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# **Synthetic Chemistry Literature Survey**

*01 Sept 2021–31 Aug 2022*

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**■ Session 1**

(Hetero)aromatic Cross-Coupling (C–C Bond-Formation)

(Hetero)aromatic Cross-Coupling (C–X Bond-Formation)

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**■ Session 2**

(Hetero)aromatic C–H Functionalisation

Heterocycle and Carbocycle Synthesis

Aliphatic C–C Bond-Formation

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**■ Session 3**

Aliphatic C–X Bond-Formation

Aliphatic C–H Functionalisation

Functional Group Interconversions & Isomerisations

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**■ Session 4**

Sulfur & Phosphorus Functional Groups

Fluorination and Fluorinated Motifs

Technologies for Synthesis

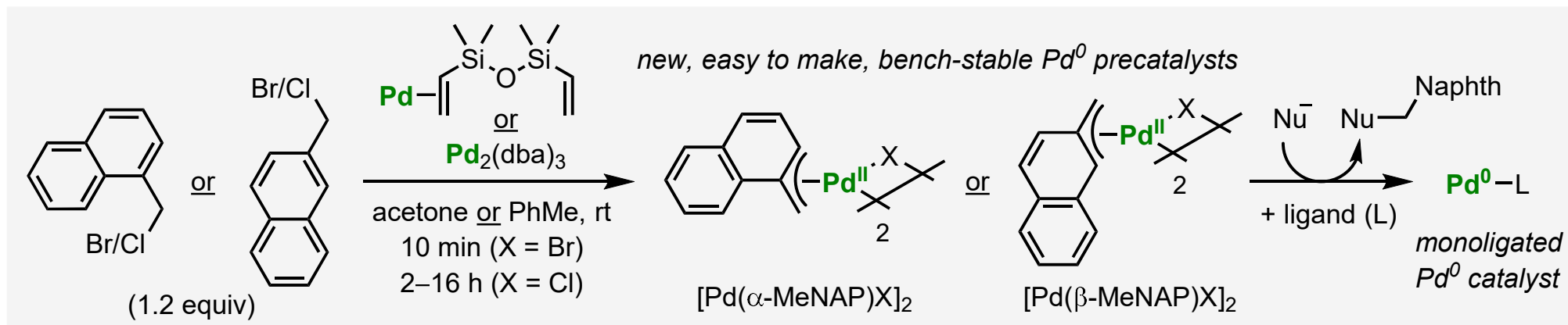
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**(Hetero)aromatic Cross-Coupling**

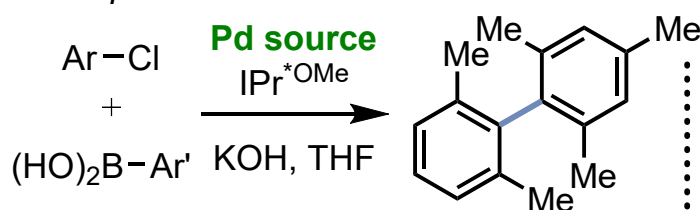
*C–C Bond Formation*

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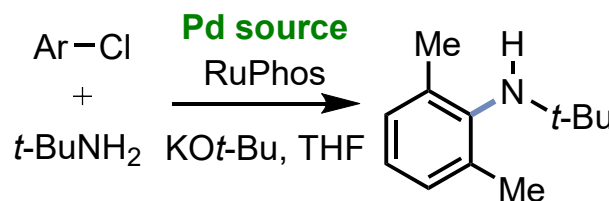
- Gooßen *et al.* report methylnaphthyl Pd dimers as new Pd<sup>0</sup>L precursors, ideally suited for catalytic method development and preparative organic synthesis. By simply mixing with phosphine or carbene ligands, they are *in situ* converted into well-defined monoligated complexes.
- Their catalytic performance was benchmarked against state-of-the-art systems in challenging Buchwald–Hartwig, Heck, Suzuki and Negishi couplings, and ketone arylations. This enabled record-setting activities, beyond that achievable by ligand optimisation alone.



## Examples

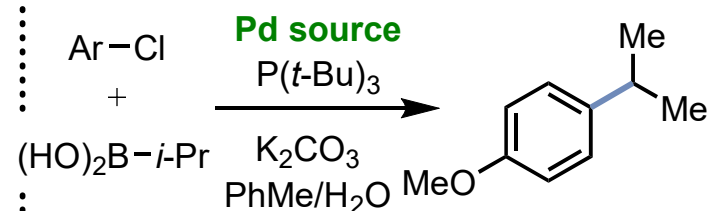


Pd source	Yield
$\text{Pd}_2\text{dba}_3$	5%
$[\text{Pd}(\text{allyl})\text{Cl}]_2$	9%
$[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$	51%
<b><math>[\text{Pd}(\alpha\text{-MeNAP})\text{Cl}]_2</math></b>	<b>&gt;99%</b>
<b><math>[\text{Pd}(\beta\text{-MeNAP})\text{Cl}]_2</math></b>	<b>&gt;99%</b>



Pd source	Yield
$\text{Pd}_2\text{dba}_3$	21%
$[\text{Pd}(\text{allyl})\text{Cl}]_2$	6%
$[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$	13%
<b><math>[\text{Pd}(\alpha\text{-MeNAP})\text{Cl}]_2</math></b>	<b>&gt;99%</b>
<b><math>[\text{Pd}(\beta\text{-MeNAP})\text{Cl}]_2</math></b>	<b>&gt;99%</b>

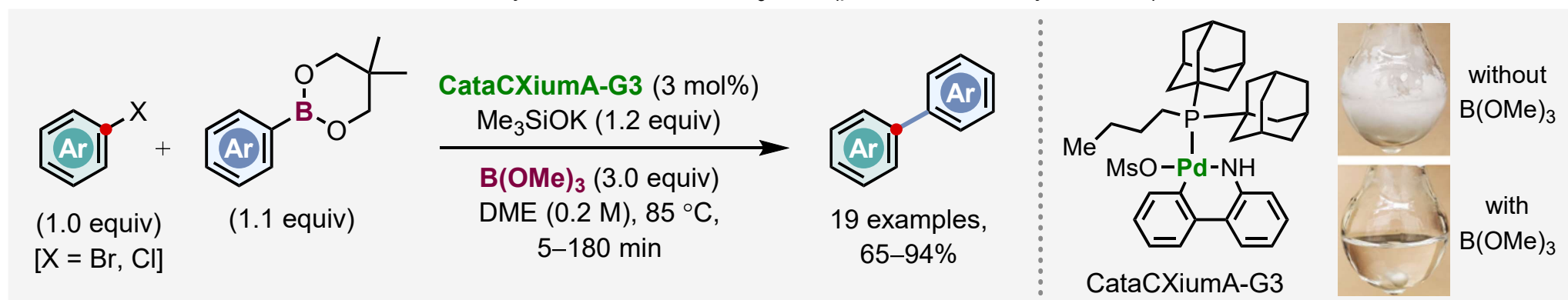
*Angew. Chem. Int. Ed.* 2021, 60, 25151



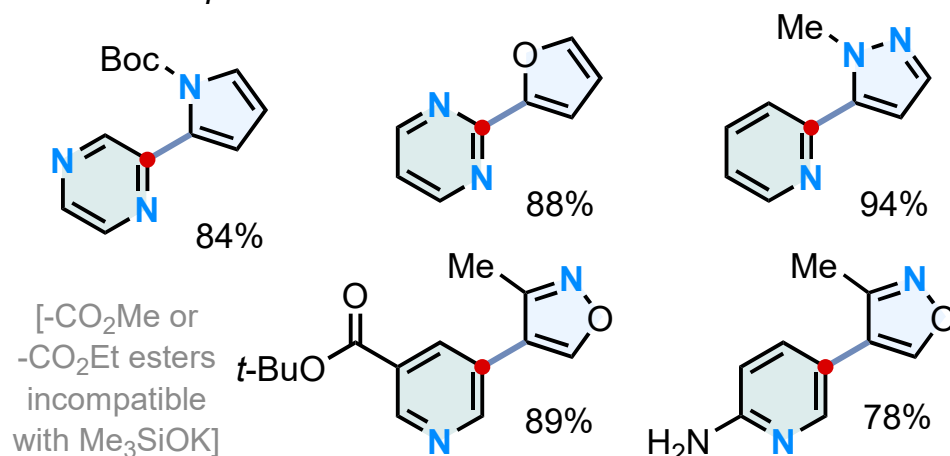
Pd source	Yield
$\text{Pd}(\text{OAc})_2$	0%
$\text{Pd}_2\text{dba}_3$	55%
$[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$	68%
<b><math>[\text{Pd}(\alpha\text{-MeNAP})\text{Cl}]_2</math></b>	<b>88%</b>
$[\text{Pd}(\beta\text{-MeNAP})\text{Cl}]_2$	61%

**Keywords:** [cross-coupling]; [palladium]; [precatalysts]; [Suzuki]; [Heck]; [Negishi]; [enolate arylation]; [Buchwald-Hartwig]

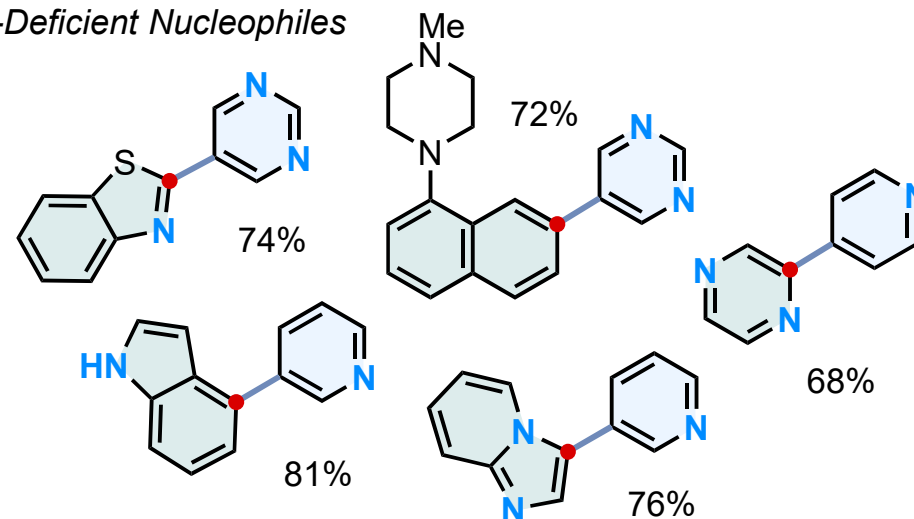
- Strictly anhydrous conditions for the SM reaction can minimise protodeboronation pathways with troublesome heteroaryl boronic acids, but the problem is often the poor solubility of these compounds without aqueous base.
- Denmark *et al.* report the use of B(OMe)<sub>3</sub> as an additive in anhydrous, homogeneous SM couplings with challenging heteroaryl substrates. Significant increases in yield and rate (5–180 min) were observed, with B(neop) esters being optimal for rate and solubility.
- B(OMe)<sub>3</sub> increases the solubility of heterocycles by forming borate complexes *in situ*, and prevents catalyst poisoning of Pd caused by N-coordination. It also buffers the inhibitory effects of excess Me<sub>3</sub>SiOK (potassium trimethylsilanoate).



### $\pi$ -Rich Nucleophiles



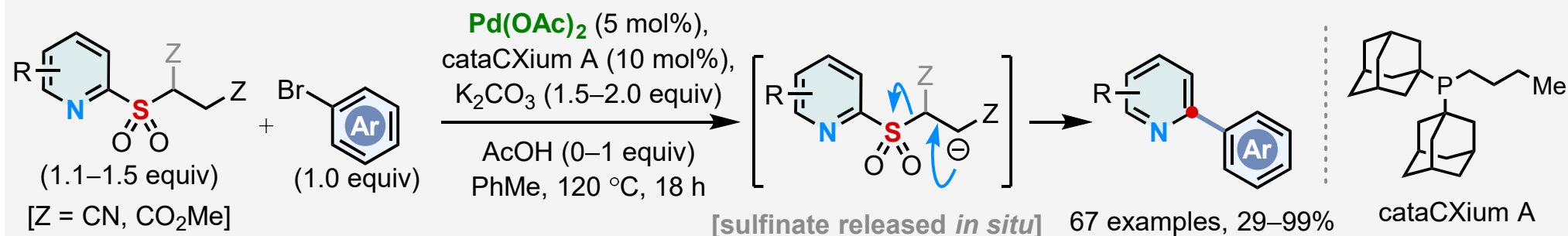
### $\pi$ -Deficient Nucleophiles



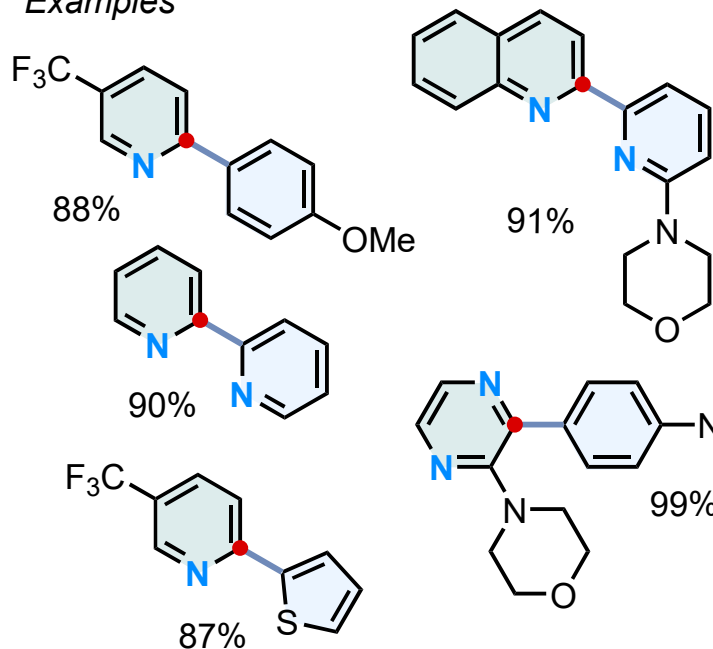
*J. Am. Chem. Soc.* **2021**, *143*, 13845

**Keywords:** [Suzuki-Miyaura]; [cross-coupling]; [arylation]; [heterobiaryls]; [boronic esters]; [trimethyl borate]

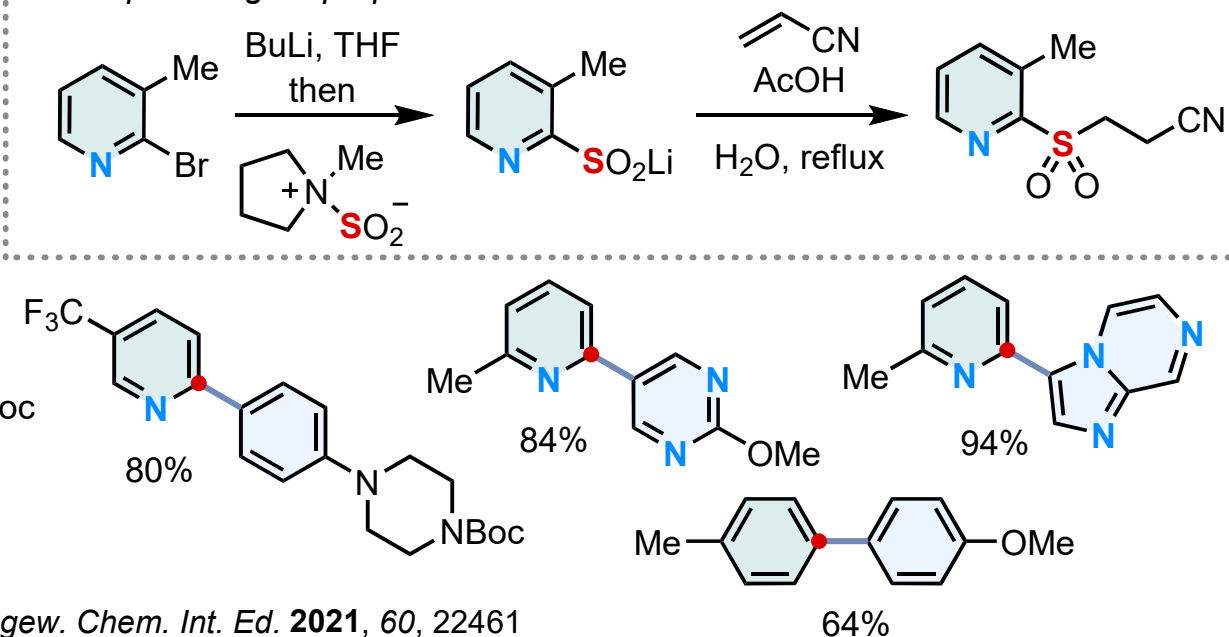
- Heteroaromatic sulfinates are effective nucleophilic reagents in Pd-catalysed cross-coupling that circumvent the '2-pyridyl problem' with 2-pyridyl boronic acids. However, sulfinate salts can be challenging to purify, poorly soluble, and not always tolerant to other reactions.
- Willis *et al.* report  $\beta$ -nitrile and  $\beta$ -ester sulfones as base-activated, latent sulfinate reagents. Under basic conditions, they generate sulfinate salts *in situ*, which then undergo efficient desulfinative cross-coupling with (hetero)aryl bromides to deliver a broad range of biaryls.



## Examples

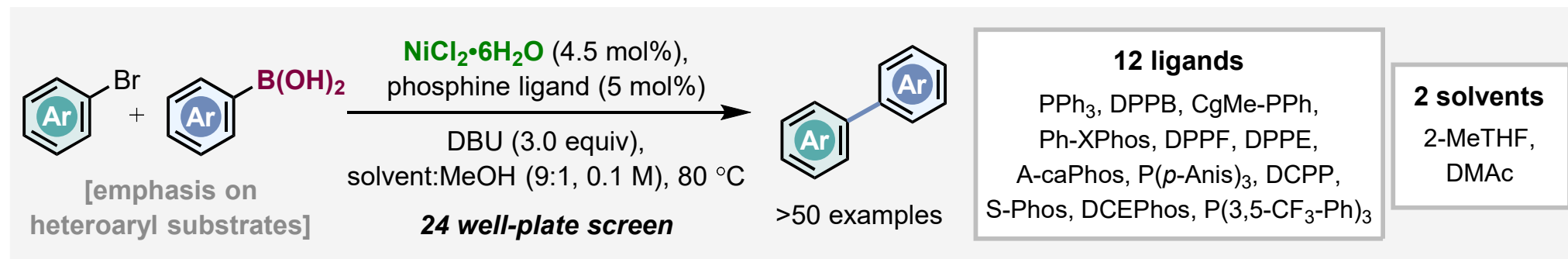


## Exemplar reagent preparation

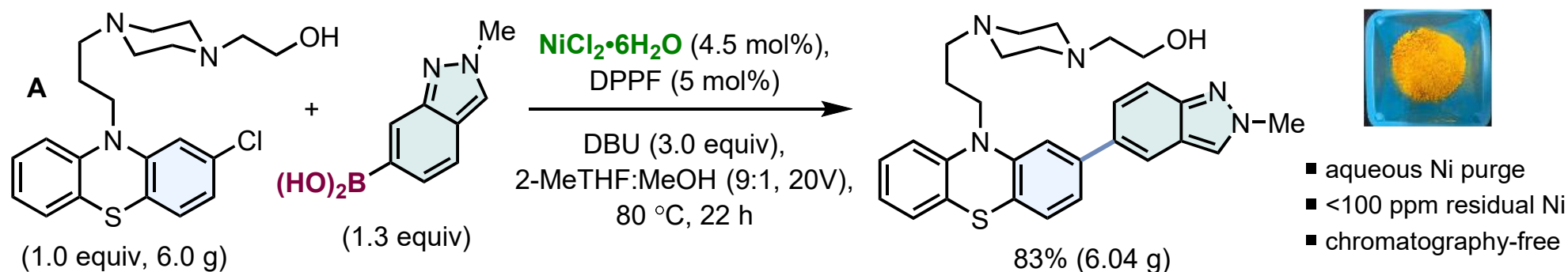


**Keywords:** [heterobiaryls]; [sulfones]; [sulfinates]; [cross-coupling]; [aryl halides]; [palladium]

- Ni-catalysed SM reactions are particularly prone to substrate inhibition, protodehalogenation, or protodeboronation (e.g., with heteroaryl and e<sup>-</sup>-poor boronic acids), and are also influenced by polar FGs more so than SM reactions with Pd.
- State-of-the-art in heteroaryl couplings (Hartwig, Stradiotto) is difficult to scale due to costly, preformed Ni complexes [e.g., from Ni(cod)<sub>2</sub>]. Also, most such reactions employ carbonate or phosphate bases in organic solvents, resulting in heterogeneous reactions.
- Goldfogel *et al.* from BMS report a 24-reaction screening platform for identifying Ni-catalysed SM conditions. It is designed to be directly applicable to process scale-up by employing homogeneous reaction conditions, alongside stable and inexpensive Ni(II) precatalysts.
- MeOH as an additive greatly improved reaction performance (possibly by forming more reactive Ar-B(OMe)<sub>2</sub> esters) and enabled use of organic-soluble amine bases. Phosphine ligands always outperformed N-donor ligands, and gave far less protodeboronation.



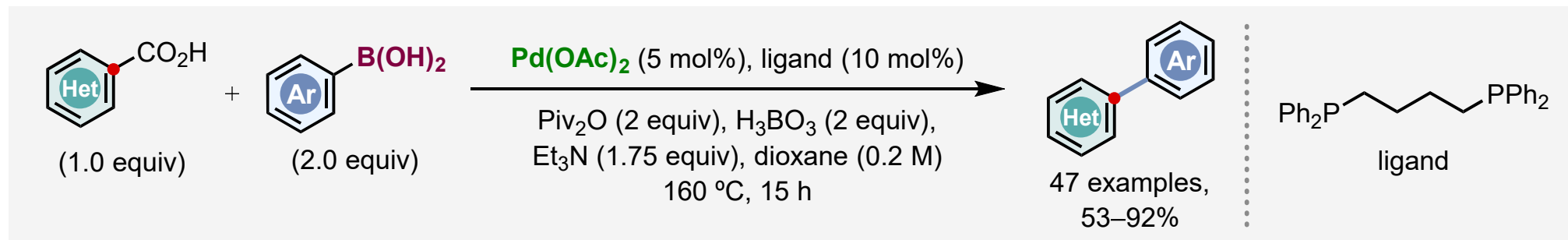
Application: Suzuki Coupling of Antipsychotic Perphenazine (A) with HetAr-B(OH)<sub>2</sub>



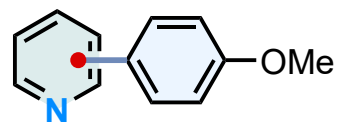
Org. Process Res. Dev. **2022**, 26, 785 [for a NiBr<sub>2</sub>-catalysed Suzuki coupling with K<sub>3</sub>PO<sub>4</sub>, see: ChemCatChem **2022**, 14, e202200440]

**Keywords:** [cross-coupling]; [Suzuki]; [biaryls]; [aryl halides]; [boronic acids]; [nickel]; [scale-up]

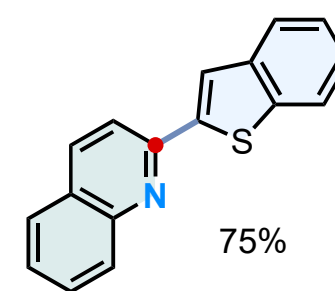
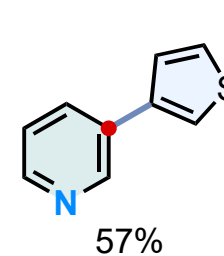
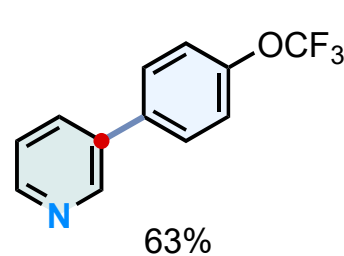
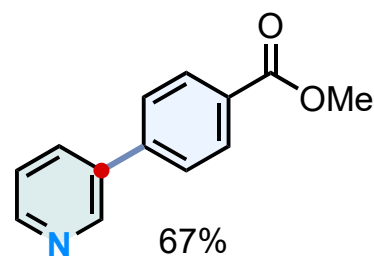
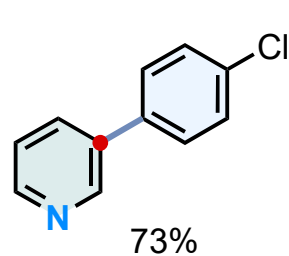
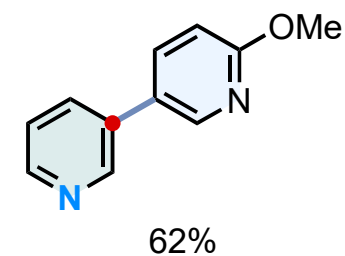
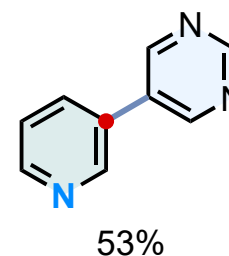
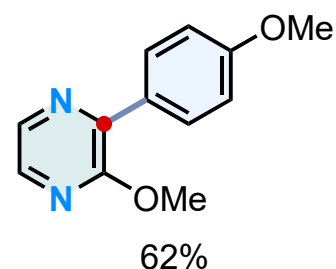
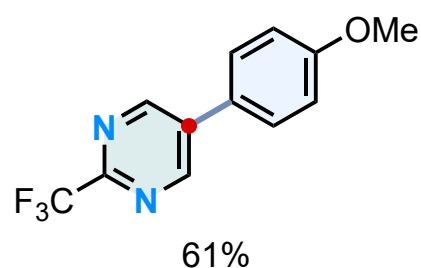
- Szostak and Smith (Pfizer) *et al.* report a Pd-catalysed decarbonylative cross-coupling for the synthesis of heterobiaryls.
- This method takes advantage of the wide availability of carboxylic acids, and it is compatible with carboxylic acids based on pyridines, pyrimidines, pyrazines, and quinolines. However, no competitions with (pseudo)halide groups on the heterocycles are provided.



### Examples



2-pyridyl = 85%  
3-pyridyl = 90%  
4-pyridyl = 82%

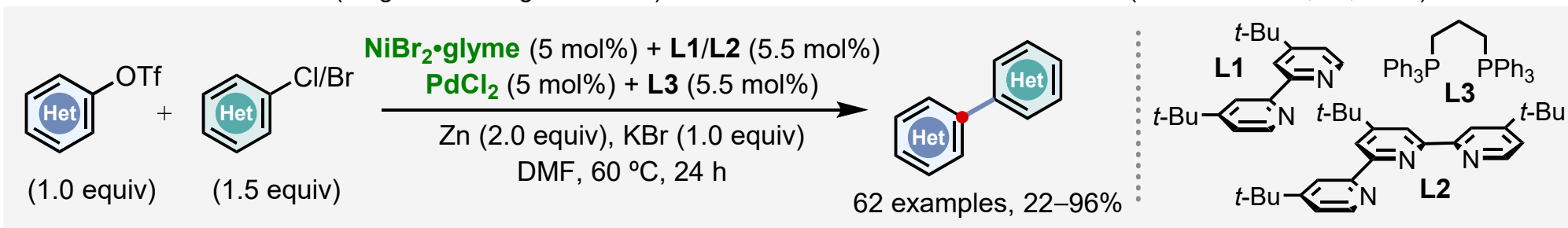


Org. Lett. **2022**, 24, 1678

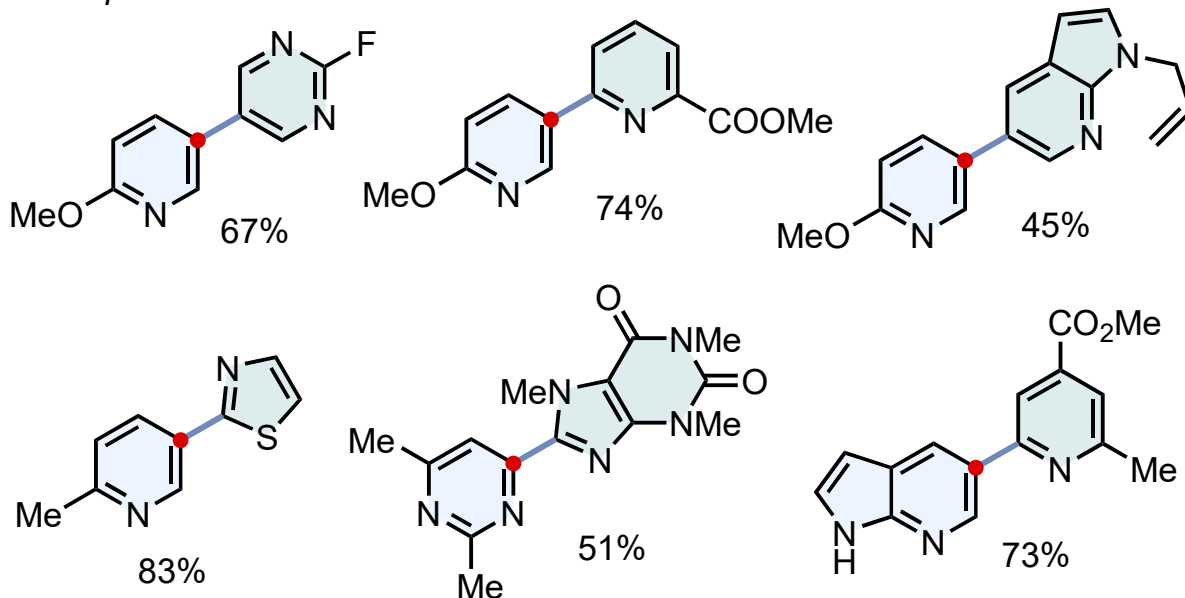
**Keywords:** [heterobiaryls]; [carboxylic acids]; [boronic acids]; [arylation]; [cross-coupling]; [decarbonylative]; [palladium]



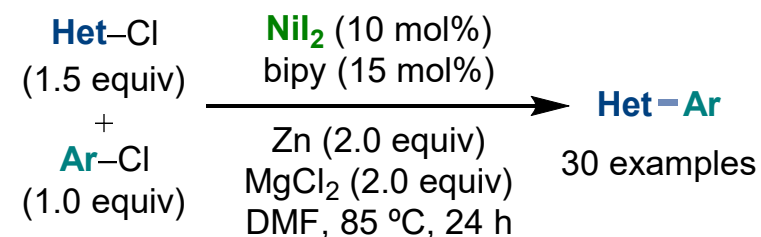
- Weix *et al.* report a reductive cross-coupling of heteroaryl bromides/chlorides with heteroaryl triflates to give heterobiaryls, using a combination of Ni- and Pd-based catalysts. [A related Ni-only heteroaryl–aryl coupling was reported by Lautens *et al.* (see bottom right)].
- Low-yielding combinations could be rapidly optimised on 10  $\mu\text{mol}$  scale with a single 96-well "Toolbox Plate" of ligands, additives, and reductants. "ChemBeads" (reagent-coated glass beads) were used for solid additives Zn and KBr (see *ACIE* **2019**, *58*, 7987).



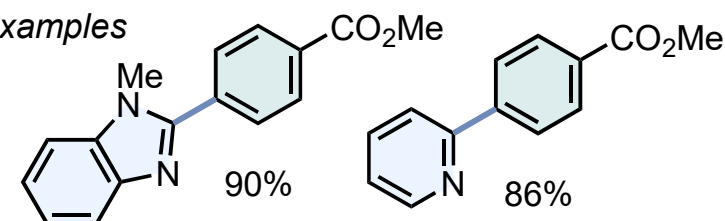
## Examples



*J. Am. Chem. Soc.* **2021**, *143*, 21484

Related Het–Ar coupling from Lautens *et al.*

## Examples

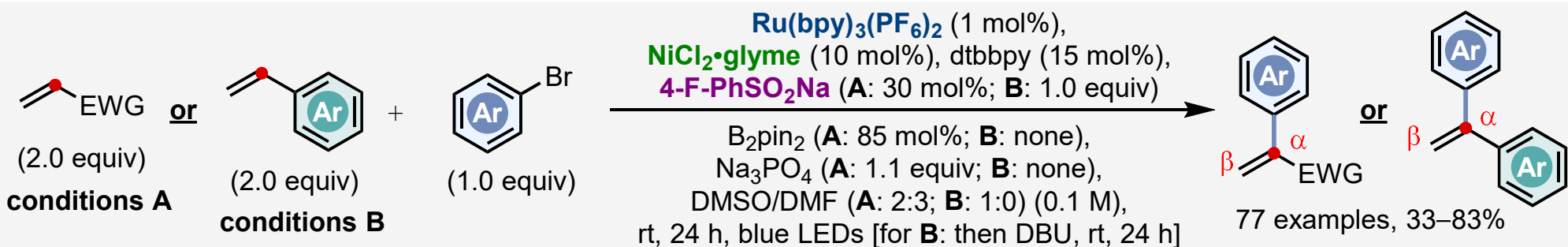


- 77% of examples were benzimidazoles
- Limited to electron-poor Ar–Cl (or else Ar–Br must be used)

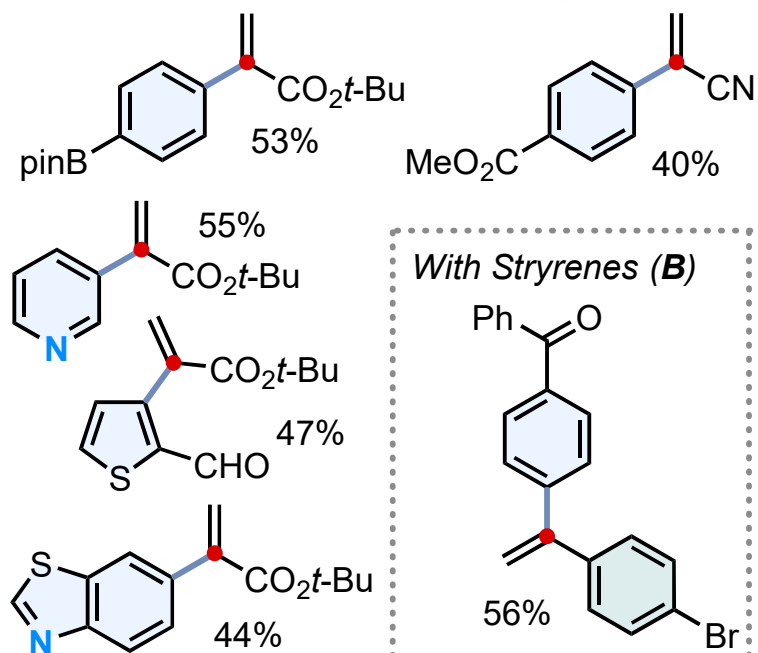
*ACS Catal.* **2021**, *11*, 12785

**Keywords:** [heterobiaryls]; [reductive cross-coupling]; [multimetallic]; [aryl halides]; [aryl triflates]; [nickel]; [palladium]

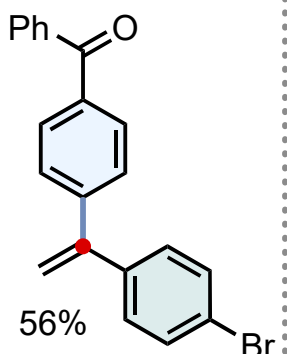
- Studer *et al.* report an  $\alpha$ -selective, Ni/photoredox-catalysed Heck-type coupling of (Het)Ar–Br with acrylates (or similar Michael acceptors) or with styrenes. Use of a sulfinate salt catalyst (or stoichiometric additive in the case of styrenes) is the key to success (see mechanism).
- This overrides the intrinsic selectivity of these types of alkenes in most Heck couplings, which tend to give  $\beta$ -arylated alkene products.
- The role of the B<sub>2</sub>pin<sub>2</sub> additive for acrylate couplings is unclear, but it does not generate Ar–Bpin species and seems to be a Lewis acid.



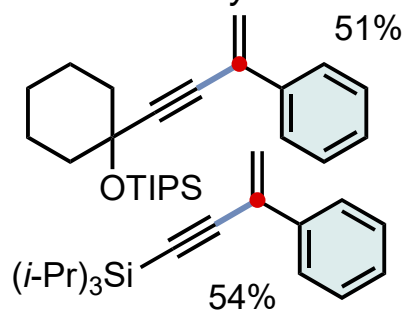
## With Acrylates &amp; Related Alkenes (A)



## With Styrenes (B)

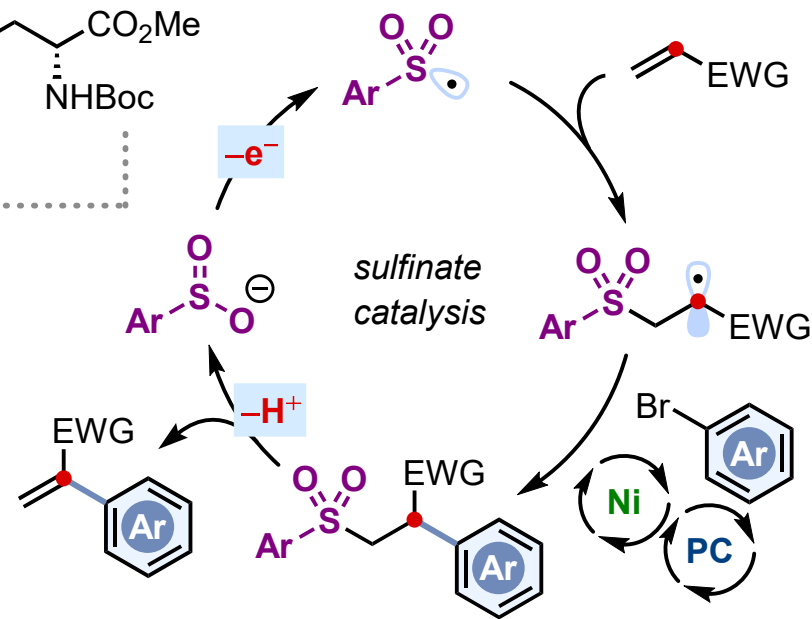


## With Bromoalkynes



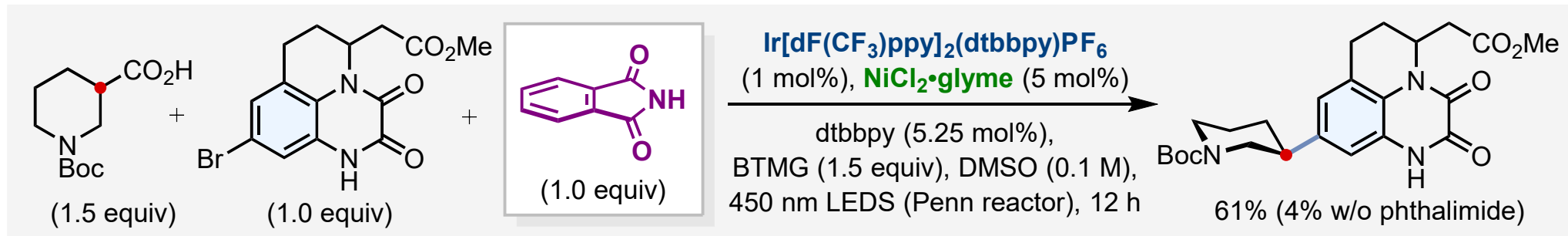
Nat. Synth. 2022, 1, 565

## Mechanism (for conditions A)

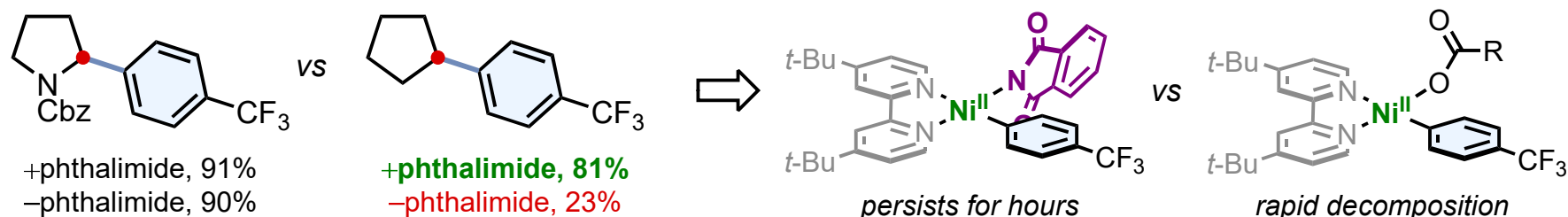


**Keywords:** [Heck]; [alkenylation]; [arylation]; [aryl halides]; [acrylates]; [styrenes]; [alkynes]; [photoredox]; [nickel]

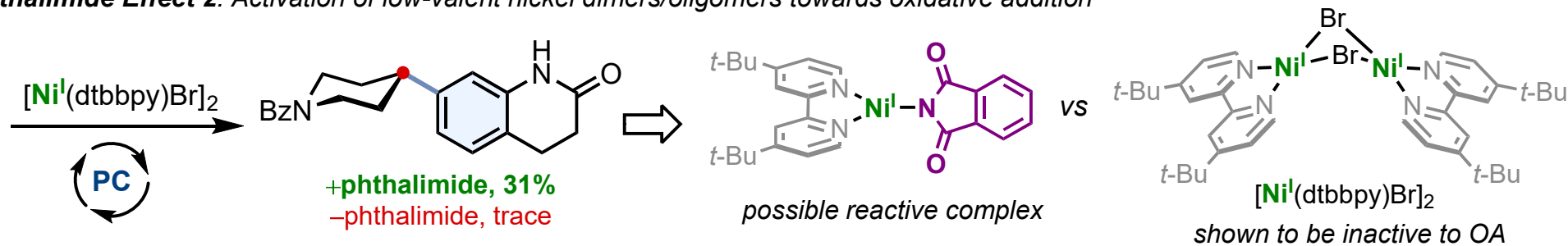
- Metallaphotoredox, decarboxylative arylations frequently perform poorly with: (i) *N*-rich substrates, (ii) Ar–Br prone to protodehalogenation, (iii) difficult oxidative additions (e.g., e<sup>-</sup>-rich Ar–Br), or (iv) 1°/2° carboxylic acids that lack adjacent radical-stabilising groups (e.g., NBoc, O).
- MacMillan *et al.* used a HTS approach to identify phthalimide as an additive that greatly increases reaction efficiency with many problematic acid and aryl halide partners. This modification was tested against 384 carboxylic acids and also 384 (hetero)aryl bromides.
- Unactivated carboxylic acids, many *N*-rich heteroarenes, and substrates bearing polar FGs (1,2-diols, aminopyridines) can now be coupled.



**Phthalimide Effect 1:** Longer-lived OA complex successfully captures radical despite slower radical formation



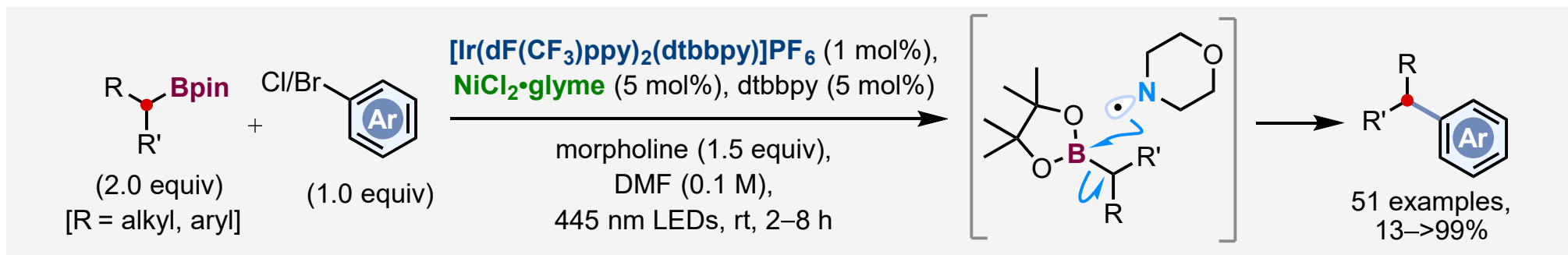
**Phthalimide Effect 2:** Activation of low-valent nickel dimers/oligomers towards oxidative addition



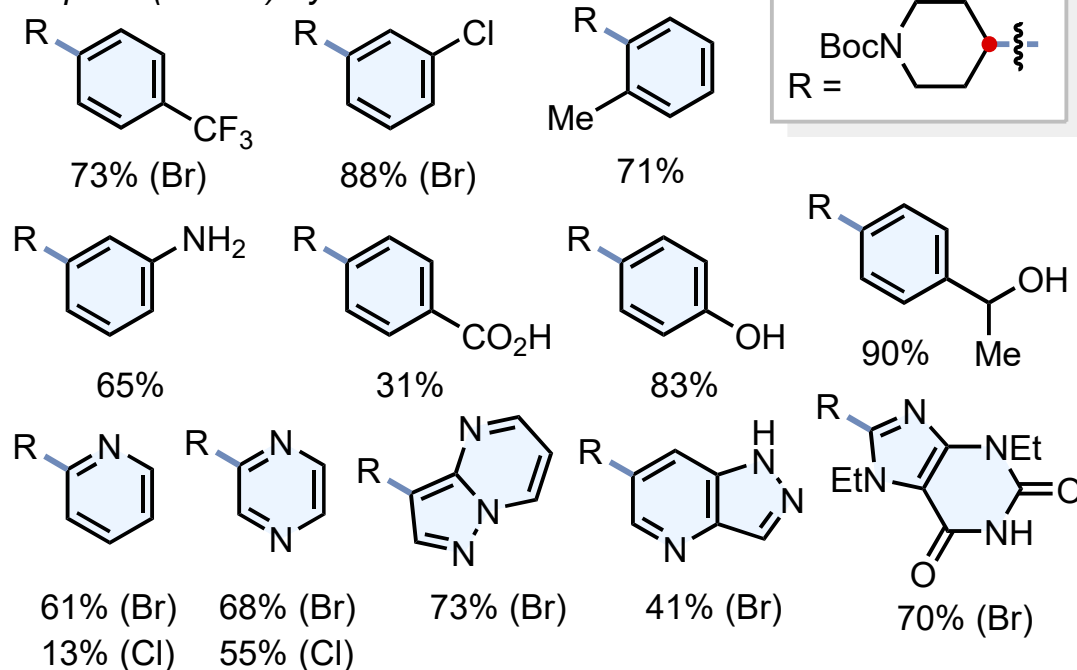
Science 2022, 376, 532

**Keywords:** [cross-coupling]; [aryl halides]; [carboxylic acids]; [alkylation]; [arylation]; [photoredox]; [nickel]; [additives]

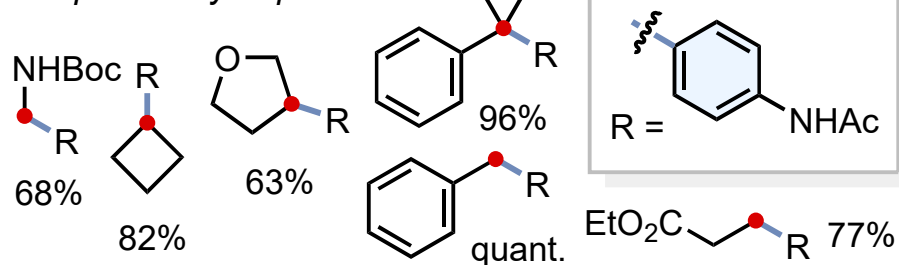
- Maier *et al.* at Sanofi report a Ni-metallaphotoredox-catalysed sp<sup>2</sup>-sp<sup>3</sup> coupling of (hetero)aryl bromides and alkyl-Bpin esters utilising morpholine as an additive. Attack of a photogenerated aminyl radical from morpholine onto the alkyl-Bpin abstracts the boron group to give an alkyl radical. A gram-scale batch reaction in a 100 mL flask could be carried out, due to the low extinction coefficient for the PC in DMF.



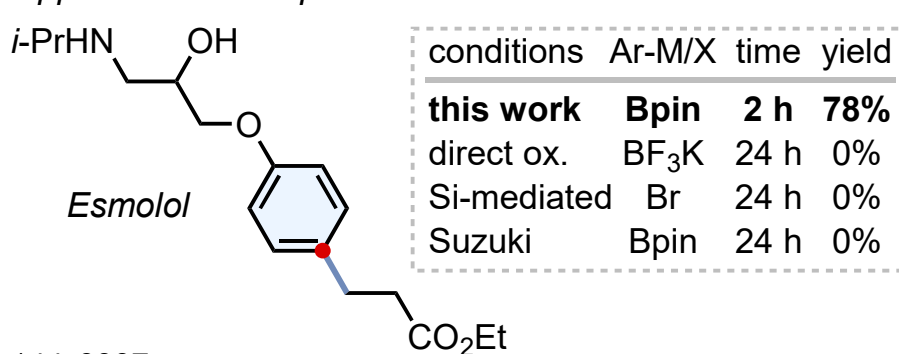
## Scope of (Hetero)aryl Partner



## Scope of Alkyl-Bpin Partner



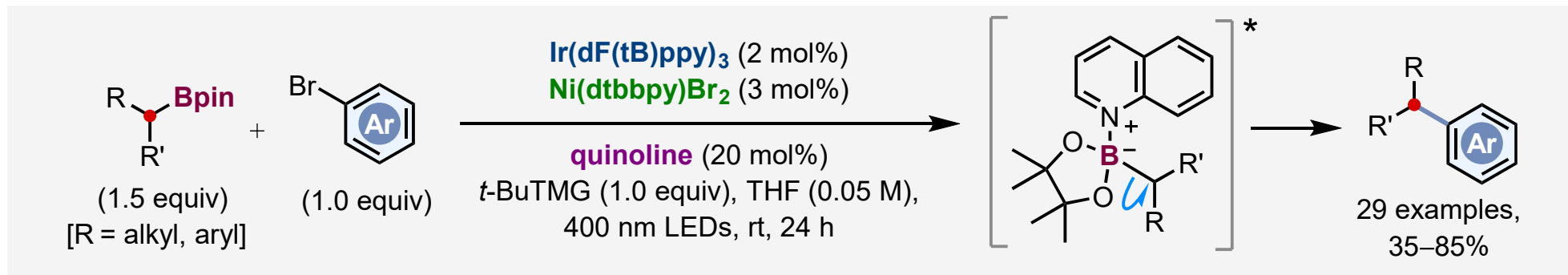
## Application &amp; Comparison to Prior Art



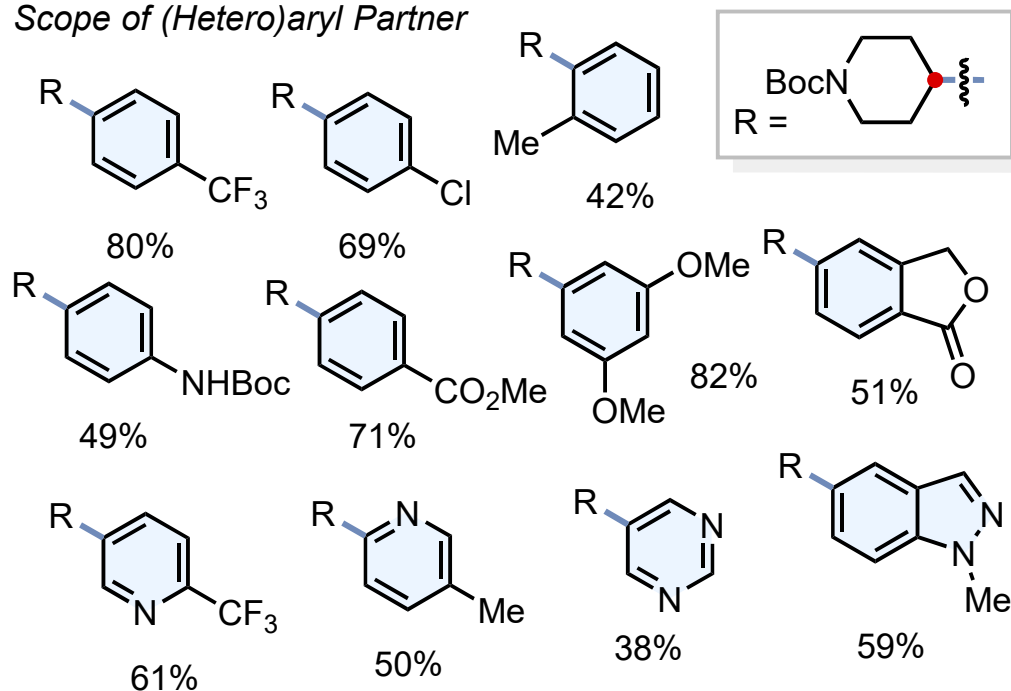
*J. Am. Chem. Soc.* **2022**, *144*, 9997

**Keywords:** [cross-coupling]; [aryl halides]; [alkyl boronates]; [alkylation]; [arylation]; [photoredox]; [nickel]

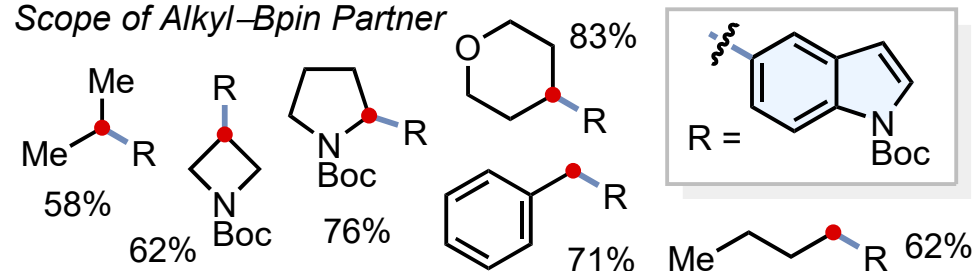
- Simmons *et al.* at BMS report a Ni-metallaphotoredox-catalysed  $sp^2$ - $sp^3$  coupling of (hetero)aryl bromides and alkyl-Bpin esters utilising quinoline as a catalytic additive. Alkyl radical generation occurs from an alkyl-Bpin-quinoline complex, which may proceed *via* a triplet-triplet energy transfer (EnT) process. Scalable conditions for continuous flow were also developed.



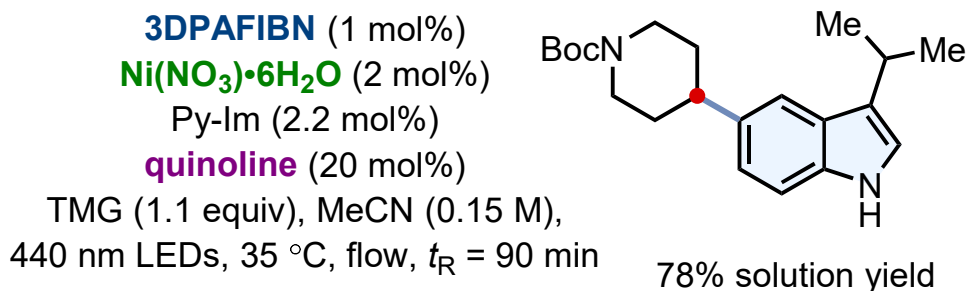
## Scope of (Hetero)aryl Partner



## Scope of Alkyl-Bpin Partner



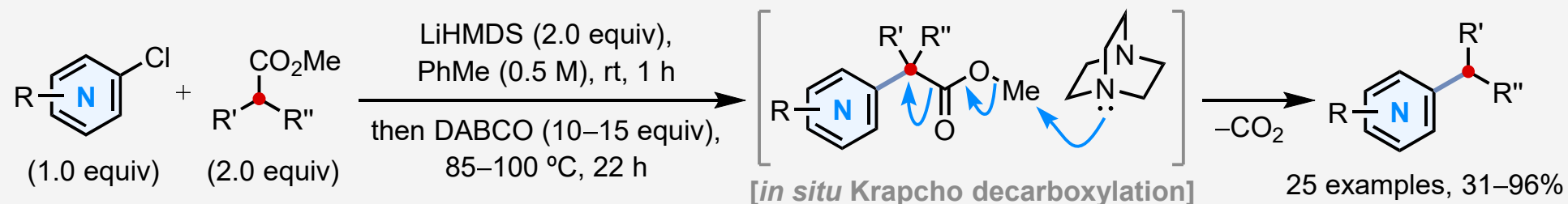
## Scalable Conditions for Continuous Flow



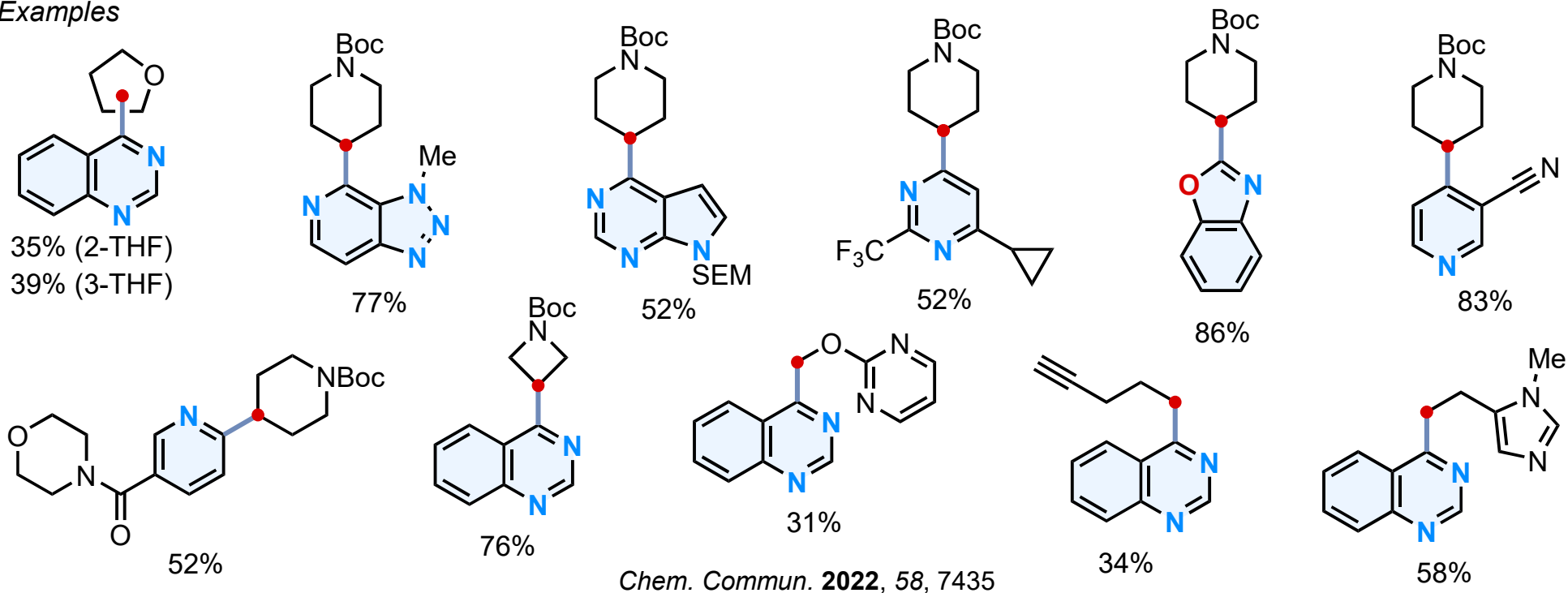
Org. Lett. 2022, 24, 5663

**Keywords:** [cross-coupling]; [aryl halides]; [alkyl boronates]; [alkylation]; [arylation]; [photoredox]; [nickel]; [flow]

- Gallego *et al.* at Pfizer report an operationally simple and functional group tolerant, two-step  $S_NAr$ -decarboxylation protocol for "traceless" formation of  $C(sp^2)-C(sp^3)$  bonds. It can be used to build fragment libraries using parallel synthesis techniques
- The enolisable nature of esters also offers increased modularity - a feature not present in carboxylic acids or alkyl halides. Thus, telescoped alkylation-arylation sequences are possible on non- $\alpha$ -branched alkyl esters (not shown).

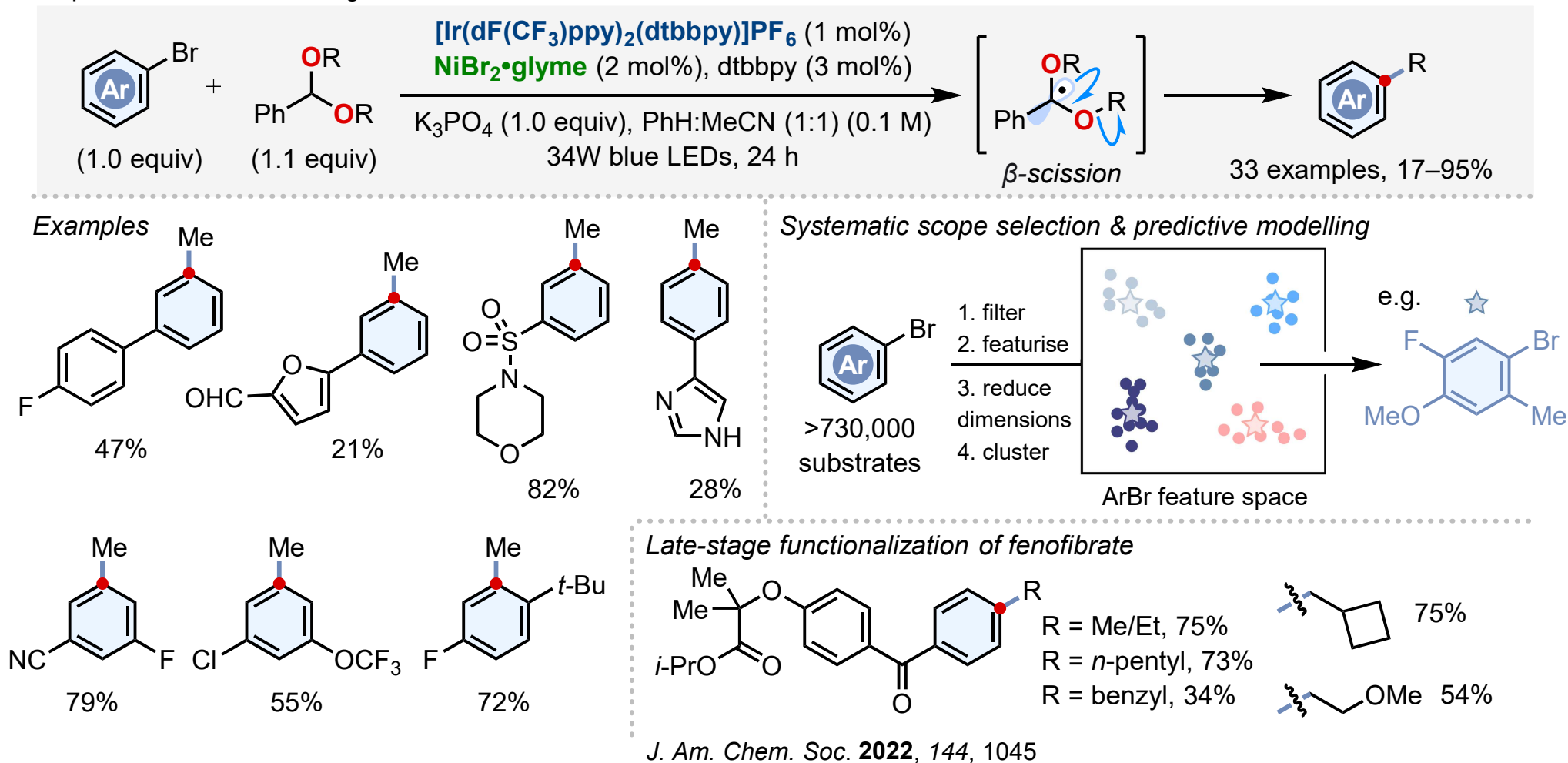


## Examples



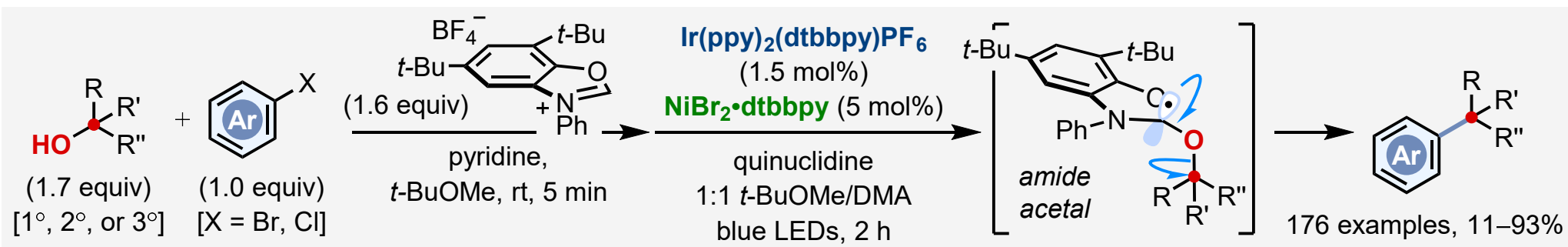
**Keywords:** [arylation]; [alkylation]; [ $S_NAr$ ]; [decarboxylation]; [metal-free]

- Doyle *et al.* report a Ni/photoredox-catalysed methylation or alkylation of aryl halides with benzaldehyde di(alkyl) acetals as radical sources.
- Data science techniques were used to derive a diverse collection of ArBr that is representative of the chemical space of the substrate class.
- By superimposing scope examples from published Ni/photoredox methods on this same chemical space, areas of sparse coverage and high vs low average yields were identified, enabling comparisons between prior art and this new method
- Population-wide reactivity trends for ArBr could also be quantified and sources of possible functional group incompatibility revealed with supervised machine learning.

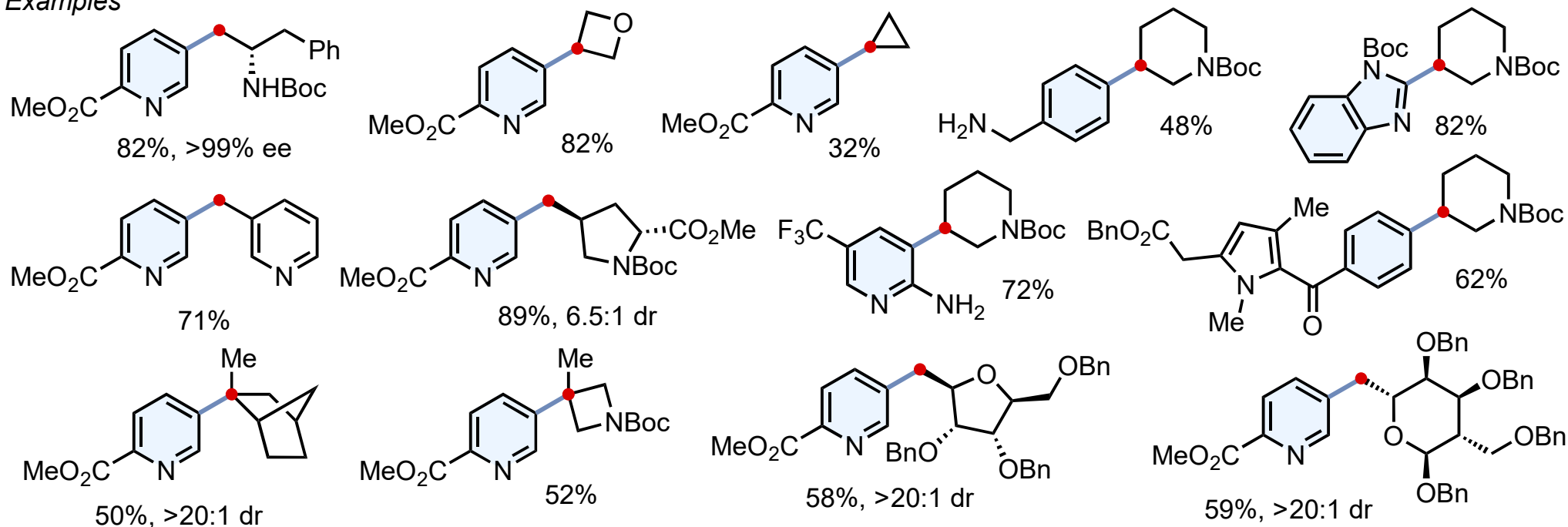


**Keywords:** [methylation]; [alkylation]; [acetals]; [aryl bromides]; [nickel]; [photoredox]; [data science]; [machine learning]

- MacMillan *et al.* report the arylation of alcohols with aryl halides using nickel metallaphotoredox catalysis. A stoichiometric azolium salt additive serves to activate the alcohol partner, generating an amide acetal intermediate as a radical precursor. The method is mild, selective and capable of accommodating primary, secondary and tertiary alcohols, as well as aryl and heteroaryl bromides or chlorides.



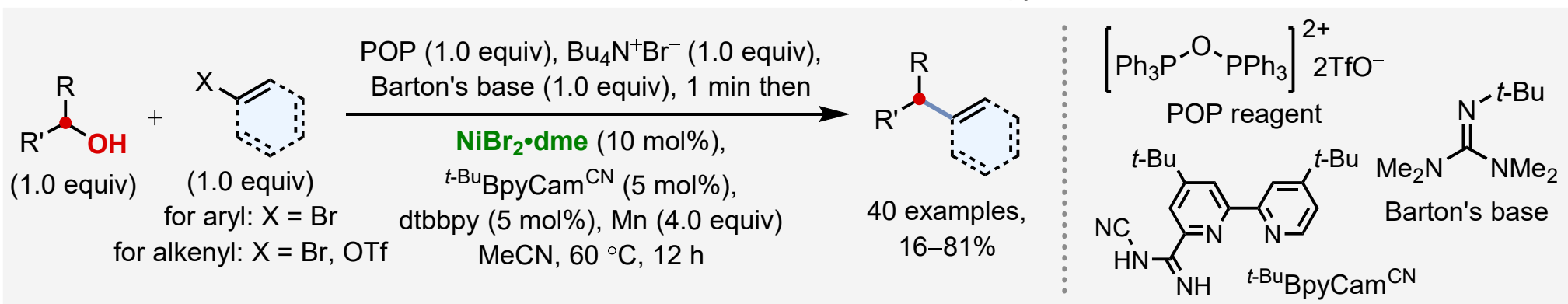
## Examples

Nature **2021**, 598, 451

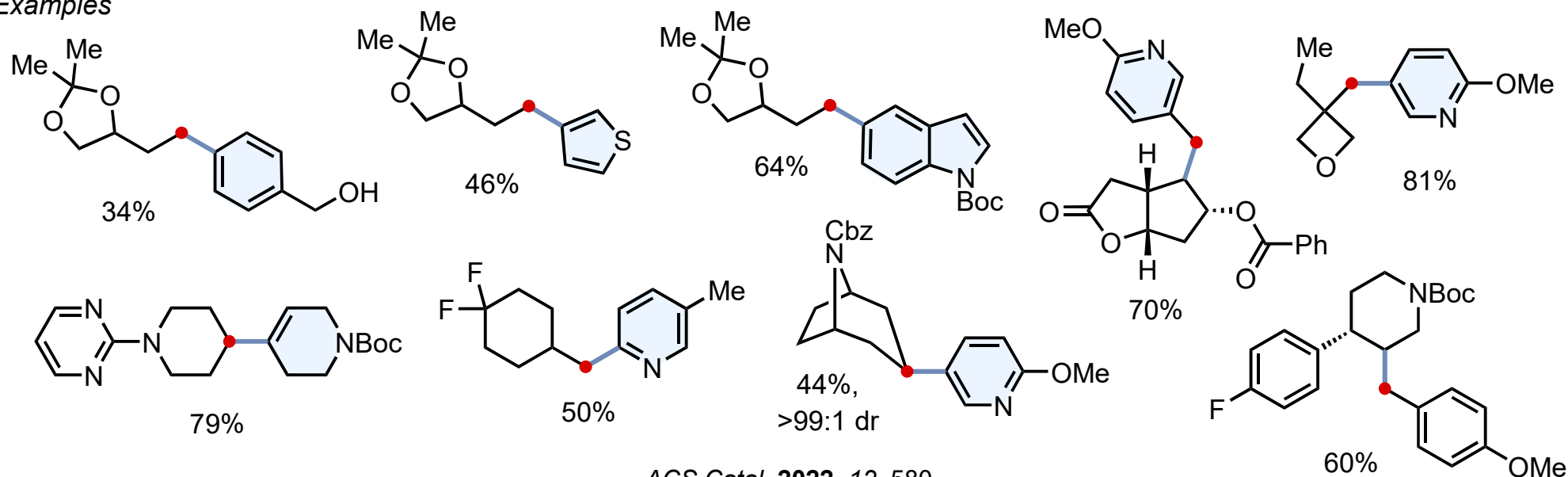
**Keywords:** [arylation]; [alcohols]; [aryl halides]; [photoredox]; [nickel]



- Weix *et al.* report a reductive arylation of 1° and 2° alcohols *via* a rapid *in situ* bromination using the (non-commercial but easy to make) Hendrickson "POP" reagent, prior to cross-coupling. The protocol was also demonstrated to be easily applicable to HTE in a 96-well plate.
- The catalyst mixture works well in MeCN, so problematic amide solvents can be avoided. Moreover, solutions of POP/Bu<sub>4</sub>N<sup>+</sup>Br<sup>-</sup> reagent solution in MeCN can be stored for months outside of a glovebox. The new ligand <sup>t</sup>BuBpyCam<sup>CN</sup> is commercially available.



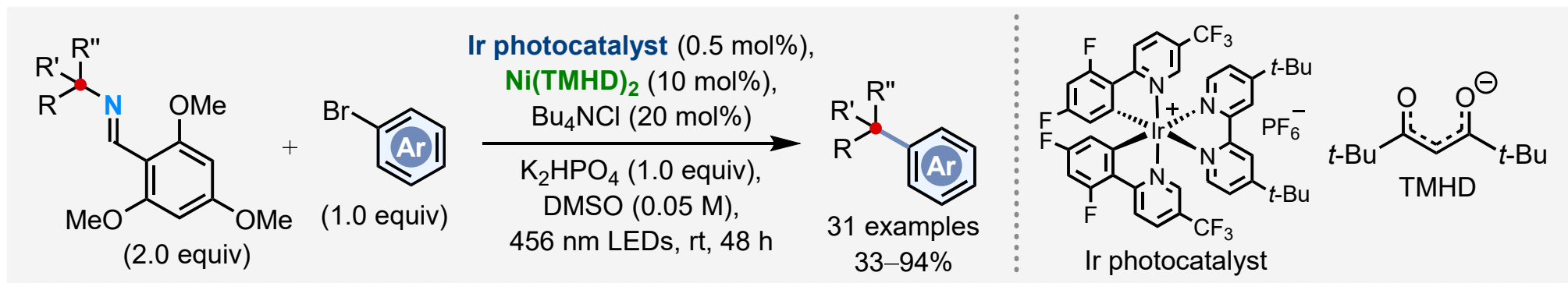
## Examples



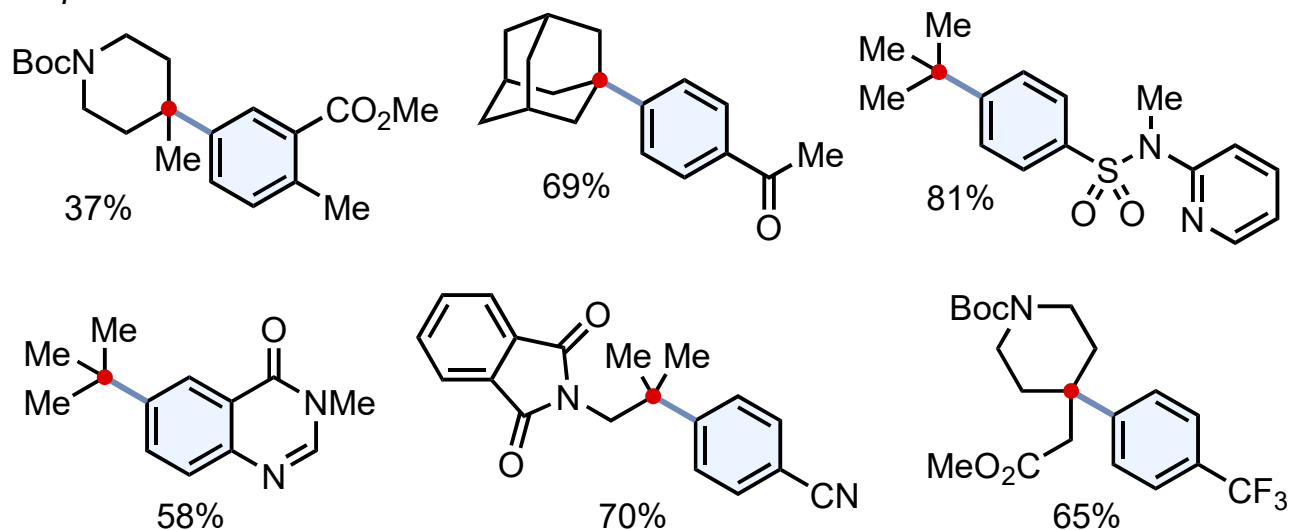
ACS Catal. 2022, 12, 580

**Keywords:** [arylation]; [alkenylation]; [alcohols]; [aryl halides]; [vinyl halides]; [reductive]; [nickel]

- Rovis *et al.* report a deaminative arylation process from sterically-hindered primary alkylamines, using Ni-metallaphotoredox catalysis. Prior activation of the amine *via* condensation with an electron-rich benzaldehyde is required, in order to generate a radical precursor.
- No examples of heteroaromatic substrates as coupling partners are given, although a few *N*-heterocycles (e.g., pyridine, pyrazole) are included as substituents. Enantioenriched amines will naturally lead to racemic products.

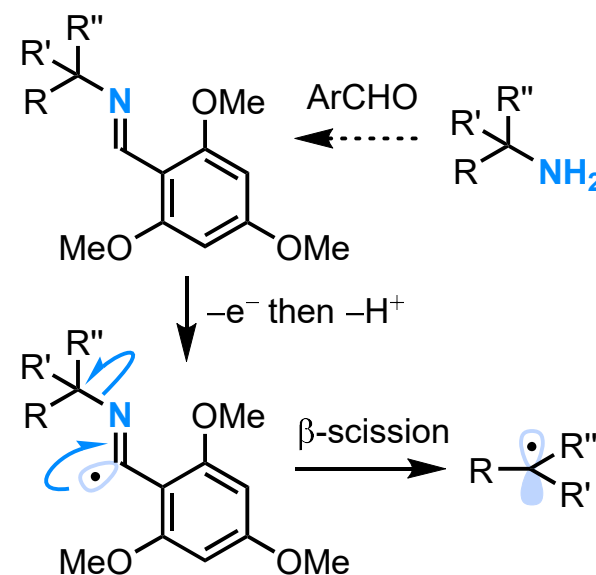


## Examples



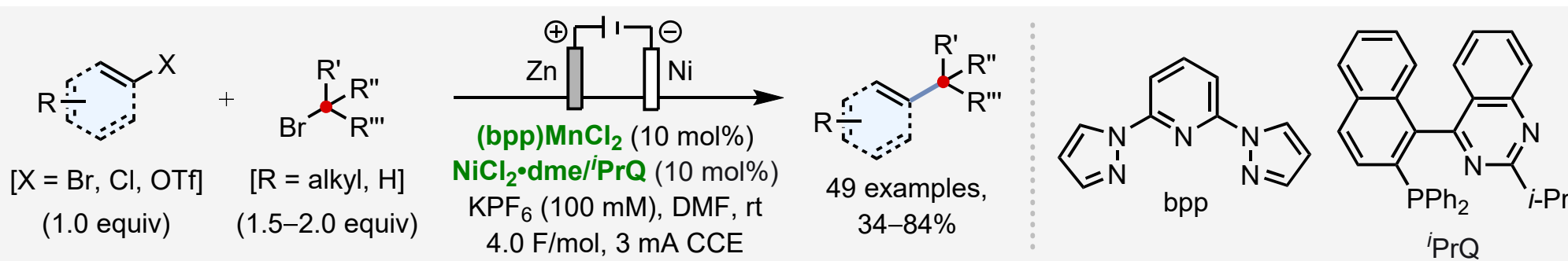
*J. Am. Chem. Soc.* **2021**, *143*, 19294

## Mechanism

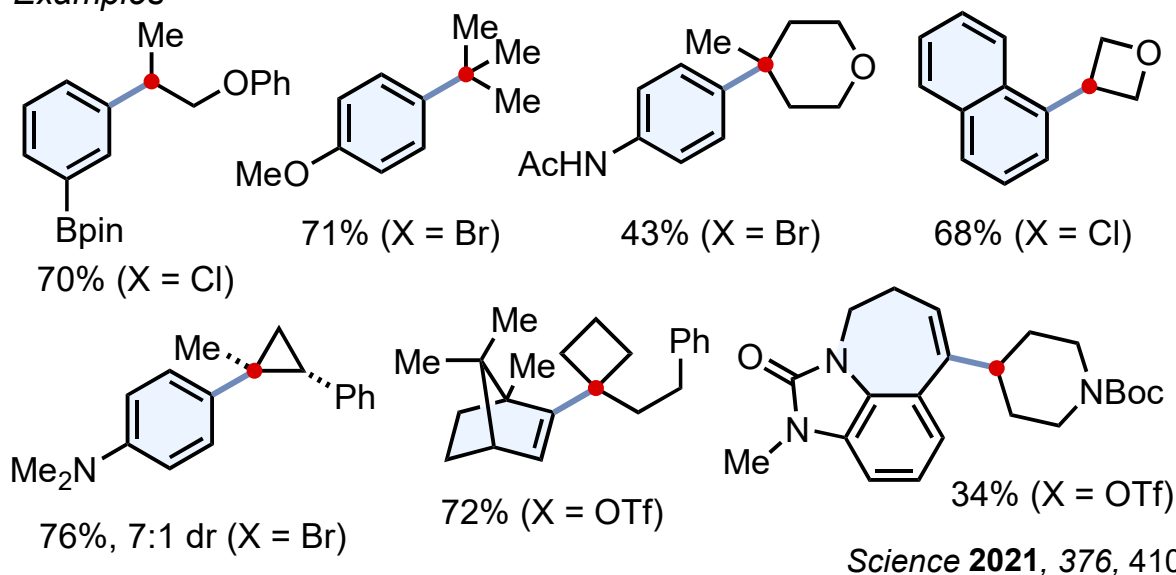


**Keywords:** [arylation]; [amines]; [aryl halides]; [quaternary centres]; [nickel]; [photoredox]

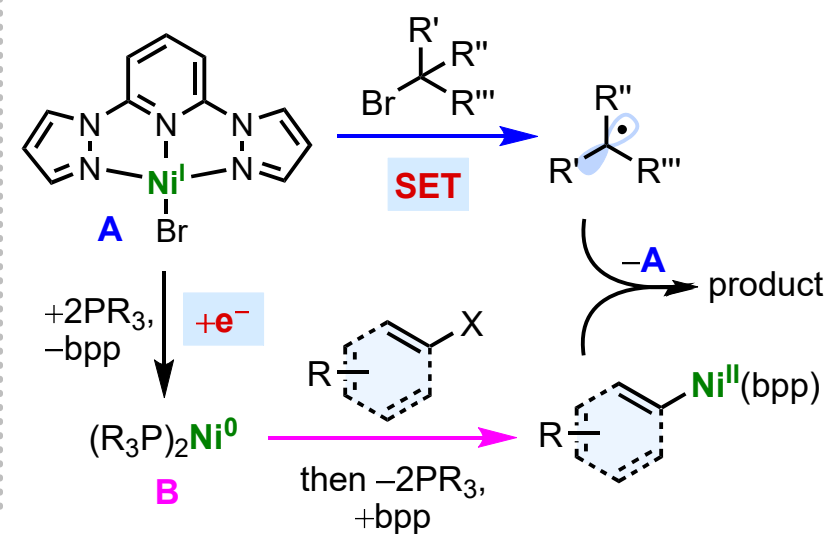
- Reductive cross-couplings of alkyl bromides with C(sp<sup>2</sup>)-X electrophiles are currently very limited with 3° alkyl bromides (i.e., e<sup>-</sup> poor Ar-Br partners only) and there are no examples whatsoever of 1°/2°/3° alkyl bromides coupling with less-activated Ar-Cl or Ar-OTf substrates.
- Sevov *et al.* report an electroreductive, Ni-catalysed cross-coupling of 3° (or 2°) alkyl bromides with aryl or vinyl bromides, chlorides, and triflates. The key advance is a combined use of two different ligands (bpp and <sup>i</sup>PrQ), with controlled generation of two discrete Ni species at the Ni(I) (**A**) and Ni(0) (**B**) oxidation states. Complex **A** exclusively activates alkyl bromides, whereas **B** only activates Ar-X species.
- Zn powder in place of electroreduction gave a similar but lower yield (60% instead of 75%), and led to some isomerised alkyl product (5%).



## Examples

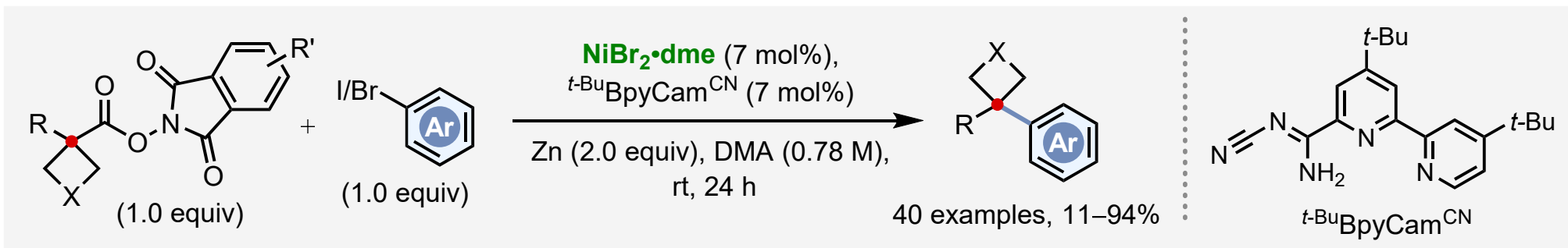


## Mechanism

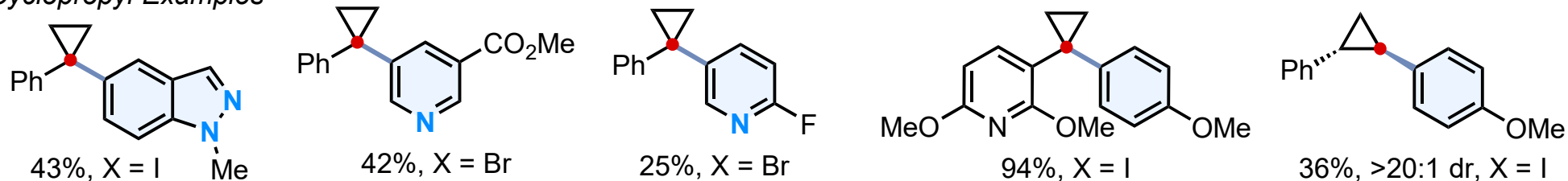


**Keywords:** [reductive cross-coupling]; [aryl halides]; [alkyl halides]; [alkylation]; [electrochemistry]; [nickel]

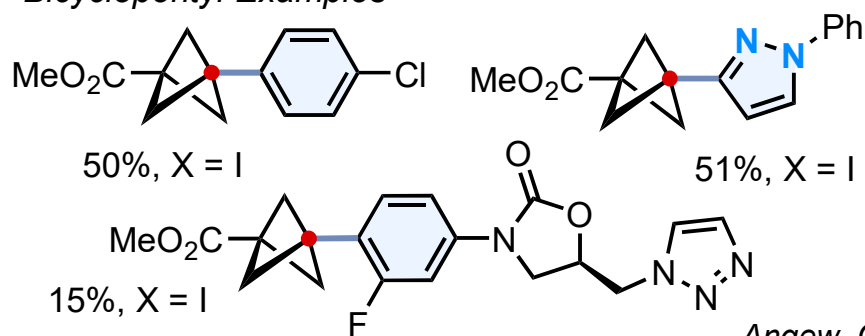
- Weix *et al.*, in collaboration with Janssen, reports the Ni-catalysed, reductive coupling of strained ring *N*-hydroxyphthalimide (NHPI) esters with (hetero)aryl halides. This allows cyclopropanation or bicyclopentylation of arenes, as well as installation of other strained rings (e.g., oxetanes, bicyclohexanes, azetidines). It is compatible with HTE (using Zn@ChemBeads) and the NPHI ester can be tuned for better yields.
- The ligand  $t\text{-BuBpyCam}^{\text{CN}}$  is commercially available, or can be made in 3 steps from dtbbpy. Using a zinc-packed bed, the reaction could be scaled with a 45 min residence time in continuous flow.



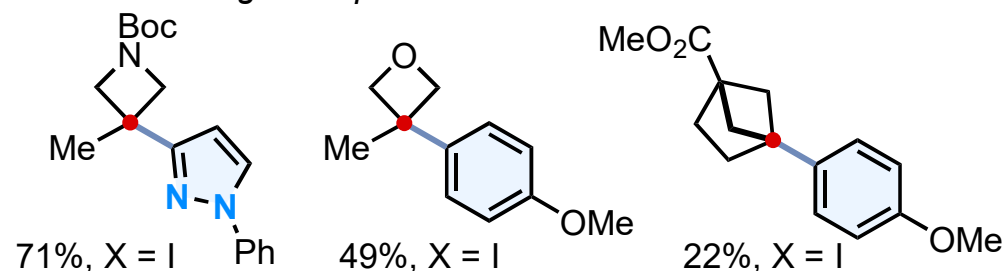
### Cyclopropyl Examples



### Bicyclopentyl Examples



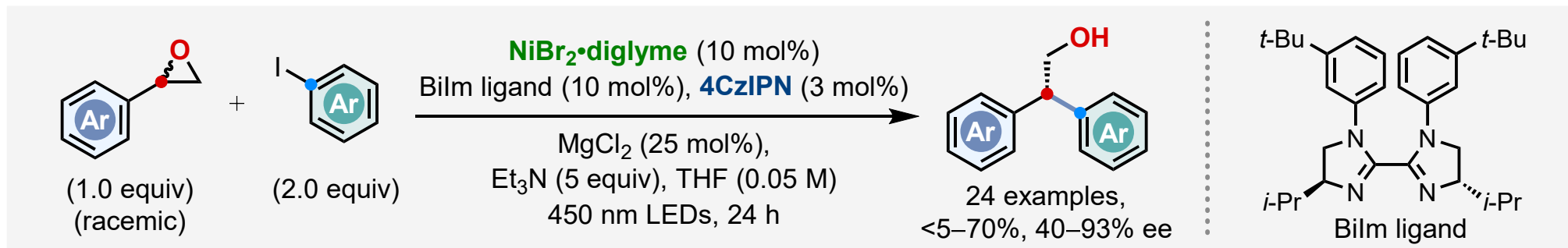
### Other Strained Ring Examples



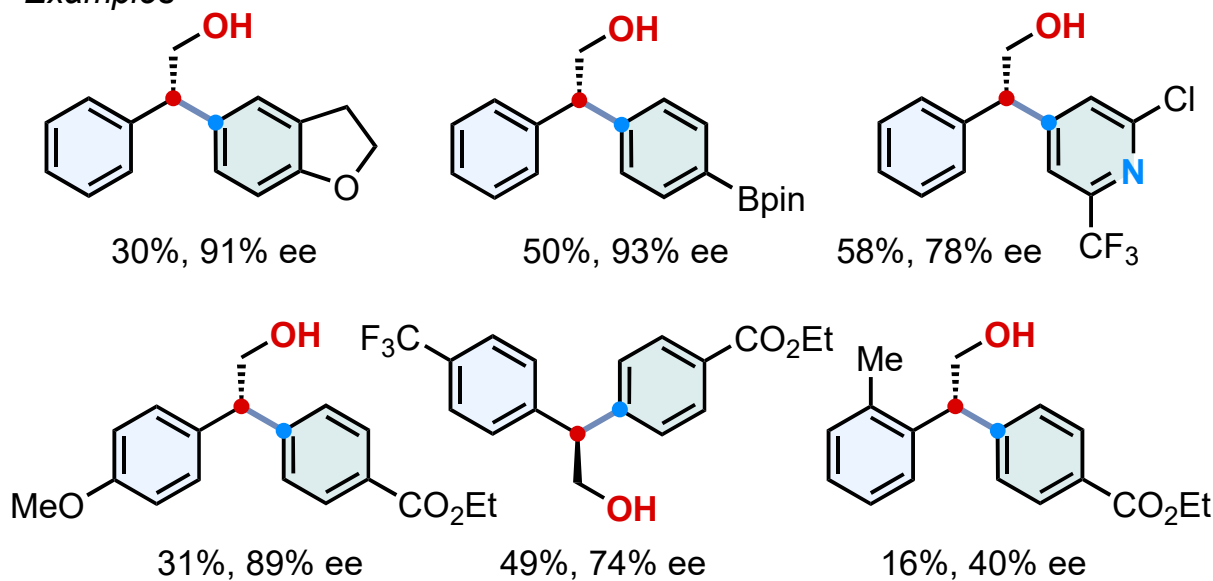
Angew. Chem. Int. Ed. **2022**, 60, e202205673

**Keywords:** [reductive cross-coupling]; [aryl halides]; [redox-active esters]; [alkylation]; [cyclopropanes]; [BCPs]; [nickel]

- Doyle *et al.* report a Ni-metallaphotoredox-catalysed, enantioconvergent coupling of racemic styrene oxides with aryl iodides using Et<sub>3</sub>N as the reductant. The chiral biimidazoline (Bilm) ligand is made in 4 steps (40% yield, 1 purification) from 845714-30-9 (£164/g).
- The scope is mostly limited to benzenoid coupling partners, and *ortho*-substitution on either partner is not well tolerated.
- Multivariate linear regression analysis with 29 Bilm and BiOx ligands showed that enantioselectivity correlates with ligand electronics, with more electron-rich ligands giving higher ee's. Mechanistic studies suggest that reductive elimination is enantiodetermining.

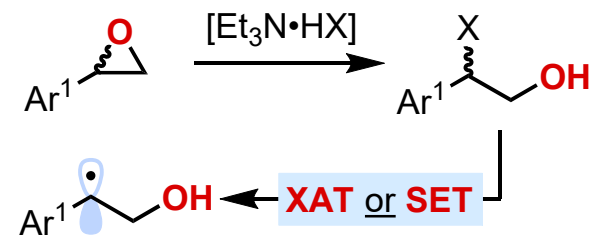


## Examples

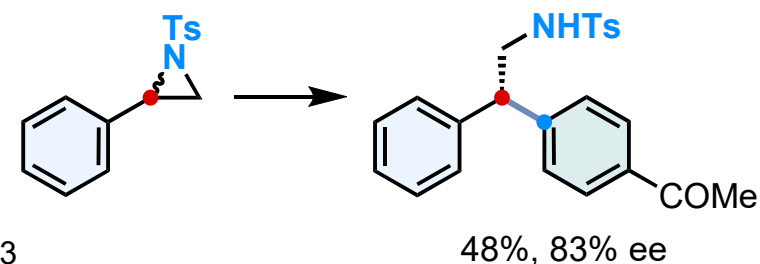


J. Am. Chem. Soc. 2021, 143, 15873

## Radical Formation via Halohydrin



## Aziridine as Coupling Partner



**Keywords:** [cross-coupling]; [epoxides]; [aryl halides]; [diarylmethanes]; [photoredox]; [nickel]; [reductive]; [enantioselective]