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Late-stage *N*-Me Selective Arylation of Trialkylamines Enabled by Ni/Photoredox Dual Catalysis

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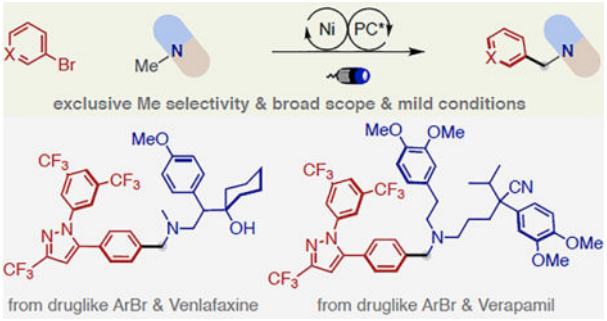
Abstract

The diversity and wide availability of trialkylamines render them ideal sources for rapid construction of complex amine architectures. Herein, we report that a nickel/photoredox dual catalysis strategy effects site-selective α-arylation of various trialkylamines. Our catalytic system shows exclusive *N*-Me selectivity with a wide range of trialkylamines under mild conditions, even in the context of late-stage arylation of pharmaceutical compounds bearing this common structural motif. Mechanistic studies indicate the unconventional behavior of Ni catalyst upon intercepting the α-amino radicals, in which only primary α-amino radical undergoes successful cross-coupling process.

Graphical Abstract



Keywords

late-stage C–H functionalization; trialkylamine arylation; nickel/photoredox dual catalysis

Trialkylamines are well-represented subunits in numerous alkaloid natural products, synthetic agrochemicals, clinical molecules and marketed pharmaceuticals (Figure 1A).[1] The functionalization of C-H bonds alpha to *N* provides endless opportunities to fine-

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tune their physical properties as well as their biological activities and pharmacokinetics.[2] The further development of direct late-stage α-C(sp^3)–H functionalization of complex trialkylamines with improved structural modularity and functional diversity would enable novel synthetic disconnections and expedite discovery of lead compounds from existing medicinal chemistry libraries. To date, the late-stage α-alkylation of complex trialkylamines has experienced rapid growth (Figure 1B);[3] however, the related arylation has remained underexplored with sporadic examples (Figure 1C, *left*).[3e]

Recently, transition-metal/photoredox dual catalysis has emerged as a transformative platform enabling a diverse set of formerly challenging chemical bond-forming events under mild conditions.[4] Given that trialkylamines are commonly used as hydride, hydrogen or electron sources in a number of transition-metal/photoredox catalysed transformations,[5] it would not be trivial to compete with the established reactivity for direct arylation of trialkylamines. However, Molander's seminal work of desilylative arylation of α-silyl trialkylamines indicates otherwise,[6] in which the silyl group is preinstalled from secondary amine to control the site-selective generation of α-amino radical.[7] As part of our interest to derivatize amines,[8] we questioned whether we could develop a general method for selective arylation of trialkylamines even in the context of late-stage functionalization with improved practicality and complexity (Figure 1C, *right*).

If accomplished, it would offer new opportunities to rapidly access novel benzyl dialkylamines — privileged moieties embedded within many bioactive molecules and lead compounds[9] — with complementarity to classical alkylation or reductive amination strategies from secondary amines, where the complex benzaldehydes or benzyl electrophiles are often difficult to access.[10]

We started our investigation by conducting arylation of *N*-Me piperidine with 4-bromobenzonitrile under Ni/photoredox conditions.[11] Gratifyingly, when reaction occurs, we observe exclusive *N*-Me arylation product **1**. Further screening revealed the optimized conditions to be $NiCl_2$(dtbbpy)$(H_2O)_4$ (**Ni-1**) (5 mol%), 4CzIPN (1 mol%) as organic photocatalyst,[12,13] and Na_2CO_3 (1.0 equiv) as a base in Dioxane (0.2 M) under blue-LEDs irradiation (440 nm), affording **1** in 50% isolated yield (see SI for extensive screening details). Our system turns out to be highly efficient as 2 mol% of **Ni-1** works equally well (entry 2). Switching to Ir-based photocatalyst leads to a decrease in yield (entry 3). While DME as solvent gives similar yield (entry 5), other solvents demonstrate lower chemoselectivity (entries 6 & 7). Using 4-iodobenzo-nitrile as aryl source (entry 4) shows low reactivity under our conditions. The use of an organic base, such as collidine, gives comparable results (entry 8). Control studies reveal the necessity of irradiation and both catalysts for arylation to occur (entries 9 & 10).

With the optimized conditions, we next studied the scope of our protocol. As shown in Table 2, the method displays exclusive *N*-Me selectivity. A variety of trialkylamines bearing various alkyl substituents underwent the desired arylation (**1**-**9**). Aryl bromides containing different functional groups and heterocycles (**10**-**18**, **21**) are well accommodated. In addition, the ketone (**11**) and aldehyde (**12**) functionalities hold promise for further reductive amination events. Interestingly, arylation of sterically encumbered trialkylamines,

often used as frustrated Lewis pair and hindered amine light stabilizers,[14] is successful upon switching to a nickel/1,3-diketone-ligand combination (**19-21**) (see Table S4 for details), a system known for forging congested bonds.[15]

Encouraged by the broad generality of this approach, we anticipated that our protocol might not only streamline the synthesis of simple benzyl dialkylamines but might also be applicable to late-stage functionalization.[16] To this end, we were pleased to find that a series of trialkylamine-containing pharmaceuticals and natural products could be coupled with complex aryl bromides. As evident by the results compiled in Table 3, a variety of valuable, yet not easily accessible druglike benzyl dialkylamines were rapidly synthesized with moderate to high yields (**22-35**), highlighting the potential impact of our protocol on generating complex amine architectures to accelerate lead compound discovery.

In general, oxidation/deprotonation of trialkylamines furnishes the less hindered α-amino radical preferentially.[7a,7b,8a] However, this does not completely explain the exclusive *N*-Me selectivity observed in our photochemical arylation, especially for substrates that are known to generate a mixture of α-amino radicals with moderate ratios upon oxidation/deprotonation sequence (*e.g.* *N*-Me piperidine gives 2:1 selectivity for 1° over 2° under typical conditions[8a,8c]). We then turned our attention to understand the source of the high site-selectivity. A simple control experiment with triethylamine under standard conditions indicated the recalcitrance of a putative $ArNi^{II}L_nBr$ (**Ni-2**) intermediate to intercept secondary α-amino radicals, as no desired arylation was observed. Instead, a considerable amount of hydrodebromination and homodimerization products from the aryl bromide were detected (Figure 2A). This helps to explain the parasitic by-products formed during the reaction screening of *N*-Me piperidine (Table 1). Further studies with α- and β-deutero-tributylamine as starting materials revealed that the H source of hydrodebromination partially comes from both α- and β-C(sp^3)–H of tributylamine (Figure 2B), with the balance likely coming from the solvent (dioxane). When optimizing the arylation on sterically hindered trialkylamines, we found significant dimerization of the amine when the reaction was conducting in polar aprotic solvents (DMF or DMA) (Figure 2C). This likely stems from the amino radical attacking an iminium ion intermediate (Figure 2C).[10b] Indeed, adding H_2O (50 equiv) to the standard arylation of *N*-Me piperidine completely shuts down the desired reactivity leading to exclusive generation of the hydrodebromination product, which presumably occurs via hydrolysis of the iminium ion intermediate (see Table S3 for H_2O titration). On the basis of these results, along with the literature precedent on the coordination of Ni-complexes and iminium ions,[10a,17] we tentatively propose that the arylation occurs through interception of α-amino radical by oxidative addition complex (**Ni-2**) to generate a Ni^{III} intermediate (**Ni-3**),[5g,6] which may undergo an off-cycle equilibrium between iminium ion and **Ni-4** intermediate (Figure 2D). While **Ni-3** may undergo reductive elimination to give rise to the desired product, the iminium ion with β-H instead results in the decomposition of **Ni-3**, leading to the hydrodebromination and homodimerization of the aryl bromide. These phenomena are consistent with the stability of $(R_3P)_2Ni(0)$/iminium ion complexation reported by Pierpont and Barefield.[17a]

In summary, we have developed a late-stage arylation of trialkylamine-containing pharmaceuticals by employing Ni/photoredox dual catalytic platform under mild conditions.

The reaction displays exclusive selectivity for *N*-Me C(sp^3)-H bonds, not only streamlining the synthesis of benzyl dialkylamines, but also holding great promise to accelerate lead molecule discovery. Studies to enable arylation at higher α-substituted positions of trialkylamines are currently ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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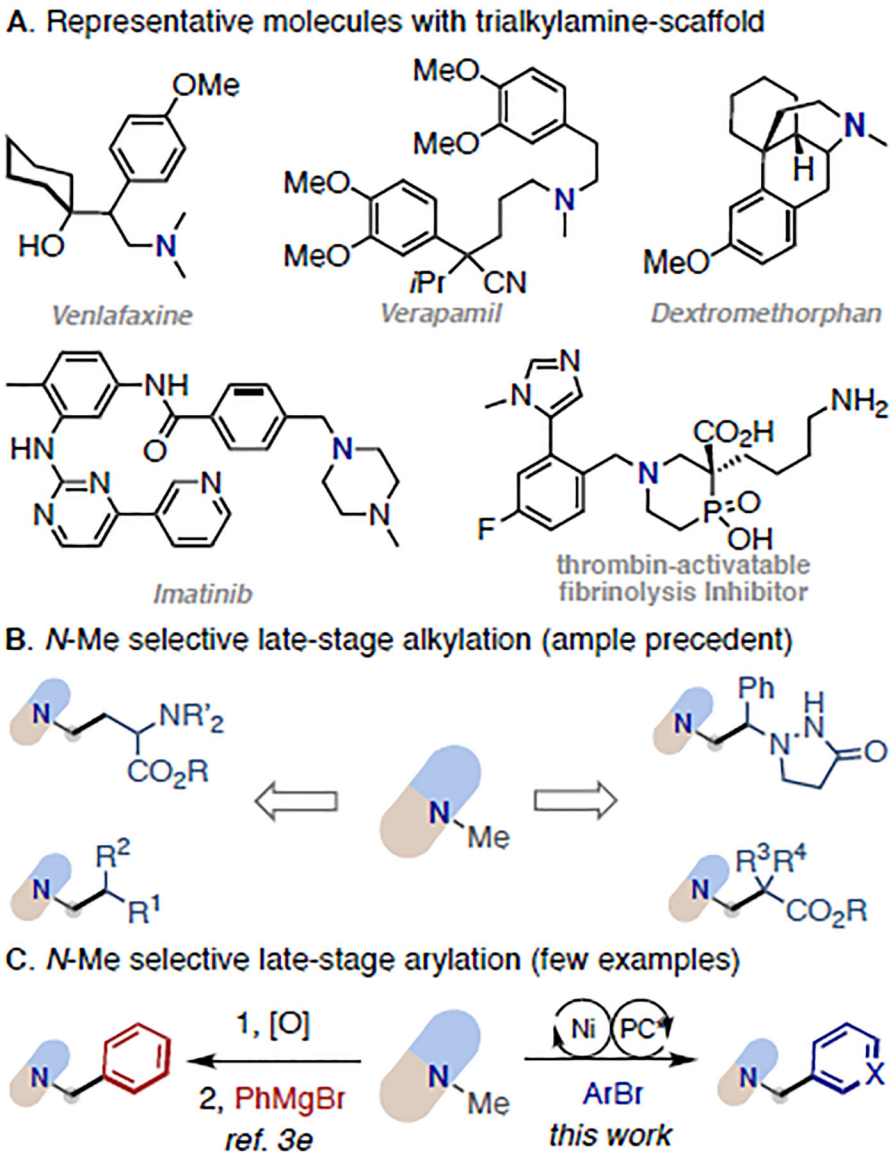


Figure 1.
Prevalence and α-Functionalization of complex trialkylamines

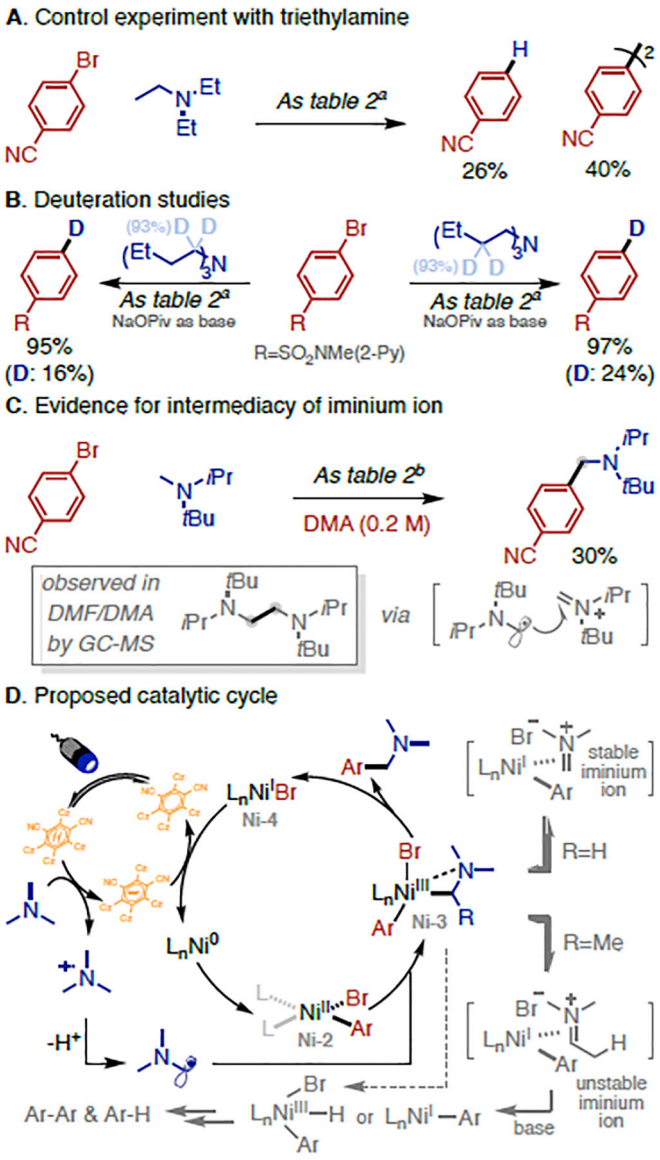
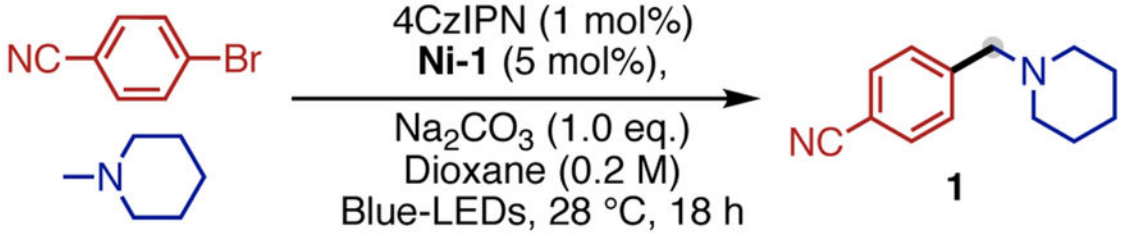


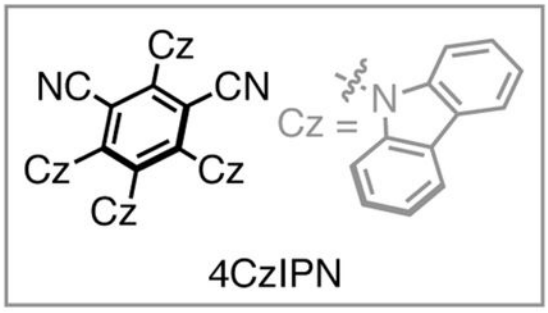
Figure 2.
Mechanistic Studies.

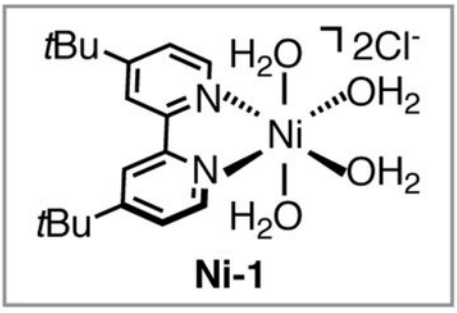
Table 1.

Optimization and Control Studies



entry	deviation	Ar-H (%)[a]	**1** (%)[a]
1	none	12	49 (50)[b]
2[c]	**Ni-1** (2 mol%)	14	49
3	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$	28	32
4[d]	4-CN-C_6H_4I	8	16
5	DME	19	47
6	THF	20	41
7	DMA	19	30
8	2,4,6-Collidine	4	43
9[e]	w/o light / 4CzIPN	0	0
10[d]	w/o **Ni-1**	6	0

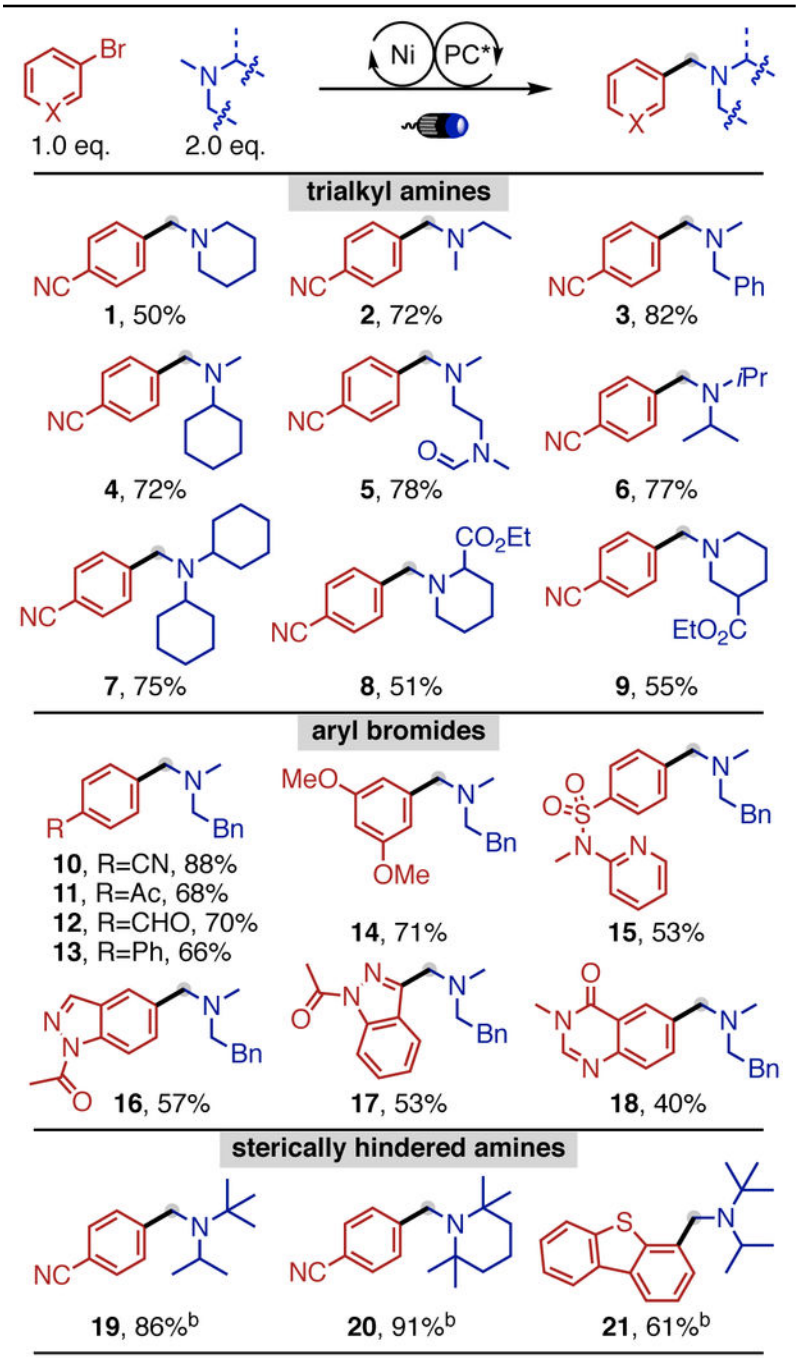




0.2 mmol scale; amine (2.0 equiv), homocoupling of ArBr accounts for mass balance. [a] GC-MS yield with ethyl benzoate as internal standard. [b] Isolated yield. [c] 24 h. [d] low conversion of ArBr. [e] no conversion of ArBr.

Table 2.

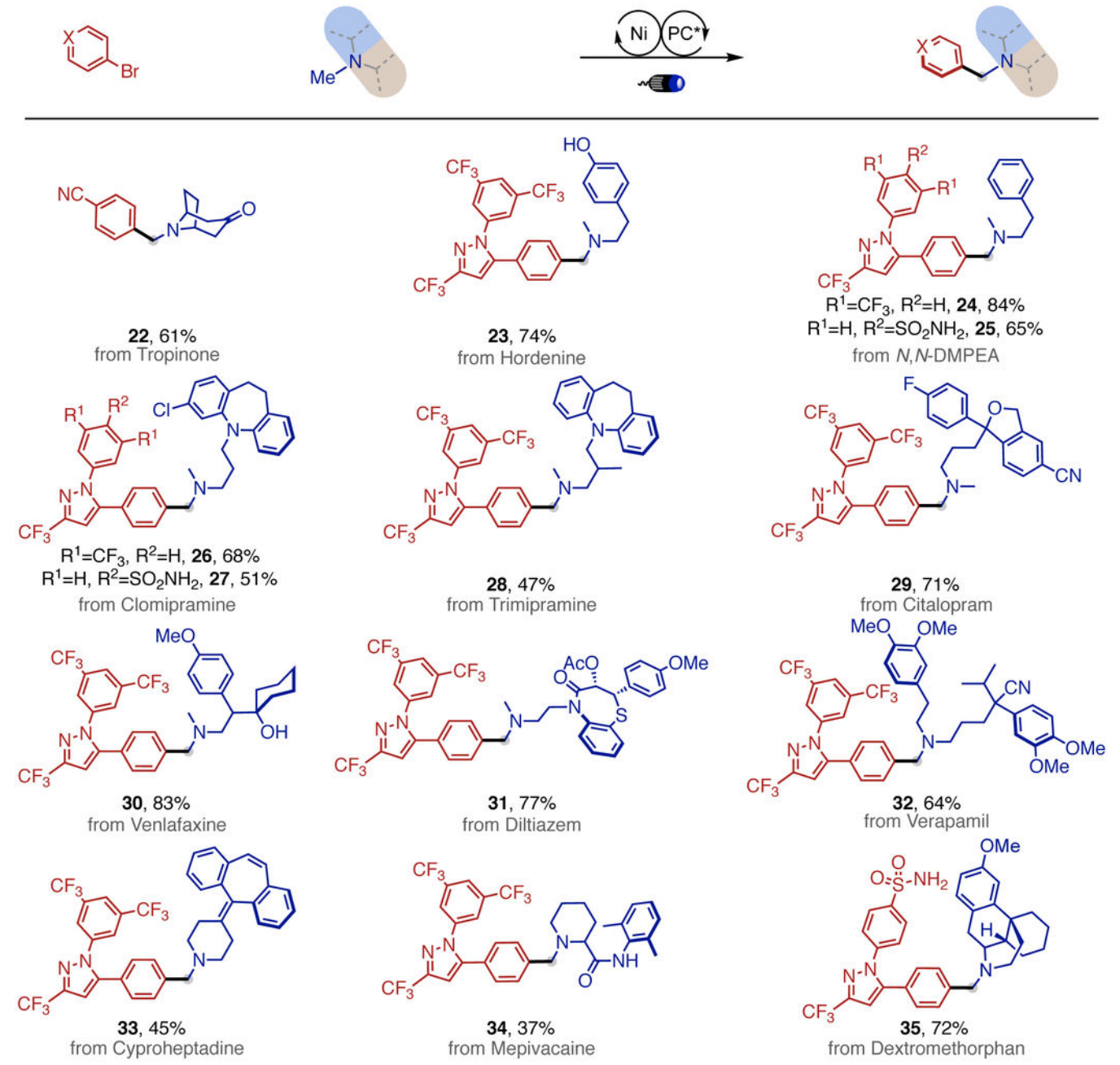
Scope of Trialkylamines and Aryl Bromides



0.2 mmol scale; [a] **Ni-1**(5 mol%), 4CzIPN (1 mol%), Na_2CO_3 (1.0 eq.) in Dioxane (0.2 M) at 28 °C for 18 h; [b] $NiCl_2(H_2O)_6$ (5 mol%), Dipivaloyl methane (10 mol%), 4CzIPN (1 mol%), Na_2CO_3 (1.0 equiv) in MeCN (0.2 M) at 28 °C for 24 h.

Table 3.

Late-stage *N*-Me Selective Arylation



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0.1 mmol scale; as Table 1 in Dioxane (0.1 M) for 24h.