

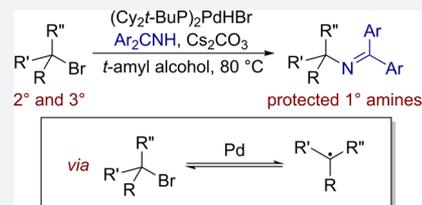
Palladium-Catalyzed Cross Coupling of Secondary and Tertiary Alkyl Bromides with a Nitrogen Nucleophile

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S Supporting Information

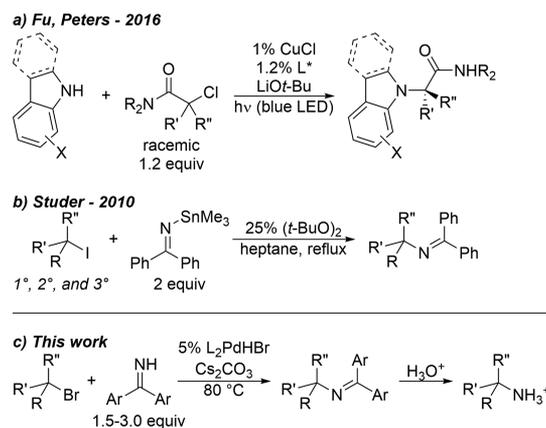
ABSTRACT: We report a new class of catalytic reaction: the thermal substitution of a secondary and or tertiary alkyl halide with a nitrogen nucleophile. The alkylation of a nitrogen nucleophile with an alkyl halide is a classical method for the construction of C–N bonds, but traditional substitution reactions are challenging to achieve with a secondary and or tertiary alkyl electrophile due to competing elimination reactions. A catalytic process could address this limitation, but thermal, catalytic coupling of alkyl halides with a nitrogen nucleophile and any type of catalytic coupling of an unactivated tertiary alkyl halide with a nitrogen nucleophile are unknown. We report the coupling of unactivated secondary and tertiary alkyl bromides with benzophenone imines to produce protected primary amines in the presence of palladium ligated by the hindered trialkylphosphine $Cy_2t\text{-BuP}$. Mechanistic studies indicate that this amination of alkyl halides occurs by a reversible reaction to form a free alkyl radical.



Cross-coupling reactions catalyzed by transition-metal complexes are now common methods for the construction of carbon–carbon and carbon–heteroatom bonds.^{1–4} Although most work has focused on reactions of aryl and vinyl halides, cross-coupling reactions of alkyl halides also have been developed, and these reactions offer significant advantages over traditional substitution reactions.^{5–7} Most notable is that the scope of alkyl halide often extends to secondary or tertiary alkyl halides, and enantioenriched chiral catalysts can form enantioenriched products from racemic alkyl halides.⁸ However, these reactions have been largely limited to those forming carbon–carbon and carbon–boron bonds. The analogous coupling reactions of alkyl halides with nitrogen nucleophiles are much less developed, despite the prevalence of alkylamines in natural products, agrochemicals, and pharmaceuticals.^{9–12}

N-Alkylation of nitrogen nucleophiles is traditionally achieved through substitution^{13–17} or reductive amination.^{18–21} Although substitutions of primary or benzylic alkyl electrophiles are facile, reactions with secondary electrophiles typically require elevated temperatures. Moreover, unactivated²² tertiary alkyl electrophiles often undergo elimination in preference to substitution,²³ and tertiary alcohols are inherently unsuitable for reductive amination or borrowing hydrogen^{24–26} strategies. Transition-metal catalysts typically react with secondary and tertiary alkyl halides by a single-electron reduction event,^{27,28} thereby creating the potential to combine the activity of radical amination reactions^{29–33} with the mild conditions and selectivity of cross-coupling reactions. Fu and Peters have reported photoinduced, copper-catalyzed alkylations of carbazoles³⁴ and amides³⁵ with alkyl bromides and iodides, including enantioconvergent alkylations of indoles and carbazoles with α -chloro amides (Scheme 1a).³⁶ However, no thermal, transition-metal catalyzed coupling of a nitrogen nucleophile with an alkyl halide has been reported, nor has any catalytic amination of an unactivated tertiary alkyl halide.³⁷

Scheme 1. Radical-Involved N-Alkylation Reactions



We envisioned that such a reaction could occur in the presence of palladium. A number of palladium-catalyzed reactions of unactivated secondary or tertiary alkyl halides have been reported to occur through alkyl radical intermediates,³⁸ including atom-transfer reactions,³⁹ Heck reactions of alkyl halides,^{40–42} and alkylations of arenes.^{43–45} The formation of this radical is typically proposed to occur by a single-electron-transfer (SET) reaction between the alkyl halide and a palladium(0) complex. The isolation and characterization of cationic $(t\text{-Bu}_3\text{P})_2\text{Pd}(\text{I})$ were reported recently. The identification of this species supports the proposed formation of Pd(I) intermediates from Pd(0)-trialkylphosphine complexes.⁴⁶

Our study to develop this process focused on the reactions of benzophenone imines. We focused on these nucleophiles

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because benzophenone imines are synthetic equivalents to ammonia and have been used in a variety of amination reactions, including palladium-catalyzed coupling with aryl halides^{47,48} and catalytic C–H amination reactions.⁴⁹ Furthermore, *N*-trimethylstannyl benzophenone imine undergoes radical alkylation reactions with secondary and tertiary alkyl halides (Scheme 1b).²⁹ The diarylmethylene protecting group can be removed by hydrolysis or transamination to release primary amines.^{48–50}

Herein, we report the thermal cross coupling of alkyl halides with benzophenone imines as the nitrogen nucleophiles catalyzed by $(\text{C}_2\text{t-BuP})_2\text{Pd}^0$, which is generated in situ from $(\text{C}_2\text{t-BuP})_2\text{PdHBr}$ and base (Scheme 1c). This method enables the preparation of protected primary amines from unactivated secondary and tertiary alkyl bromides. Mechanistic experiments confirm that the coupling process occurs through an alkyl radical, and the intermediacy of this radical allows the process to be extended to the intramolecular carboamination of unsaturated alkyl bromides with imines. The radical mechanism also allows the substitution process to occur in the presence of auxiliary electrophilic functional groups.

Initial experiments to identify conditions for the coupling of a secondary alkyl bromide with benzophenone imine showed that a series of palladium complexes catalyzed the reaction between 3-bromo-1-phenylbutane (**1**) and the parent benzophenone imine (**2a**) to produce the *N*-alkyl imine **3a** in alcohol solvents, but olefins (**4**) and an alkane (**5**) formed as side products. Furthermore, in many cases, the combined yield of **3a**, **4**, and **5** was significantly lower than the conversion of **1**, which indicates that other side products also formed. These studies showed that high yields with limiting alkyl bromide would be more difficult to achieve than high yields with limiting imine. However, for most applications, the alkyl bromide would be the more valuable coupling partner because the imine would likely serve as the source of a final NH_2 group.

To achieve high yields with limiting alkyl halide, we evaluated the effect of the structure of the dative ligand on catalyst activity and product distribution. We studied the reaction of **1** with **2a** and cesium carbonate as base in *tert*-amyl alcohol catalyzed by 3% $[\text{Pd}(\text{allyl})\text{Cl}]_2$ alone or 3% $[\text{Pd}(\text{allyl})\text{Cl}]_2$ with 12% of a series of phosphines (Table 1). The reaction catalyzed by $[\text{Pd}(\text{allyl})\text{Cl}]_2$ alone consumed only 28% of the alkyl bromide and formed only 5% of the *N*-alkyl imine product **3a** (entry 1). Reactions conducted with catalysts bearing phosphines occurred in higher yield, and the identity of the phosphine ligand had a large impact on the conversion of the alkyl bromide and on the ratio of product to alkene, while the identity of the phosphine did not significantly affect the ratio of product to alkane (3:1 to 5:1). Reactions catalyzed by complexes of arylphosphines (entries 2–5) consumed less alkyl bromide and were less selective for formation of the *N*-alkyl imine product than were reactions catalyzed by complexes of trialkylphosphines. Reactions catalyzed by complexes bearing bulky trialkylphosphines occurred to high conversion (entries 6–12). Of these, the reaction catalyzed by 3 mol % $[\text{Pd}(\text{allyl})\text{Cl}]_2$ and 12 mol % $\text{C}_2\text{t-BuP}$ formed the *N*-alkyl imine product in the highest yield and selectivity (entry 12). Similar results were obtained with the single-component precatalyst $(\text{C}_2\text{t-BuP})_2\text{PdHBr}$ (Table 2, entry 1), which is convenient to use in place of the metal and ligand combination, and this complex was used in all further experiments. The effects of additional reaction parameters on the yield of coupled product were also investigated. These studies showed that the

Table 1. Effect of Dative Ligands^a

entry	L	% conv 1	% yield 3a	% yield 4 ^b	% yield 5
1	none	28	5	11	1
2	$\text{C}_2\text{t-BuP}$	86	36	5	11
3	<i>t</i> -Bu ₂ PhP	49	16	9	4
4	Ph_3P	46	6	21	2
5	Ph_2EtP	67	13	25	5
6	dcpe (6%)	96	34	13	11
7	C_3P	96	39	4	13
8	<i>t</i> -Bu ₃ P	77	17	13	5
9	<i>t</i> -Bu ₂ CyP	77	31	8	9
10	<i>t</i> -Bu ₂ MeP	96	41	5	12
11	Ad_2MeP	>99	41	7	12
12	$\text{C}_2\text{t-BuP}$	98	44	3	14

^aYields determined by corrected GC integration against 1,3,5-trimethoxybenzene (TMB). ^bCombined signals for four olefin isomers.

Table 2. Effect of Imine Substituents and Equivalents^a

entry	imine	Ar	equiv 2a–2d	% conv 1	% yield 3a–d
1	2a	Ph	1.1	88	46
2	2b	<i>p</i> -Tol	1.1	96	39
3	2c	(4-OMe) C_6H_4	1.1	93	35
4	2d	(3- CF_3) C_6H_4	1.1	96	74
5	2d	(3- CF_3) C_6H_4	1.2	99	78
6	2d	(3- CF_3) C_6H_4	1.5	>99	83

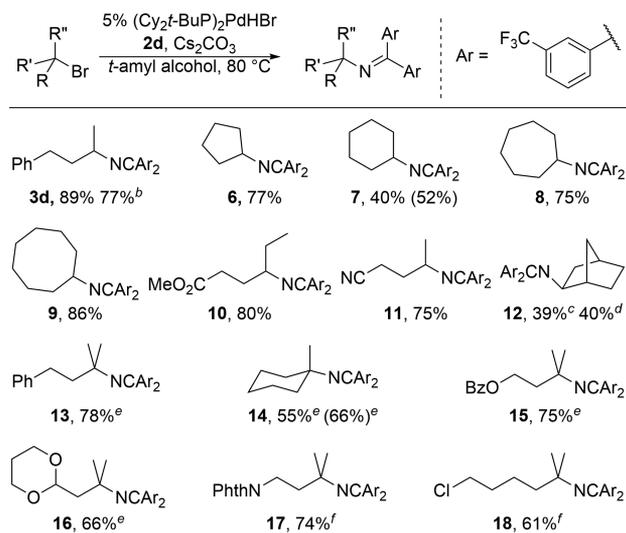
^aYields determined by corrected GC integration against TMB.

substitution reactions did not occur without a catalyst or with nickel in place of palladium. They also showed that reactions in tertiary alcohols gave more product than those in other solvents and that reactions with inorganic carbonate bases occurred in higher yield than those with alkoxide or tertiary amine bases (Table S-1, see Supporting Information).

The identity of the benzophenone imine had a significant effect on selectivity for substitution and yield. The reactions with a variety of symmetrically substituted benzophenone imine derivatives (**2b–d**) (Table 2) showed that the electronic properties of the imine had a small effect on the consumption of the alkyl bromide, but they had a large effect on the selectivity for *N*-alkylation. Reactions of the electron-deficient imine **2d** (entries 4–6) produced higher yields of *N*-alkyl imine and lower yields of alkane and olefin than did reactions with electron-rich imines (entries 2 and 3). Reactions conducted with a higher concentration of the imine also occurred with a higher ratio of *N*-alkyl imine to side products. The reaction containing 1.5 equiv of **2d** produced the corresponding *N*-alkyl imine product **3d** in 83% yield. Moreover, the products containing this trifluoromethyl group were found to be stable to silica gel chromatography (see Supporting Information, SI). These conditions appeared suitable for the preparation of a variety of *N*-alkyl imines.

The scope of the reactions of both secondary and tertiary alkyl halides to form *N*-alkyl imines is represented in Table 3.⁵¹

Table 3. Scope of Alkyl Bromides^a



^aConditions unless otherwise noted: alkyl bromide (0.300 mmol), imine **2d** (1.5 equiv), cesium carbonate (1.5 equiv), $(Cy_2t\text{-BuP})_2PdHBr$ (5.3 mol %), and *t*-amyl alcohol (0.40 mL) at 80 °C with stirring for 20 h. Reaction mixtures prepared inside an N_2 -filled glovebox. Isolated yields of purified *N*-alkyl imines (yields determined by ¹H NMR spectroscopy). ^bReaction mixture prepared under air; vial flushed with N_2 prior to heating. ^cFrom *exo*-2-bromonorbornane. ^dFrom *endo*-2-bromonorbornane. ^eThe product **12** was >97% *exo*. ^f3 equiv of **2d** and 3 equiv of Cs_2CO_3 , 3 equiv of **2d** and 3 h reaction time.

The acyclic 3-bromo-1-phenylbutane (**1**) reacted to give **3d** in 89% isolated yield. Hydrolysis of **3d** with 1.5 equiv of HCl in wet MeOH produced the corresponding primary ammonium chloride salt in 90% isolated yield after 1 h at ambient temperature (see SI). The coupling reaction also occurred with cyclopentyl, cycloheptyl, and cyclooctyl bromides to give the *N*-alkyl imines **6**, **8**, and **9** in similar yields of 75 to 86%. However, the reaction with cyclohexyl bromide occurred in a lower yield of 40% (**7**). The tolerance of the reaction to electrophilic functionality was demonstrated by the formation of **10**, which contains a methyl ester, and **11**, which contains a nitrile. The product **10** formed as a single constitutional isomer, which rules out a possible mechanism involving elimination and hydroamination. Both *exo*- and *endo*-2-bromonorbornane reacted to give the *N*-*exo*-norborn-2-yl imine product **12** in 39 and 40% yields, respectively. The formation of the same diastereomer from the two diastereomeric reactants suggests the intermediacy of an alkyl radical (vide infra).

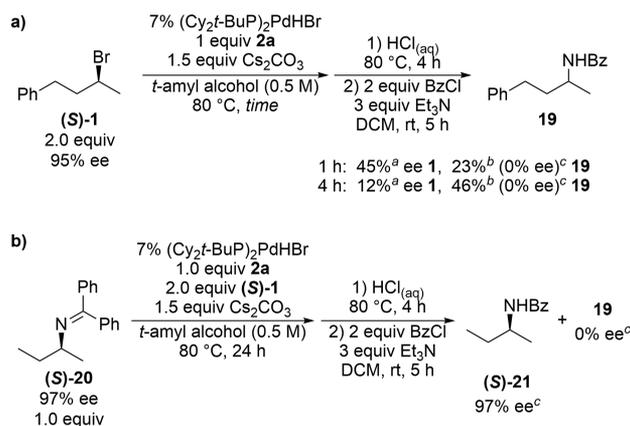
Even tertiary alkyl bromides reacted to form the corresponding *N*-alkyl imines. By increasing the equivalents of imine and base, the substitution product **13** from reaction of 2-bromo-2-methyl-4-phenylbutane formed in 78% yield. The reaction of the cyclic 1-bromo-1-methylcyclohexane also occurred, in this case to form the tertiary imine **14** in 55% yield. The reaction tolerated esters and acetals, and products **15** and **16** were isolated in 75 and 66% yields, respectively. The reactions of acyclic, tertiary alkyl bromides were faster than those of secondary alkyl bromides. Thus, **17** and **18** were obtained in good yields after only 3 h; this short time was necessary to prevent decomposition of the tertiary alkyl imine. Transition

metal-catalyzed coupling reactions of unactivated tertiary alkyl electrophiles are typically more challenging to effect than reactions of secondary alkyl halides,^{52–63} and no examples of *N*-alkylation of an unactivated tertiary alkyl electrophile have been reported as part of the prior work on photochemical substitution.^{34–36}

The higher rate observed with tertiary alkyl bromides suggests that the alkylation of an imine could occur selectively with a tertiary alkyl bromide in the presence of a secondary alkyl bromide. Indeed, the reaction of **2a** with 2 equiv each of *tert*-butyl bromide and *sec*-butyl bromide produced the corresponding *N*-*tert*-butyl and *N*-*sec*-butyl imines in a 7.1:1 ratio (Scheme S-1, see SI).

To investigate the stereochemical outcome further, we studied the reaction of enantioenriched 3-bromo-1-phenylbutane ((*S*)-**1**) with benzophenone imine (**2a**) (Scheme 2a).

Scheme 2. Stereochemical Outcome of Pd-Catalyzed *N*-Alkylation



^aEnantiomeric excess of unconverted **1** was measured by chiral GC. ^bIsolated yield of the purified *N*-alkyl benzamide **19**. ^cEnantiomeric excess was measured by chiral SFC.

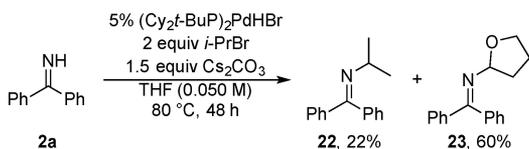
The unconverted (*S*)-**1** was enantioenriched, although partially racemized, after 1 and 4 h at 80 °C, whereas the *N*-alkyl imine product was completely racemic at all reaction times. To assess whether the product racemizes under the reaction conditions, the reaction of (*S*)-**1** was conducted with added authentic (*S*)-*N*-*sec*-butylbenzophenone imine ((*S*)-**20**) (Scheme 2b). The enantioenriched *N*-*sec*-butyl imine was recovered from the reaction without any detectable loss of ee. These results indicate that the reaction proceeds through an achiral intermediate or transition state, such as the alkyl radical intermediate in the proposed mechanism.

No significant reaction of (*S*)-**1** was observed with cesium carbonate, cesium bromide, or the $(Cy_2t\text{-BuP})_2PdHBr$ precatalyst individually. However, when allowed to react with the palladium precatalyst and cesium carbonate at 80 °C for 20 h, the alkyl bromide racemized, and the corresponding alkane byproduct formed (Table S-4, see SI). These experiments indicate that the racemization occurs by reaction of the alkyl bromide with a palladium(0) complex, and this observation is consistent with reversible generation of a free alkyl radical.

Reactions run in THF provided further evidence for the intermediacy of an alkyl radical. These reactions formed an *N*-tetrahydrofuryl imine as a side product. At 0.5 M, both the *N*-isopropyl imine **22** and *N*-tetrahydrofuryl imine **23** formed in 75 and 14% yields, respectively. At 0.05 M, the reaction formed

22 and **23** in 22 and 60% yields, respectively (Scheme 3). We propose that this product forms by abstraction of a hydrogen

Scheme 3. Amination of Tetrahydrofuran^a

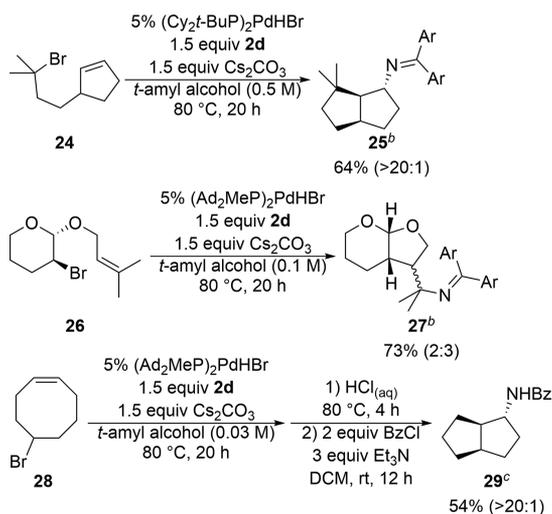


^aYields determined by ¹H NMR spectroscopy.

atom from the THF solvent by an alkyl radical, and the resulting tetrahydrofuryl radical intermediate generates the observed *N*-tetrahydrofuryl imine product. The effect of concentration on the product distribution is consistent with this proposal because the reaction of an alkyl radical with solvent is favored in dilute solutions, and amination is favored in concentrated solutions.

The intermediacy of an alkyl radical suggested that this method could be extended to the intramolecular carboamination of olefins.^{29–33,64} Furthermore, these substrates serve as radical clocks to approximate the lifetime of the radical intermediate. Indeed, the reaction of imine **2d** with the unsaturated alkyl bromide **24** produced the corresponding carboamination product **25** in 64% yield and >20:1 dr (Scheme 4). Similarly, the bromoacetal **26** underwent a Ueno-Stork type

Scheme 4. Palladium-Catalyzed Intramolecular Carboamination^a



^aCompounds **24**–**29** are racemic. ^bIsolated yields of purified *N*-alkyl imines. ^cIsolated yield of purified *N*-alkyl benzamide. ^{b,c}(*exo/endo* ratio). See the SI for assignments of relative configurations.

cyclization⁶⁵ and subsequent amination to yield a 3:2 mixture of *endo*- and *exo*-**27** in 73% combined yield. In both cases, the product from direct cross-coupling was not detected by gas chromatography. These results indicate that the amination step is significantly slower than the cyclization of these substrates.

However, the reaction of (*Z*)-5-bromocyclooct-1-ene (**28**) produced a 2:1 mixture of products favoring cyclization when run at 0.50 M, and this substrate is thus an appropriate radical clock for the cross-coupling reaction. Renaud and co-workers have measured the rate constant of cyclization of cyclooct-4-

enyl radical as $3.3 \times 10^4 \text{ s}^{-1}$ at 80 °C.⁶⁶ Therefore, the formation of a mixture of products indicates that the observed rate constant for the amination of a secondary alkyl radical is on the order of 10^4 s^{-1} . When the reaction was run at 0.03 M, the carboamination product formed predominately and was isolated as the corresponding benzamide **29** in 54% yield. The relatively small rate constant and the dependence of the extent of cyclization on concentration argue against reaction of the radical within a solvent cage.

The stereochemical outcomes of these carboamination reactions are consistent with free radical cyclizations. The reactions of **24** and **28** form structurally similar products *exo*-**25** and *exo*-**29** in high dr. However, the product *exo*-**25** results from addition of the carbon and nitrogen to the opposite faces of the alkene in **24** (*anti*-carboamination), while *exo*-**29** results from addition to the same face of the alkene in **28** (*syn*-carboamination). These products could also form by reaction of an alkylpalladium complex with an alkene. However, an alkylpalladium(II) complex would be expected to react by *syn*-carbopalladation to form the *syn*-carboamination product after reductive elimination.⁶⁷ The formation of the *anti*-carboamination product **25**, therefore, corroborates the other data supporting a free radical cyclization.

Although the process we describe constitutes the first thermal, transition metal-catalyzed coupling of unactivated secondary and tertiary alkyl halides with a nitrogen nucleophile, significant additional studies will be needed to make this process into a practical synthetic method. Benzophenone imines are commonly used as ammonia surrogates for palladium-catalyzed coupling of aryl halides,^{47,48} but these reagents are larger than typical ammonia equivalents. A catalyst capable of coupling a wide range of nitrogen nucleophiles to form a variety of *N*-alkyl products would make the process most valuable. Such a catalyst could also expand the scope of alkyl halides by reducing reaction times and temperatures to avoid competitive background reactions, such as elimination. Finally, our results support the intermediacy of a free alkyl radical, but the intimate mechanism by which the C–N bond forms and the Pd(0) species regenerates remains to be revealed by ongoing studies (see the SI for some plausible mechanisms). The significant current scope suggests that these initial findings, in combination with further work, should point the way to a valuable new methodology for the synthesis of alkylamines by a catalytic version of a classical transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00187.

Experimental procedures, characterization data, and supplemental tables (PDF)

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Notes

The authors declare no competing financial interest.

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