Published in final edited form as:

J Am Chem Soc. 2018 February 14; 140(6): 2292–2300. doi:10.1021/jacs.7b12212.

Ni-Catalyzed Carbon-Carbon Bond-Forming Reductive Amination

Christoph Heinz^{#†}, J. Patrick Lutz^{#†,⊥}, Eric M. Simmons[‡], Michael M. Miller[§], William R. Ewing[§], Abigail G. Doyle^{*†}

[†] Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

[‡] Chemical and Synthetic Development, Bristol-Myers Squibb, New Brunswick, New Jersey 08903, United States

[§] Discovery Chemistry, Bristol-Myers Squibb, P.O. Box 5400, Princeton, New Jersey 08543-5400, United States

[#] These authors contributed equally to this work.

Abstract

This report describes a three-component, Ni-catalyzed reductive coupling that enables the convergent synthesis of tertiary benzhydryl amines, which are challenging to access by traditional reductive amination methodologies. The reaction makes use of minium ions generated *in situ* from the condensation of secondary *N*-trimethylsilyl amines with benzaldehydes, and these species undergo reaction with several distinct classes of organic electrophiles. The synthetic value of this process is demonstrated by a single-step synthesis of antimigraine drug flunarizine (Sibelium) and high yielding derivatization of paroxetine (Paxil) and metoprolol (Lopressor). Mechanistic investigations support a sequential oxidative addition mechanism rather than a pathway proceeding via α -amino radical formation. Accordingly, application of catalytic conditions to an intramolecular reductive coupling is demonstrated for the synthesis of endo- and exocyclic benzhydryl amines.

Graphical Abstract

*Corresponding Author agdoyle@princeton.edu.

⊥Present Address: Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109, United States.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b12212.

Experimental details, characterization data, optimization tables (PDF)

Crystallographic data (CIF)

The authors declare no competing financial interest.

INTRODUCTION

Reductive amination is among the most important methods for the synthesis of alkylamines and has seen widespread application in the preparation of bioactive compounds. A recent analysis of drug candidate syntheses published by three pharmaceutical companies revealed that reductive amination is the sixth most frequently used transformation in medicinal chemistry, representing 5.3% of the data set and accounting for approximately one-quarter of all heteroatom alkylations/arylations.¹ Reductive amination has been carried out on large scale for the industrial manufacture of a number of pharmaceutical agents.² Notably, it was the process chemistry group at Johnson & Johnson that developed sodium triacetoxyborohydride (STAB), the reducing agent of choice for reductive amination, when they found that previously reported reagents either were not selective for imine over carbonyl reduction or resulted in the formation of toxic and inseparable byproducts.³ Using STAB, a wide range of aldehydes/ketones and 1°/2° amines proved amenable to reductive amination, which provided a reliable and modular method to access complex alkylamine products (Scheme 1a).⁴

Despite the overwhelming utility of reductive amination for the synthesis of 2°/3° alkylamines, the methodology is not universal. Most notably, acetophenone and benzophenone derivatives typically undergo reaction very slowly, if at all, due to low iminium concentration and/or favorable enamine tautomerization.⁴ This limitation impedes access to benzyl and benzhydryl amines, which represent common motifs in pharmaceutical agents.⁵ While many powerful methods exist for the synthesis of benzyl amines, the synthesis of benzhydryl amines typically involves a multistep protocol and the use of toxic alkylating reagents or reactive organometallic species (Scheme 1b).⁶ The Petasis reaction represents a useful three-component approach to the synthesis of complex amines that avoids many of these disadvantages, though it too suffers from substantial limitations with respect to substrate scope, typically requiring aldehydes with proximal coordinating functionality.⁷ Le Gall and co-workers have published several reports of Barbier-type conditions that deliver benzhydryl amines.⁸ However, use of heteroaryl halides was not successful, and examples of intramolecular coupling reactions have not been reported (*vide infra*). Moreover, the reported scope of α -branched amines is limited to L-proline methyl ester.^{8c} In related work, the Saidi group has demonstrated LiClO₄-promoted reactions of iminium ions with alkyl- and alkynylzinc halides, α -halozinc esters, and nucleophilic arenes.⁹ As an alternative, we envisioned a direct Ni-catalyzed C–C bond-forming three-component coupling between benzaldehydes, amines, and organohalides. Such a strategy would avoid the challenges associated with iminium formation from aromatic ketones while maintaining

the positive attributes of reductive amination, namely the ability to deliver rapid and modular access to a broad range of amines from abundant and structurally diverse feedstocks.

We have previously disclosed two strategies for Ni-catalyzed coupling reactions with iminium and oxocarbenium ions that prompted us to investigate Ni catalysis for this three-component coupling. In one approach, the iminium or oxocarbenium ion serves as a two-electron oxidant for Ni; transmetalation of the resulting oxidative adduct with an organometallic reagent and reductive elimination deliver the α -substituted amine or ether product.¹⁰ Whereas this approach was generally limited to heteroaromatic electrophiles (quinolinium, pyridinium, benzopyrylium ions)¹¹ and required the use of organometallic reagents, we recently demonstrated an alternative approach based on a cross-electrophile coupling manifold for the reaction of benzaldehyde-derived acetals and aryl iodides.¹² In this approach, single-electron reduction of an oxocarbenium ion generated from the acetal and a Lewis acid delivers an α -oxy radical that can be intercepted by Ni. Oxidative addition of a Ni adduct with an aryl halide, followed by reductive elimination, furnishes the benzhydryl ether product, and finally, single-electron transfer from a stoichiometric reductant turns over the Ni catalyst. We elected to pursue this strategy for the reductive amination since cross-electrophile couplings are compatible with Lewis acids of the sort necessary to induce iminium formation from the condensation of an amine and aldehyde (Scheme 1c).^{13,14} Furthermore, a broad range of stable and commercially available organic electrophiles (aryl, vinyl, alkyl, and acyl halides) have been shown to be effective partners in cross-electrophile couplings.¹⁵

RESULTS AND DISCUSSION

Optimization Studies.

At the outset of our studies, we anticipated a number of challenges in applying a Ni-catalyzed cross-electrophile coupling strategy to reductive amination. These included achieving selectivity for iminium over oxonium coupling, preventing electrophile homocoupling pathways, and avoiding catalyst poisoning by the secondary amine substrate and tertiary amine product. To simplify reaction development, we began our studies by investigating the two-component coupling of preformed iminium triflate **1** and 4-fluoriodobenzene in the presence of Zn dust. In the absence of a transition metal catalyst, no product formation was observed (Table 1). With the addition of 10 mol % NiBr₂-glyme under “ligandless” conditions, benzhydryl amine **2** was formed in 20% yield. The addition of bi- and tridentate amine ligands substantially improved the reaction outcome, with the highest yields of **2** obtained when quinox, pybox, or 2,6-bis(*N*-pyrazolyl)pyridine (bpp) was employed (**L6–L8**). For a number of classes of amine ligands, substitution proximal to the metal binding sites led to decreased yields relative to those observed with the corresponding unsubstituted ligand (see Table S1).

Although pybox (**L7**) provided the highest yield in the two-component coupling with preformed iminium ion **1**, in our efforts to develop a three-component coupling, bpp (**L8**) proved to be superior (see Table S8). This ligand is easy to prepare on multigram scale and has previously been identified by our lab as effective at promoting Ni-catalyzed reductive couplings of aryl iodides with oxocarbenium ions and with styrenyl aziridines.^{12,16}

With these optimized conditions, we turned our attention to the three-component coupling by selecting the reaction of 4-fluorobenzaldehyde (**3**), morpholine, and 4-fluoriodobenzene as a model system. An evaluation of Lewis acid additives revealed that TMSCl provided only trace **4** (Table 2, entry 1), while the use of TBSOTf led to an enhanced 43% yield (entry 2). In a separate set of experiments, addition of tetra-*n*-butylammonium chloride (TBACl) to the coupling reaction of **1** led to a substantially diminished yield of **2**, suggesting that the difference in reactivity between TMSCl and TBSOTf is primarily due to poisoning of the Ni catalyst by chloride anion (see Table S3 for details). A similar control experiment with exogenous dimethyl-amine indicated that free secondary amines also have a deleterious effect on the reaction outcome. In contrast, the addition of *N*-trimethylsilyl dimethylamine had no negative effect on the yield (see Supporting Information). With this knowledge at hand, we reasoned that using *N*-trimethylsilyl morpholine in place of morpholine in the three-component reaction might therefore lead to more efficient formation of **4**. Notably, the use of *N*-trimethylsilyl amines in conjunction with silyl triflates has been previously reported for the generation of iminium ions.¹⁷ In the event, enhanced yields were observed under these conditions with both TMSCl and TBSOTf as the Lewis acid (entries 3–4). The optimized reaction conditions with TBSOTf provide high selectivity for the desired functionalization of the iminium ion over the intermediate oxosilenium ion; < 5% yield of a benzhydryl TBS ether side product is observed. In addition, cross coupling is strongly favored over homocoupling of both the iminium ion and the aryl iodide. Accordingly, the organohalide loading could be lowered from 3.0 to 1.5 equiv without strongly affecting the yield of the reaction.

While the ability to effect the three-component reaction of aldehydes, aryl iodides, and *N*-trimethylsilyl amines in high yield was gratifying, we recognized that the practical scope of the reaction would be decreased due to the limited commercial availability of *N*-trimethylsilyl amines.¹⁸ Furthermore, these species are challenging to isolate cleanly due to facile hydrolysis. Therefore, we sought convenient conditions for the synthesis and use of *N*-trimethylsilyl amines that did not require their isolation. On the basis of a procedure from Dilman and co-workers,^{17b} we found that exposing secondary amine **5** to proton sponge and TMSOTf, followed by filtration, resulted in a dioxane solution of *N*-trimethylsilyl amine **6** of sufficient purity for direct use in the three-component reaction (Scheme 2). In this study, proton sponge was uniquely effective in promoting the silylation; other organic or inorganic bases we examined did not lead to complete silylation or only did so for especially nucleophilic secondary amines.

Intermolecular Scope Elucidation.

With optimized conditions in hand, we sought to evaluate the scope of the C–C bond-forming reductive amination reaction. Drawing on commercially available *N*-trimethylsilyl amines, we first established the scope of the benzaldehyde and aryl iodide components (Table 3a). Aromatic aldehydes bearing electron-withdrawing (**8a**, **8b**), -neutral (**8d**), and -donating substituents (**8e**, **8f**) all perform extremely well under the reaction conditions. Gratifyingly, a broad tolerance was observed with respect to the electronic properties of the aryl iodide component as well (*cf.* **8c**, **8d**). We were pleased to find that a variety of heteroaromatic aldehydes were compatible with the reaction conditions. Thus, α -branched

tertiary amines containing furan (**8g**), benzothiophene (**8h**), indole (**8i**), and pyridine (**8j**) groups were all accessed in good to excellent yields. Even ferrocenecarboxaldehyde provided the corresponding reductive amination product (**8l**), albeit in a somewhat reduced yield. In general, moderately electron-rich aldehydes and aryl halides tend to provide higher yields than electron-deficient partners. In particular, electron-deficient heteroaromatic aldehydes, such as 3-pyridinecarboxaldehyde, afford only trace amounts of the desired C–C coupled product (see Table S13). Nevertheless, owing to the modularity of the method, the same substituent may be introduced as the halide instead: 3-iodopyridine afforded cross-coupled product **8k** in 62% yield.

Regarding the scope in amine for the Ni-catalyzed iminium functionalization disclosed herein, application of the TMSOTf/ proton sponge silylation conditions substantially widens the diversity of products accessible by this three-component transformation (Table 3b). Thus, efficient reductive coupling was realized utilizing acyclic aliphatic (**7**, **9b**), benzylic (**9c**), homobenzylic (**9a**), and allylic amines (**9d**). A noteworthy example is compound **9c**, which is generated in 77% isolated yield and features distinct handles for orthogonal functionalization at the amino group after selective PMB-deprotection¹⁹ and at the Cl or BPin groups by metal-catalyzed cross coupling. Further, numerous exo- and endocyclic secondary amines (**9f–9i**) are well tolerated under the reaction conditions, including highly sterically congested cis-2,6-dimethylpiperidine.

The potential of the method with respect to library synthesis for the pharmaceutical and agrochemical industries was explored further using more complex amine substrates. Thus, pyrimidine- and benzoisothiazole-derived amines are competent substrates for this transformation (**9j** and **9k**). We were pleased to find that excellent diastereoselectivities were achieved employing chiral secondary amine starting materials (**9l** and **9m**). By utilizing (–)-ephedrine as the amine component, simple replacement of both exchangeable protons by TMS groups during the *in situ* silylation step allows isolation of silylated nicotine aldehyde derivative **9m** in 81% yield. Further support for a synthetically valuable process is demonstrated by the high yielding, single-step synthesis of flunarizine (**9n**), the active agent of antimigraine drug Sibelium.

For comparison, established syntheses of flunarizine require four synthetic steps and use toxic alkylating agents.²⁰ Traditional reductive amination is ineffective for the synthesis of flunarizine and other benzhydryl amines in this study. For example, attempted syntheses of flunarizine using recently identified conditions for reductive amination of benzophenones²¹ or Ti(*Oi*-Pr)₄/NaBH₄ failed to produce the active ingredient. Additionally, homoveratrylamine-derived product **9a** is inaccessible by reductive amination using STAB but is generated in 93% yield under the Ni-catalyzed conditions (see Supporting Information). Our reductive iminium coupling protocol is also suitable for the late-stage derivatization of secondary amine pharmaceuticals, as the active ingredients of antihypertensive drug Lopressor (metoprolol) and antidepressant Paxil (paroxetine) perform well under the Ni-catalyzed coupling conditions (**9o**, **9p**). Finally, the reductive cross coupling can easily be scaled up and performed on the benchtop using solvent as purchased. For example, benzhydryl amine **9i** was furnished in 69% yield under these user-friendly conditions (Scheme 3).

Aside from aryl iodides, other aryl, vinyl, and alkyl halides serve as coupling partners. Only minor changes to the reaction conditions were required to effect cross coupling with aryl bromides (Table 3c). Benzhydryl amines **10a–10c** were formed in high yield employing quinox (**L6**) as a ligand and 2.0 equiv of the electrophile at slightly elevated temperature (65 °C). Since more aryl bromides are commercially available than aryl iodides, we expect that these results will enhance the versatility of the reaction. Couplings using vinyl triflates (**11**), vinyl bromides (**12**), and alkyl bromides (**13**) are also possible (Table 3d). However, it is important to note that control reactions on the alkyl coupling reveal background reactivity in the absence of a Ni catalyst (up to 11% yield **13**) and may therefore implicate a different overall mechanism.

Intramolecular Scope Elucidation.

Having established the scope of the three-component coupling, we questioned whether the process might be amenable to intramolecular variants as well. In particular, we sought to explore the reductive coupling of organohalides tethered to aromatic aldehydes or to secondary amines. We envisioned that this two-component cyclization would provide convenient access to valuable exo- and endocyclic tertiary amine products while maintaining high degrees of modularity.

Under the standard reaction conditions, intramolecular reductive amination of tethered bromoaldehydes is possible. Thus, exocyclic tertiary amines derived from fluorene (**15a**), xanthene (**15b**), and benzoxepane (**15c**) were obtained in high yields (Table 4a). The reaction of vinyl bromide substrate **14d** was somewhat less efficient but provided dimethylamino-chromane **15d** in a preparatively useful 50% yield. Interestingly, aryl bromides were found to be more efficient cyclization substrates than aryl iodides; aryl iodides underwent unproductive protodehalogenation under the reaction conditions. It is also notable that the intramolecular reactions are much more sensitive to the amine identity, presumably because the rigidity and steric hindrance conferred by the intramolecular substrate impose additional constraints on the chemistry taking place at the Ni center.²² For example, in case of substrate **14c**, use of TMS-pyrrolidine and TMS-NMeCy in place of TMS-NMe₂ delivered cyclized products in only 33% and 14% yield, respectively.²³

We next turned to the reactivity of tethered bromoamines with benzaldehydes en route to pharmaceutically relevant 1-aryl benzocyclic amines. We found that bidentate quinox provided far superior yields than tridentate bpp for this class of cyclizations, possibly due to relief of steric hindrance around the Ni center. All examined cyclization substrates furnished the targeted endocyclic benzhydrylamines irrespective of the length of the methylene spacer (Table 4b). However, the overall efficiency of these cyclizations is diminished compared to that for the exocyclic amine synthesis described above. For example, 1-(4-fluorophenyl)-substituted isoindoline **17a**, tetrahydroquinoline **17b**, and tetrahydrobenzazepine **17c** were obtained in 26–67% yield. Nevertheless, the modularity renders this two-component coupling an attractive alternative to traditional, more linear syntheses of exo- and endocyclic benzhydryl amines.

Mechanistic Investigations.

While the iminium functionalization is clearly Ni-catalyzed (see Table 1), we sought evidence to distinguish among various possible mechanisms.²⁴ We considered three pathways in which Ni directly mediates C–C bond formation from a Ni^{III} intermediate (Scheme 4). Related to our previously proposed mechanism for the reductive coupling of acetals, the iminium coupling could proceed by oxidative addition of Ni⁰ **I** to the organohalide electrophile. Concurrently, Zn-mediated single-electron reduction of the iminium ion provides α -amino radical **B** that intercepts Ni^{II} complex **II** to provide Ni^{III} adduct **III**. C–C reductive elimination then affords the alkylamine product and Ni^I halide **IV**, which is reduced to complete the catalytic cycle (Scheme 4a).^{12,25} Alternatively, if Zn-mediated reduction of the iminium ion is not facile, the reaction may instead occur by a radical chain process. In this process, Ni^I complex **IV** serves as a single-electron reductant for the iminium ion, and the resultant Ni^{II} halide is reduced by Zn to Ni⁰ species **I**.

A third alternative that we considered is a sequential oxidative addition pathway, which differs from the first two possible mechanisms in that it altogether avoids formation of a discrete free α -amino radical (Scheme 4b). Specifically, Ni could undergo two sequential two-electron oxidative additions to the aryl halide and iminium ion, enabled by an intermediate one-electron reduction of Ni^{II} complex **II** by Zn. Reductive elimination of Ni^{III} adduct **III** delivers the benhydryl amine product and Ni^I halide **IV**, which is reduced by Zn to turn over the catalytic cycle. The stoichiometric oxidative addition of Ni⁰ to the chloride analogue of Eschenmoser's salt was demonstrated by Pierpont and Barefield in the 1970s, and our lab has described catalytic coupling chemistry of quinolinium and pyridinium ions according to this elementary step.^{10,26}

A fourth distinct mechanism proceeds by Ni-catalyzed generation of an organozinc reagent, followed by noncatalyzed addition of that species to the iminium ion. Indeed, in the case of aldehyde **3**, a preformed arylzinc bromide is a competent nucleophile toward addition to the iminium ion formed *in situ*, providing **2** in similar yield to the standard reaction conditions (Table 5, entries 1–2). The work of Le Gall and co-workers provides precedent for this mechanism via cobalt catalysis, though in most cases the zinc reagent is formed prior to the introduction of the iminium precursors.⁸ In contrast, Gosmini and co-workers have reported that NiCl₂ does not promote arylzinc generation under similar conditions.²⁷

As a first mechanistic probe, we evaluated the use of tetrakis(dimethylamino)ethylene (TDAE) as an organic reductant. In a number of previously published examples of Ni-catalyzed cross-electrophile couplings, the intermediacy of organometallic reagents has been unambiguously ruled out by demonstrating high levels of product formation when TDAE was used in place of Zn or Mn.²⁸ However, because TDAE ($E^{\text{red}}_{1/2} = -0.78$ V vs SCE in MeCN)²⁹ is a soluble reductant, whereas Zn ($E^{\text{red}}_{1/2} = -1.0$ V vs SCE in MeCN) is not, the failure of TDAE to replicate the Zn/Mn conditions cannot necessarily be taken as evidence in favor of an organometallic intermediate. In our case, a reaction with preformed iminium ion **1** ($E^{\text{red}}_{1/2} = -0.97$ V vs SCE in MeCN) and TDAE afforded <1% yield of cross-coupled product **2** (Scheme 5a). Instead, the majority of the mass balance was accounted for by dimerized iminium ion **18**, formed upon exposure of the iminium ion to TDAE even in the

absence of Ni. Thus, TDAE's failure as a reductant did not allow us to rule out organozinc formation.

We next hypothesized that it might be possible to gain insight into the presence or absence of organozinc species by modulating the reactivity of the iminium ion. All of the Ni cross-coupling pathways in Scheme 4 involve a formal 1- or 2-electron reduction of the iminium ion at some point in the catalytic cycle. In such a scenario, an iminium ion with a low enough reduction potential would be an unsuitable substrate for the Ni-catalyzed reaction but might still be susceptible to nucleophilic 1,2-addition by a preformed arylzinc halide. Consistent with this hypothesis, a reaction involving electron-rich iminium ion **20** ($E_{1/2}^{\text{red}} = -1.26$ V vs SCE in MeCN for the corresponding dimethylamine-derived iminium ion) does not form reductive amination product **21** under the standard conditions, while a reaction of the same electrophile with a preformed arylzinc bromide provides **21** in 78% yield (Scheme 5b). This result, in combination with further experiments presented below, argues against the formation of organozinc species in the arylation reaction.

We next turned our attention to evaluating the three mechanistic scenarios involving Ni-mediated C–C bond formation (see Scheme 4). Initially, we sought evidence for the formation of α -amino radical **B** by introducing various intermolecular radical traps. The addition of 1 equiv TEMPO almost completely shut down productive reactivity, which suggested the presence of some odd-electron intermediate (Table 5, entry 3). However, no TEMPO adducts were observed by NMR following the reaction. In the absence of direct evidence for such a species, the deleterious effect of TEMPO cannot be taken as confirmation of organic radical formation under the reaction conditions, as TEMPO could serve to poison the Ni catalyst instead.

Attempts to trap an organic radical species intermolecularly with styrene or 1,1-diphenylethylene additives were unsuccessful, as only a small decrease in the yield of **2** was observed in both cases (entries 4–5). A similar experiment was carried out in the presence of ethyl acrylate in the anticipation that a pathway involving radical trapping and functionalization by Ni would lead to the formation of adduct **22**. Instead, we observed formation of the alternate regioisomer **23**; importantly, acrylate incorporation does not occur in the reaction with a preformed arylzinc reagent in the absence of a Ni^{II} catalyst (Scheme 6a). The formation of **23** is consistent with the Heck insertion of a Ni^{II}–Ar complex across the acrylate π -bond; a mechanism proceeding by a Ni^{0/I/III} cycle would be anticipated to generate **22** or a mixture of **22** and **23**. Interestingly, this result stands in contrast to the recent reductive cross-coupling work of Nevado and co-workers in which alkyl radical addition to acrylonitrile is observed over Heck insertion of preformed (dtbbpy)Ni^{II}ArCl.^{28d} The differing regiochemical outcome in the iminium coupling is most consistent with a sequential oxidative addition mechanism that avoids formation of a free α -amino radical.

Further evidence in favor of this mechanism was obtained when we evaluated substrates that might undergo intramolecular radical cyclization.³⁰ Specifically, when we exposed preformed homoallyl iminium ion **24** to the standard reaction conditions, we did not observe formation of radical cyclization product **25** or more than trace amounts of direct arylation product **26**.³¹ Rather, the major product was homoallyl benzene **27**, which could result from

an aza-Cope rearrangement of **24** to **28** and subsequent Ni-catalyzed methylene functionalization (Scheme 6b). Notably, computational analysis indicates that **24** is the thermodynamically favored iminium ion by 7.7 kcal/mol, and **29** is the more stable radical by 9.6 kcal/mol. Since **27** arises from the less stable iminium ion that is also harder to reduce,³² the result is inconsistent with a mechanism wherein Zn mediates reduction by single electron transfer. Instead, these data suggest that Ni reacts with the iminium ion directly and selectively, favoring reaction with **28** presumably for steric reasons. Product **27** could thereby arise via either a Curtin–Hammett scenario or with Ni involved in both the iminium rearrangement and reduction.

We also evaluated 2-allylbenzaldehyde **31** as a radical cyclization probe. Once again, **32**, the anticipated product of radical cyclization/functionalization, was not formed under the standard coupling conditions. Further, only 1% yield of direct addition product **33** was formed. Instead, the major product was tetrahydronaphthalene **34** (Scheme 6c). We propose that **34** is formed by cationic cyclization of the iminium ion with the pendant alkene, followed by a transannular hydride shift to afford a methylene iminium ion that can be functionalized in a Ni-catalyzed process. Rearranged products are not observed in greater than trace amounts in the reactions of 4-fluorophenylzinc bromide with **24** or **31** in the absence of Ni/bpp and Zn⁰, reinforcing that ArZnX are not intermediates in this reaction.

Our inability to trap an organic radical in these inter- and intramolecular experiments contradicts a radical chain mechanism. Indeed, the fact that (bpp)Ni^ICl (**19**, $E^{\text{red}}_{1/2} = -0.8$ V vs SCE in MeCN),¹² like Zn, is not a competent single electron reductant for inducing iminium dimerization of **1** also speaks against this mechanism (Scheme 5c).³³ Instead, a sequential oxidative addition mechanism best accounts for all of the results. The failure of TDAE as a reductant for the coupling reaction despite its ability to reduce the iminium substrates is in line with this proposal. Furthermore, a sequential oxidative addition mechanism is the only mechanism that can account for the success of the intramolecular coupling reactions. A zinc reduction mechanism or a radical chain mechanism, wherein radical formation is decoupled from Ni oxidative addition, would not be expected to favor an intra- over an intermolecular process.

CONCLUSION

In conclusion, we have developed a Ni-catalyzed, three-component reductive coupling for the synthesis of tertiary alkylamines from benzaldehydes, organic electrophiles, and *N*-trimethylsilyl amines, which are conveniently prepared and used without isolation. We have demonstrated C-C bond formation with several distinct classes of organic electrophiles including aryl iodides/bromides, vinyl bromides/triflates, and alkyl bromides. We anticipate that this reaction will prove useful in circumstances where the ketone precursor to a desired amine product is not commercially available or does not readily undergo reductive amination. Furthermore, the convergent nature of this approach should make it ideal for library synthesis. While the precise details of the reaction mechanism remain under active study, preliminary experiments advocate a sequential oxidative addition mechanism and strongly mitigate against *in situ* organozinc formation. We are optimistic that an increased

understanding of the role of Ni in this reaction can lead to the development of an enantioselective reductive amination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Financial support from NIGMS (R01 GM100985) and Bristol-Myers Squibb is gratefully acknowledged. This material is based upon work supported by the National Science Foundation Graduate Research Fellowship under Grant No. DGE-1148900 (to J.P.L.). C.H. is grateful to the Swiss National Science Foundation for generous financial support through an Early Postdoc Mobility Fellowship. Benjamin J. Shields is gratefully acknowledged for computational support of our mechanistic studies; Dr. Philip D. Jeffrey for X-ray analysis of compound ($\pm$)-9l; and Dr. James Kempson for helpful suggestions.

REFERENCES

- (1). Roughley SD; Jordan AMJ. *Med. Chem.* 2011, 54, 3451–3479.
- (2). (a) Baumann M; Baxendale IR; Ley SV; Nikbin N *Beilstein J. Org. Chem.* 2011, 7, 442–495. [PubMed: 21647262] (b) Baumann M; Baxendale I R *Beilstein J. Org. Chem.* 2013, 9, 2265–2319.
- (3). Abdel-Magid AF; Carson KG; Harris BD; Maryanoff CA; Shah R D. *J. Org. Chem.* 1996, 61, 3849–3862. [PubMed: 11667239]
- (4). Abdel-Magid AF; Mehrman SJ *Org. Process Res. Dev.* 2006, 10, 971–1031.
- (5). (a) Bhatnagar AS; Häusler A; Schieweck K; Lang M; Bowman RJ *Steroid Biochem. Mol. Biol.* 1990, 37, 1021–1027. (b) Lee Barnes C; McKenzie CA; Webster KD; Poinsett-Holmes K *Ann. Pharmacother.* 1993, 27, 464–470. [PubMed: 8477125] (c) Naito R; Yonetoku Y; Okamoto Y; Toyoshima A; Ikeda K; Takeuchi MJ *Med. Chem.* 2005, 48, 6597–6606. (d) Chang K-J; Rigdon GC; Howard JL; McNutt RW *J. Pharmacol. Exp. Ther.* 1993, 267, 852–857. [PubMed: 8246159]
- (6). (a) Bohme H; Plappert P *Chem. Ber.* 1975, 108, 2827–2833. (b) Murai T; Asai F *J. Am. Chem. Soc.* 2007, 129, 780–781. (c) He S; Xiao J; Dulcey AE; Lin B; Rolt A; Hu Z; Hu X; Wang AQ; Xu X; Southall N; Ferrer M; Zheng W; Liang TJ; Marugan JJ *J. Med. Chem.* 2016, 59, 841–853. [PubMed: 26599718] (d) Xie L-G; Dixon DJ *Chem. Sci.* 2017, 8, 7492–7497. [PubMed: 29163902]
- (7). (a) Petasis NA; Boral S *Tetrahedron Lett.* 2001, 42, 539–542. (b) Candeias NR; Montalbano F; Cal PMSD; Gois PM P. *Chem. Rev.* 2010, 110, 6169–6193.
- (8). (a) Le Gall E; Troupel M; Ned el ec J-Y *Tetrahedron* 2006, 62, 9953–9965. (b) Le Gall E; Haurena C; Sengmany S; Martens T; Troupel MJ *Org. Chem.* 2009, 74, 7970–7973. (c) Haurena C; Le Gall E; Sengmany S; Martens T *Tetrahedron* 2010, 66, 9902–9911.
- (9). (a) Saidi MR; Khalaji HR; Ipaktschi JJ *Chem. Soc., Perkin Trans. 1* 1997, 1983–1986. (b) Saidi MR; Azizi N; Naimi-Jamal MR *Tetrahedron Lett.* 2001, 42, 8111–8113.
- (10). (a) Graham TJA; Shields JD; Doyle AG *Chem. Sci.* 2011, 2, 980–984. (b) Sylvester KT; Wu K; Doyle AG *J. Am. Chem. Soc.* 2012, 134, 16967–16970. [PubMed: 23030789] (c) Graham TJA; Doyle AG *Org. Lett.* 2012, 14, 1616–1619. [PubMed: 22385385] (d) Chau ST; Lutz JP; Wu K; Doyle AG *Angew. Chem., Int. Ed.* 2013, 52, 9153–9156. (e) Shields JD; Ahneman DT; Graham TJA; Doyle AG *Org. Lett.* 2014, 16, 142–145. [PubMed: 24279380] (f) Lutz JP; Chau ST; Doyle AG *Chem. Sci.* 2016, 7, 4105–4109. [PubMed: 28058106]
- (11). For an example of cross coupling with benzylic oxocarbenium ions, see: Wu K; Doyle AG *Nat. Chem.* 2017, 9, 779–784. [PubMed: 28754948]
- (12). Arendt KM; Doyle AG *Angew. Chem., Int. Ed.* 2015, 54, 9876–9880.
- (13). For reviews of metal-catalyzed cross-electrophile coupling, see: (a) Ullrich J *Top. Curr. Chem.* 2012, 320, 121–190. [PubMed: 22025066] (b) Ullrich J *Top. Curr. Chem.* 2012, 320, 191–322. [PubMed: 22143610] (c) Ullrich J *Top. Curr. Chem.* 2012, 320, 323–452. [PubMed: 22143611]

- (d) Knappke CEI; Grupe S; Gärtner D; Corpet M; Gosmini C; von Wangelin AJ Chem. - Eur. J. 2014, 20, 6828–6842. [PubMed: 24825799] (e) Moragas T; Correa A; Martin R Chem. - Eur. J. 2014, 20, 8242–8258. [PubMed: 24905555] (f) Everson DA; Weix DJ Org. Chem. 2014, 79, 4793–4798. (g) Gu J; Wang X; Xue W; Gong H Org. Chem. Front. 2015, 2, 1411–1421. | (h) Weix DJ Acc. Chem. Res. 2015, 48, 1767–1775. [PubMed: 26011466] (i) Lucas EL; Jarvo ER Nat. Rev. Chem. 2017, 1, 0065.
- (14). For a Ni-catalyzed cross-electrophile coupling of α -amido sulfones that is believed to proceed via intermediate formation of imines, see: Caputo JA; Naodovic M; Weix DJ Synlett 2015, 26, 323–326.
- (15). Selected examples of alkyl halides in cross-electrophile coupling: (a) Everson DA; Shrestha R; Weix DJ Am. Chem. Soc. 2010, 132, 920–921. (b) Yu X; Yang T; Wang S; Xu H; Gong H Org. Lett. 2011, 13, 2138–2141. [PubMed: 21434609] (c) Wang X; Wang S; Xue W; Gong H J Am. Chem. Soc. 2015, 137, 11562–11565. (d) Poremba KE; Kadunce NT; Suzuki N; Cherney AH; Reisman SE J. Am. Chem. Soc. 2017, 139, 5684–5687. Vinyl halides: (e) Cherney AH; Reisman SE J. Am. Chem. Soc. 2014, 136, 14365–14368. [PubMed: 25245492] (f) Qiu C; Yao K; Zhang X; Gong H Org. Biomol. Chem. 2016, 14, 11332–11335. [PubMed: 27878154] (g) Johnson KA; Biswas S; Weix DJ Chem. - Eur. J. 2016, 22, 7399–7402. Acyl electrophiles: [PubMed: 27017436] (h) Yin H; Zhao C; You H; Lin K; Gong H Chem. Commun. 2012, 48, 7034–7036. (i) Wotal AC; Weix DJ Org. Lett. 2012, 14, 1476–1479. [PubMed: 22360350] (j) Cherney AH; Kadunce NT; Reisman SE J. Am. Chem. Soc. 2013, 135, 7442–7445. [PubMed: 23634932] (k) Zheng M; Xue W; Xue T; Gong H Org. Lett. 2016, 18, 6152–6155. [PubMed: 27934381]
- (16). Woods BP; Orlandi M; Huang C-Y; Sigman MS; Doyle AG J Am. Chem. Soc. 2017, 139, 5688–5691.
- (17). (a) Schroth W; Jahn U; Strohl D Chem. Ber. 1994, 127, 2013–2022. (b) Tsymbal AV; Kosobokov MD; Levin VV; Struchkova MI; Dilman AD J. Org. Chem. 2014, 79, 7831–7835. [PubMed: 25116859]
- (18). At the time of writing, the only N-trimethylsilyl-N,N-dialkyl-amines available from major chemical suppliers are those derived from N,N-dimethylamine, N,N-diethylamine, pyrrolidine, and morpholine.
- (19). (a) Bull SD; Davies SG; Fenton G; Mulvaney AW; Prasad RS; Smith AD Chem. Commun. 2000, 337–338. (b) Bull SD; Davies SG; Fenton G; Mulvaney AW; Prasad RS; Smith AD J. Chem. Soc. Perkin Trans. 1 2000, 3765–3774.
- (20). For a recently published four-step synthetic approach, see: Narsaiah AV; Kumar JK Int. J. Ind. Chem. 2011, 2, 154–157.
- (21). Chandrasekhar S; Reddy CR; Ahmed M Synlett 2000, 2000, 1655–1657.
- (22). In the cyclization reactions of tethered bromoaldehydes, bpp generally provided higher yields than quinox.
- (23). Reactions run in dioxane (0.05 M) in place of THF.
- (24). For mechanistic studies of cross-electrophile coupling reactions, see: (a) Everson DA; Jones BA; Weix DJ J. Am. Chem. Soc. 2012, 134, 6146–6159. [PubMed: 22463689] (b) Biswas S; Weix DJ J Am. Chem. Soc. 2013, 135, 16192–16197. (c) Wotal AC; Ribson RD; Weix DJ Organometallics 2014, 33, 5874–5881. [PubMed: 25364092] (d) Ren Q; Jiang F; Gong H J Organomet. Chem. 2014, 770, 130–135.
- (25). A variant of this mechanism that differs only by the ordering of the oxidative addition and radical addition steps ($\text{Ni}^0/\text{I}/\text{I}^{\text{I}}$) is also possible but less likely, as the experiment discussed in Scheme 6a suggests the intermediacy of a $\text{Ni}^{\text{II}}\text{-Ar}$ complex. For a recently developed Ni-catalyzed aminomethylation reaction proposed to proceed via capture of Ni^0 by photochemically generated α -amino radicals, see: Remeur C; Kelly CB; Patel NK; Molander GA ACS Catal 2017, 7, 6065–6069. [PubMed: 29354317]
- (26). Sepelak DJ; Pierpont CG; Barefield EK; Budz JT; Poffenberger CA J Am. Chem. Soc. 1976, 98, 6178–6185.
- (27). Fillon H; Gosmini C; Perichon J J Am. Chem. Soc. 2003, 125, 3867–3870.
- (28). For examples of TDAE used as a mechanistic probe in Ni-catalyzed cross-electrophile couplings, see refs 15a, d, e, 16, and: (a) Zhao Y; Weix DJ J Am. Chem. Soc. 2014, 136, 48–51. For the use of TDAE under optimized reaction conditions, see: [PubMed: 24341892] (b) Anka-Lufford LL;

Huihui KMM; Gower NJ; Ackerman LKG; Weix DJ Chem.- Eur. J. 2016, 22, 11564–11567. [PubMed: 27273457] (c) Suzuki N; Hofstra JL; Poremba KE; Reisman SE Org. Lett. 2017, 19, 2150–2153. [PubMed: 28375631] (d) Garcia-Dominguez A; Li Z; Nevado CJ Am. Chem. Soc. 2017, 139, 6835–6838.

- (29). Murphy JA J. Org. Chem. 2014, 79, 3731–3746. [PubMed: 24605904]
- (30). Cross coupling of cyclopropanecarbaldehyde under standard reaction conditions provided the cyclopropyl benzylamine S12 in 39% ¹⁹F NMR yield (see Supporting Information, p S-78). However, since an intermediate α -amino radical is more stable than the primary radical that would result from ring-opening, this experiment does not conclusively rule out the intermediacy of an organic radical.
- (31). Several literature reports indicate that α -amino radicals without electron-withdrawing N-substitution do not typically react with electron-neutral alkenes, even when constrained to an intramolecular system: (a) Sathe AA; Hartline DR; Radosevich AT Chem. Commun. 2013, 49, 5040–5042. (b) Padwa A; Nimmesgern H; Wong GSKJ Org. Chem. 1985, 50, 5620–5626. (c) Aurrecoechea JM; Fernandez A; Gorgojo JM; Saornil Tetrahedron 1999, 55, 7345–7362. (d) Katritzky AR; Feng D; Qi M; Aurrecoechea JM; Suero R; Aurrekoetxea NJ Org. Chem. 1999, 64, 3335–3338.
- (32). Wayner DDM; McPhee DJ; Griller DJ Am. Chem. Soc. 1988, 110, 132–137.
- (33). While (bpy)Ni^ICl (19) or Zn alone do not induce dimerization of 1, the combination of these two reagents provides 18 in 42% yield. A control experiment revealed that Ni(cod)₂/bpy also induces the same dimerization. Both of these results can be explained by a mechanism proceeding by oxidative addition of Ni(0) to 1, transmetalation of the resulting Ni(II) complex to afford Ni(OTf) and a Ni(II) dialkyl species, and C-C reductive elimination of 18. See Supporting Information, pp S-66–67.¹

a) Traditional reductive amination

b) Benzhydryl amines: synthetic approaches & pharmaceutical agents

c) This work

Scheme 1. Traditional versus Proposed Reductive Amination

Scheme 2. *N*-Trimethylsilyl Amine Preparation and Immediate Use in Three-Component Coupling^a

^aIsolated yield on 0.5 mmol scale with 1.5 equiv ArI (Ar = 4-chlorophenyl).

Scheme 3. Benchtop Reaction Scale-Up^a

^aSet up on the benchtop using Schlenk techniques and dioxane (anhydrous) purchased from Sigma-Aldrich: proton sponge (1.2 equiv), TMSOTf (1.25 equiv) for amine silylation; then NiBr₂ glyme (10 mol %), bpp (12 mol %), Zn⁰ (2.0 equiv), TBSOTf (1.2 equiv), dioxane (0.2 M), 50 °C, 24 h.

a) Mechanisms proceeding via α -amino radical formation

b) Sequential oxidative addition mechanism

Scheme 4. Possible Reaction Mechanisms

Scheme 5. Assessing the Roles of Ni and Zn^a

^aSee Supporting Information for complete details of reaction conditions. Yields are determined by ¹⁹F/¹H NMR versus 1-fluoronaphthalene or dimethyl terephthalate as a quantitative external standard. Ar = 4-fluorophenyl; Ar' = 2,3-dihydrobenzofuran-5-yl.

a) Ethyl acrylate additive

b) Homoallyl iminium ion

c) 2-Allylbenzaldehyde

Scheme 6. Additional Mechanistic Experiments^a

^aSee Supporting Information for complete details of reaction conditions. Yields are determined by ¹⁹F NMR versus 1-fluoronaphthalene as a quantitative external standard. Ar = 4-fluorophenyl.

Table 1.

Ligand Evaluation^a

conv. 1 ^{b,c} / yield^b / biaryl ^b (%)		
no Ni / ligand: 77 / 0 / 0		
no ligand: 70 / 20 / 1	L1: 55 / 46 / 4	L2: 75 / 49 / 4
L3: 69 / 53 / 4	L4: 75 / 63 / 3	L5: 73 / 67 / 20
L6: 92 / 87 / 29	L7: 95 / 94 / 6	L8: 94 / 88 / 3

^aReactions run on 0.2 mmol scale with 3.0 equiv ArI (Ar = 4-fluorophenyl).^bDetermined using ¹⁹F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard.^cDetermined from the yield of 4-fluorobenzaldehyde (3) following aqueous workup.

Table 2.Development of a Three-Component Coupling^a

entry	X	Lewis acid	Conv 3 (%) ^b	yield (%) ^b	biaryl (%) ^b	Dimer (%) ^{b,c}
1	H	TMSCl	87	1	0	20
2	H	TBSOTf	78	43	2	1
3	TMS	TMSCl	99	37	9	7
4	TMS	TBSOTf	99	90	1	0

^aReactions run on 0.25 mmol scale with 3.0 equiv ArI (Ar = 4-fluorophenyl).^bDetermined using ¹⁹F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard.^cYield of 1,2-bis(5-fluorophenyl)-1,2-dimorpholinoethane (dimerized iminium ion).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 3.

Substrate Scope for Three-Component Coupling^a

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

^b Isolated yields on 0.5 mmol scale.

^q Performed using 2.0 equiv aryl iodide.

^c Relative configuration determined by X-ray crystallography.

^d Starting material was the free amino alcohol with 2.4 equiv proton sponge and 2.5 equiv TMSOTf used in the silylation step.

^e Performed at 65 °C using 2.0 equiv of aryl bromide and quinox (12 mol %) in place of bpp.

^f Performed in THF (0.2 M).

^g Performed in toluene (0.2 M) using 2.0 equiv alkyl bromide and 3.0 equiv Zn⁰ under ligandless conditions.

Table 4.

Intramolecular Reductive Amination^aa) Exocyclic amine synthesis via tethered bromoaldehydes^b b) Endocyclic amine synthesis via tethered bromoamines^c ^a Isolated yields on 0.5 mmol scale.^b Reactions run in THF (0.05 M). Reactions run in dioxane (0.1 M) with quinox (12 mol %) in place of bpp.

Table 5.

Additives as Mechanistic Probes^a

entry	additive (equiv)	conversion 3 (%) ^b	yield (%) ^b
1	none	94	95
2	ArZnBr (2 equiv) ^c	100	85
3	TEMPO (1 equiv)	52	1
4	styrene (3 equiv)	87	80
5	1,1-diphenylethylene (5 equiv)	96	89

^aReactions run on 0.5 mmol scale with 1.5 equiv ArI (Ar = 4-fluorophenyl).^bDetermined using ¹⁹F NMR analysis versus 1-fluoronaphthalene as a quantitative external standard.^cNo ArI was added.