Dual Nickel/Photoredox-Catalyzed Deaminative Cross-Coupling of Sterically Hindered Primary Amines
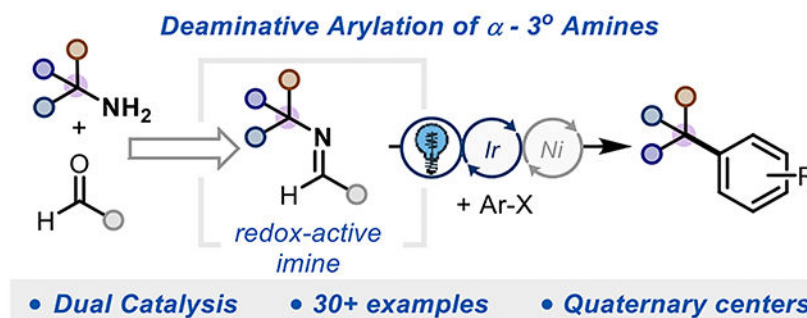
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Abstract

We report a method to activate a–3° amines for deaminative arylation via condensation with an electron-rich aldehyde and merge this reactivity with nickel metallaphotoredox to generate benzylic quaternary centers, a common motif in pharmaceuticals and natural products. The reaction is accelerated by added ammonium salts. Evidence is provided in support of two roles for the additive - inhibition of nickel black formation and acceleration of the overall reaction rate. We demonstrate a robust scope of amine and haloarene coupling partners and show an expedited synthesis of ALK2 inhibitors.

Graphical Abstract

Primary amines are present in a variety of building blocks, easily prepared and purified, and are amenable to late-stage functionalization. The ubiquity of primary alkyl amines as advanced intermediates and drugs[1,2] makes them attractive reagents for alkyl precursors. Thus, discovery chemists can take advantage of the plethora of primary amines that they obtain in their inventories to utilize them as coupling partners. In 2017, the Watson group published a nickel-catalyzed Suzuki-Miyaura coupling demonstrating the use of unactivated primary amines as alkyl precursors via formation of Katritzky pyridinium salts (Scheme 1A).[3] Since this seminal publication, the use of Katritzky salts as a functional handle has

been widely popularized due to their ease of synthesis and accessible reduction potential (~ −0.9 V vs SCE).[4] The corresponding pyridinium salts are amenable to many transition metal-catalyzed[5–12] and photoredox-catalyzed[13–19] deaminative transformations,[20,21] but are limited to α-1° and α-2° amines, as sterically encumbered α-3° amines are unable to condense onto triphenyl-pyrylium salts (Scheme 1B).[10,21] In an effort to address this shortcoming, we developed a complementary method to activate the C-N bond of α-3° amines via condensation onto an electron rich aldehyde activating group (Scheme 1C, **top**).[22] This allows for generation of a nucleophilic carbon radical via single-electron oxidation that can be coupled to electron-deficient olefins to generate Giese products. This deaminative method complements the Katritzky salts in two ways: (1) tertiary alkyl amines are used as viable alkyl precursors, and (2) the radical reactivity is revealed through an oxidative rather than reductive pathway.

Expanding the coupling partner from electron deficient olefins to aryl halides through dual photoredox/nickel catalysis (Scheme 1C, **bottom**) would allow for the use of primary α-3° amines as radical precursors in $C(sp^3)$-$C(sp^2)$ cross coupling, a bond construction recently identified as a missing link in crosscoupling technology,[23] and of increasing interest to medicinal chemistry as a way to expand and diversify the chemical landscape of pharmaceuticals.[23–27] While similar $C(sp^3)$-$C(sp^2)$ cross couplings can be achieved with other alkyl precursors, namely halides,[28,29] alkyl trifluoroborates,[30] Grignard reagents,[31,32] olefins,[33,34] and redox-active esters,[35] our strategy adds a valuable building block to the synthetic toolbox for generating quaternary centers from ubiquitous primary amines.

We began our initial screen by using tetramethylheptanedionato (TMHD) nickel(II),[28,30] 1 equivalent of imine, and 1.2 equivalents of aryl halide (Table 1, entry 2) to afford the product in 31% yield (see SI for additional ligands screened). An extensive additive screen identified tetra-alkyl ammonium salts and imidazolium salts as helpful for reactivity, with nBu$_4$NCl giving the best results (see SI for full list of additives screened). The use of nBu$_4$NBr did not cause the same increase in yield.[36] 2,4,6-trimethoxybenzonitrile, the byproduct of imine fragmentation, was consistently formed in 10–20% higher yield than **3**. With heavier aliphatic amine-derived imines, we observe the products of C-N reduction and elimination (alkane and alkene). Therefore, adjusting stoichiometries of the starting material and adding an equivalent of inorganic base increased the yield to 94%. As we noticed in our previous work, the imine nitrogen is sufficiently basic to promote desired reactivity in the absence of other bases, giving a 72% yield (entry 10).

With respect to the scope of the reaction, electron-deficient aryl bromides give desired products in excellent yield (Scheme 2). Scaling the reaction up by 10x results in only a slight decrease in yield (**3**). Notably, electrophilic moieties that are incompatible with organometallic reagents[31,32,35] are tolerated, including nitriles (**3, 6**), ketones (**4, 8**), aldehydes (**16**), and esters (**7, 9–11**). Aryl bromides containing heteroatoms proceed with high efficiency – cyclic amide **12**, sulfonamide **13**, quinazolinone **14**, and Celecoxib derivative **15** – while *N*-heterocycles provide trace product.[30,37] Electron-neutral aryl bromides still provide modest yields, whereas electron-rich bromides afford trace product. This is accompanied by the formation of nickel black, suggesting that electron-rich aryl bromides lead to catalyst deactivation.[38] Notably, we found that replacing the electron-rich

bromide with the corresponding aryl iodide and adding LiCl as an additive can restore yields to ~30–40% (18,19).[29,39]

Acyclic α-tertiary amines provide desired product in good yields, tolerating protected alcohols (**22**) as well as protected amines (**23**). Five- and six-membered ring systems containing functional groups such as esters, protected amines, and ethers deliver product in high yields (**24–28**, **32–34**), tolerating additional substitution in modest yields. Notably, no isomerization is observed using our methodology. Alpha methyl cycloheptyl amine also proved to be a competent coupling partner, furnishing **29** in moderate yield. Adamantylamine **30** and Nemanda derivative **31** also provide desired product. Notably, bipyridines are also capable ligands with these substrates, due to a more sterically accessible, pseudo-tetrahedral carbon-centered radical. This allows for facile inner-sphere reductive elimination, whereas traditional tertiary planar radicals proceed via an outer-sphere mechanism.[40] Amines used as intermediates en route to pharmaceuticals, such as TNF-α converting enzyme (TACE) inhibitor intermediate **32**, give desired product in good yields.[41] Drug derivatives, such as NK1 analog **33** and CCR5 inhibitor intermediate **34**, can also be synthesized utilizing our method.[42,43]

We next turned our attention to the role of additive on the reaction. Both nBu$_4$NCl and *tert*-butyl imidazolium chloride were found to be beneficial to reactivity. Interestingly, without an additive, an appreciable amount of nickel black is observed in the reaction. Because tetra-alkyl ammonium salts and imidazolium salts are known to provide electro-steric stabilization of nanoparticles,[44–48] we propose that the first role of the additive may be to prevent catalyst death by preventing aggregation that would lead to the irreversible formation of nickel black.[38] By doing so, this preserves the necessary equilibrium with the active catalyst. Indeed, tracking the reaction progress over time indicates that with nBu$_4$NCl, product formation increases steadily over time, whereas without nBu$_4$NCl the product formation plateaus around 50% (see SI for more details). In addition, substituting chloride for other anions still provides an increase in yield (Table 1, entries 5 & 6), in line with a nanoparticle stabilization argument.[49]

In-situ LED-NMR kinetic analysis indicates that nBu$_4$NCl also provides a rate acceleration within the first hour of the reaction (Scheme 3A), demonstrating that preventing catalyst death is not its only role. In this case, exchanging the chloride anion does not provide the same rate acceleration (see SI for kinetics data), indicating that chloride is necessary. The rate of starting material consumption tracks linearly between 0, 5, and 10% of nBu$_4$NCl loading, but increased loadings (20, 50%) do not improve arene consumption. Therefore, adding more nBu$_4$NCl than nickel catalyst loading does not affect the initial rate of reaction but improves the yield of reaction, presumably due to preventing catalyst death. This observation is consistent with saturation kinetics, where more additive relative to catalyst loading has no effect on the reactivity due to complete saturation of the catalyst. We hypothesized that we may be forming an anionic nickel complex that would undergo accelerated oxidative addition, similar to what has been seen for anionic palladium species in combination with alkyl ammonium chlorides.[48,50] Thus, we attempted to form the active Ni(I) catalyst *in situ* via cyclic voltammetry and add in nBu$_4$NCl in hopes of generating the anionic complex, but did not see the formation of a new species. In addition, nBu$_4$NCl has

no effect on the reduction potential from Ni(II) to Ni(I), indicating accelerated reduction to the active catalyst is not responsible for the rate acceleration.[51] Lastly, UV-Vis experiments indicate no change in the catalyst upon addition of nBu$_4$NCl, in contrast to recent work.[51] Alternatively, the chloride could exchange with the Ni(III) oxidative addition complex, similar to observations in Gong's reductive coupling,[29] generating a Ni(II)-Cl species after reductive elimination, which has been shown to be more reducible than its bromide analogue.[52,53]

Our proposed mechanism begins with oxidation of the redox-active imine by the excited state of the Ir photocatalyst (Scheme 3B). In our previous work, we provided evidence that the tertiary alkyl radical is generated via an imidoyl radical intermediate.[22] Meanwhile, the nickel catalyst can undergo oxidative addition to generate a Ni(III) species. Because anionic diketone-based ligands were necessary to achieve productive reactivity, we propose that outer-sphere reductive elimination, as described by the Molander and Gutierrez groups,[40] generates the desired product and Ni^{II}-X. Single electron transfer between the reduced photocatalyst and Ni(II) turns over both catalytic cycles.

Our reaction can also be applied to medicinally relevant scaffolds, highlighting the ability to install quaternary carbons for pharmaceutical applications (Scheme 4). The reported convergent synthesis of Activin receptor-like kinase-2 inhibitors relies on N-Boc piperidine compound **37** as a key intermediate.[54] This compound is synthesized in a seven-step linear sequence starting with pinacol borane **35** with a 5% overall yield. The formation of the quaternary center (**36**) is the bottleneck of the current route, providing product in only a 15% yield. Utilizing our method and starting from the commercially available amine allows for the expedited synthesis of compound **37**, with only two steps and a 67% overall yield.

In summary, we have developed a protocol to activate the C-N bond of sterically encumbered α-3° amines to utilize them as alkyl precursors for a dual photoredox/nickel-catalyzed C(sp^3)-C(sp^2) cross-coupling. Upon condensing primary amines onto an electron-rich activating group, we generate tertiary alkyl radicals that couple with a Ni^{III} aryl-halide complex to generate benzylic quaternary centers. Using nBu$_4$NCl as an additive increased the rate of the reaction while also resuscitating the nickel catalyst. Given increasing use of deaminative functionalizations with α-1° and α-2° amines via Katritzky salts, our complementary deamination addresses a synthetic need by unveiling α-3° as alkyl precursors for arylation. By leveraging amines as tertiary radical precursors, we have expanded the synthetic toolbox which will assist in diversifying the chemical space in pharmaceutical chemistry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.
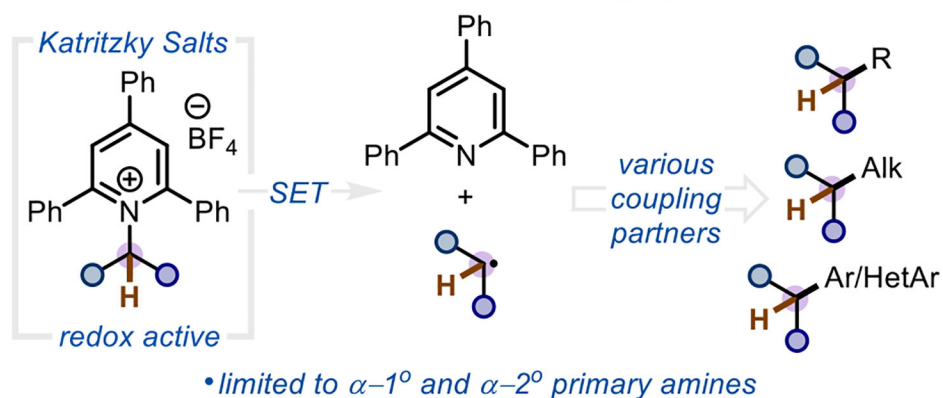
ACKNOWLEDGMENT

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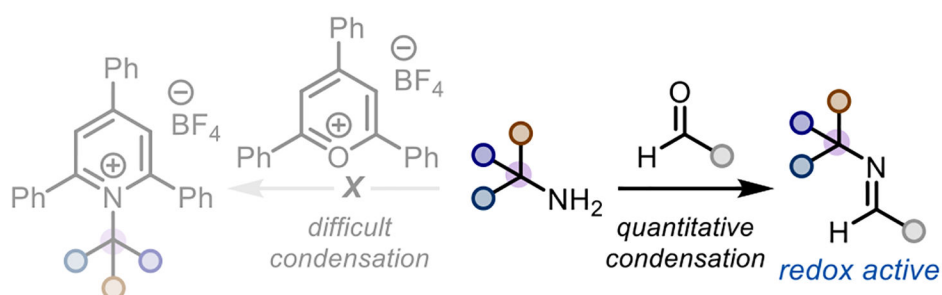
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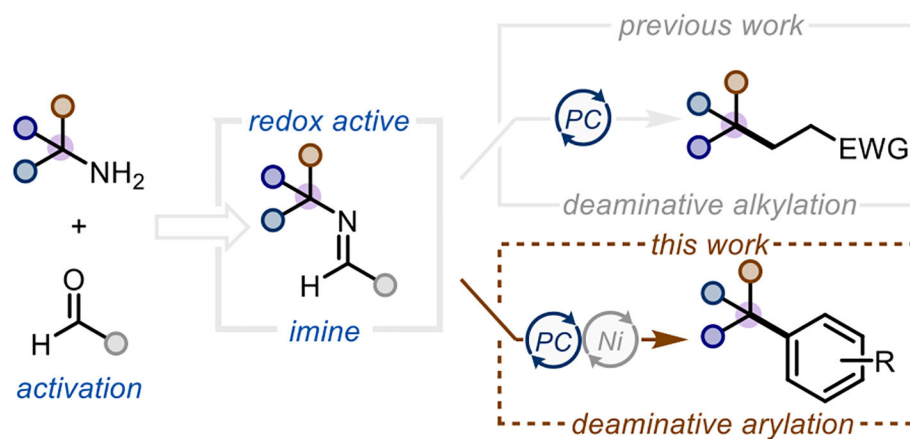
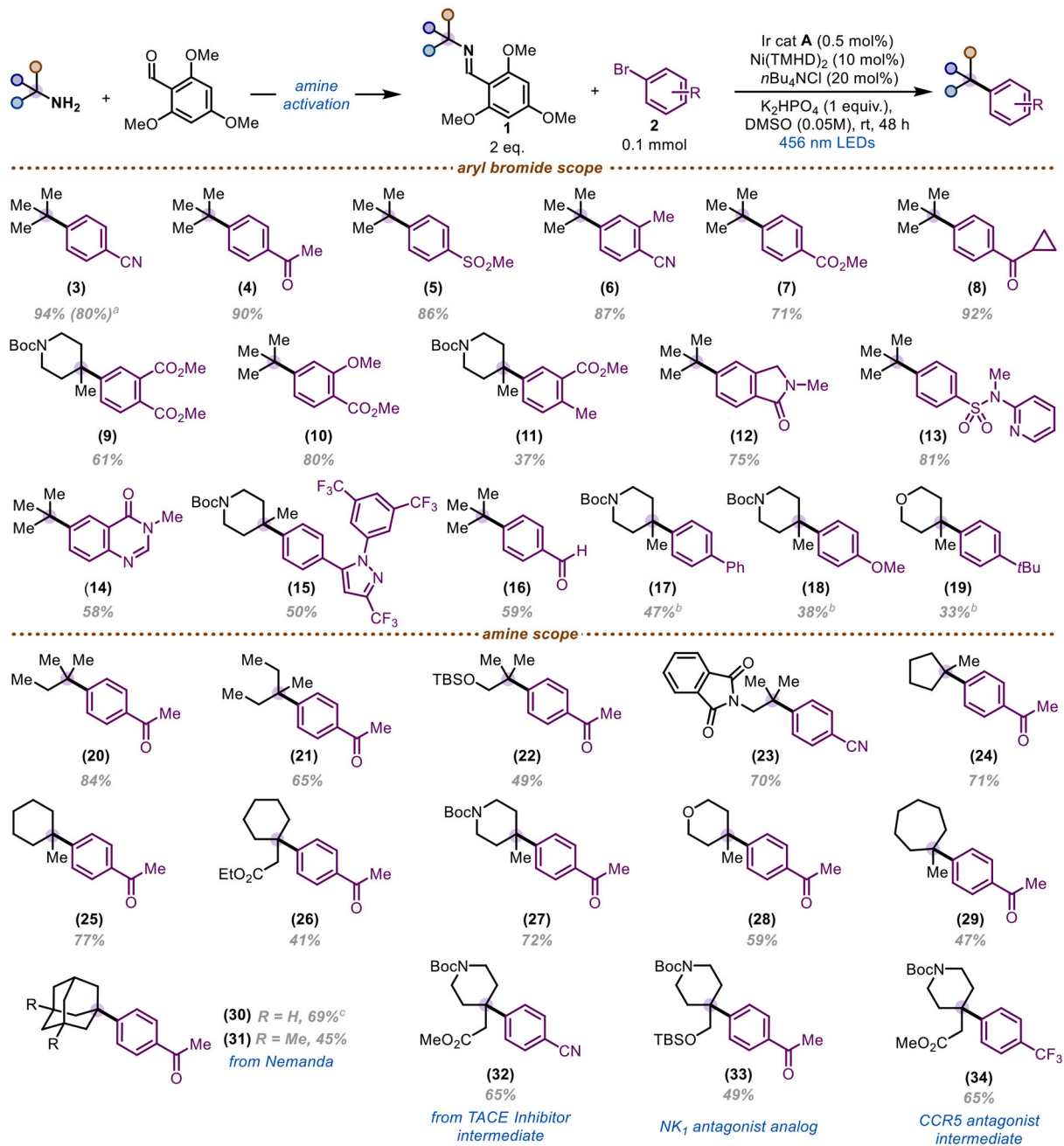## A. C-N Activation of Primary Amines: *N*-Alkylpyridinium Salts

Katritzky Salts

SET →

various coupling partners →

redox active

• *limited to α–1° and α–2° primary amines*

B. C-N Activation of α - 3° Primary Amines

difficult condensation

quantitative condensation *redox active*

C. Deaminative Functionalization of Sterically Hindered Amines

previous work

activation

redox active

imine

PC →

deaminative alkylation

this work

PC Ni →

deaminative arylation

Scheme 1.
Use of Primary Amines as Alkyl Precursors.

Scheme 2.

Scope

a) done on a 1.0 mmol scale. b) from the aryl iodide and 1 equiv. of LiCl was added. c) NiCl$_2$(dtbbpy)(H$_2$O)$_4$ was used in place of Ni(TMHD)$_2$

A. Rate Dependence on *n*Bu₄NCl Concentration

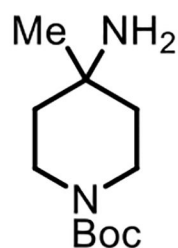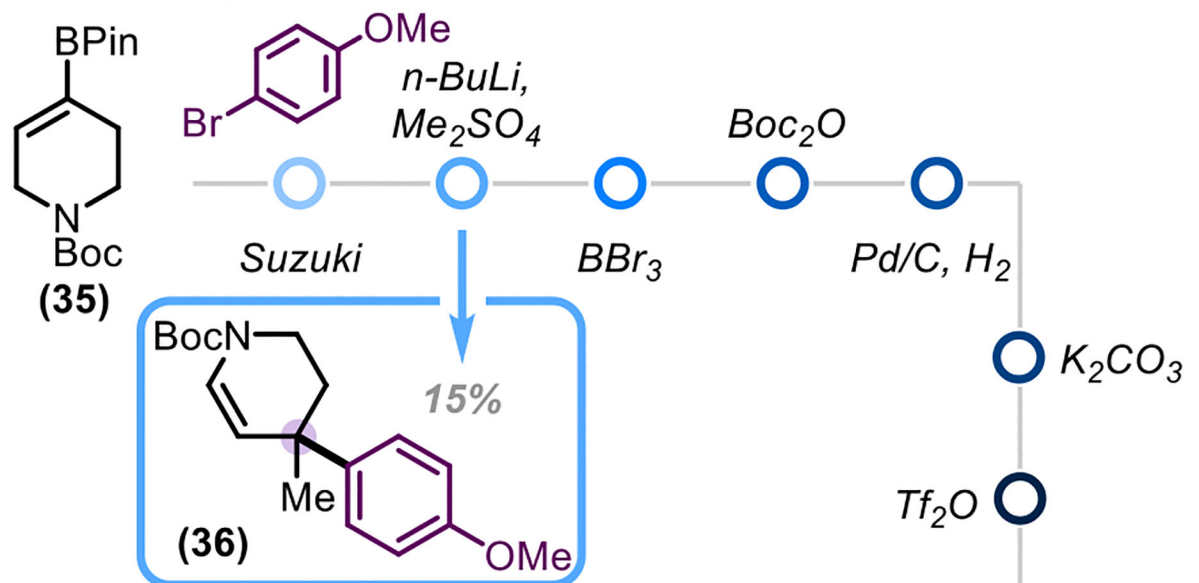**B. Proposed Mechanism of Deaminative Arylation**
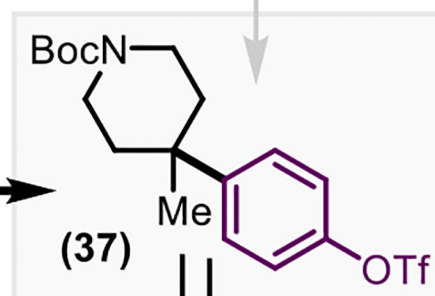

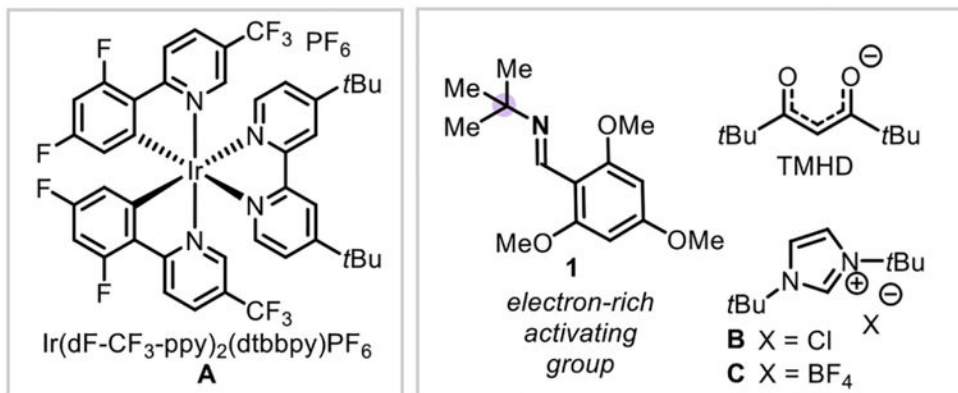**Scheme 3.**
Mechanistic Investigation

Scheme 4.
Streamlined Synthesis of ALK2 Inhibitors

Table 1.

Optimization and Control Reactions.

Entry	Deviation from Standard Conditions	Yield (%)[a]
1	no changes	94[b]
2	no base, no nBu_4NCl, 1 equiv **1**, 1.2 equiv **2**	31
3	1 equiv **1**, 1.2 equiv **2**	58
4	**B** instead of nBu_4NCl	81
5	**C** instead of nBu_4NCl	84
6	nBu_4NPF_6 instead of nBu_4NCl	81
7	nBu_4NBr instead of nBu_4NCl	50
8	24 h	73
9	no nBu_4NCl	50
10	no K_2HPO_4	72
11	no Ni	0
12	no Ir cat **A**	0
13	no 456 nm LEDs	0

[a] GCMS yields with mesitylene as an internal standard.

[b] isolated yield.