactions.

André B. Charette was born in 1961 in Montréal, Quebec. Upon completion of his B.Sc. from Université de Montréal in 1983, he pursued his graduate studies at the University of Rochester, earning his M.Sc. (1985) and Ph.D. (1987) with Robert Boeckman, Jr. Following NSERC postdoctoral fellowship at Harvard University with D. A. Evans, he began his academic career at Université Laval in 1989. In 1992, he returned to his alma mater, where he is today

full professor and holder of a Canada Research Chair. His research focuses on the development of new methods for the stereoselective synthesis of organic compounds. Recent honors include a Cope Scholar Award (2007), the Prix Marie-Victorin (2008), and the Alfred Bader Award (2009).

FOOTNOTES

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The authors declare no competing financial interest.

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