Recent Methodologies that Exploit Oxidative Addition of C-N Bonds to Transition Metals

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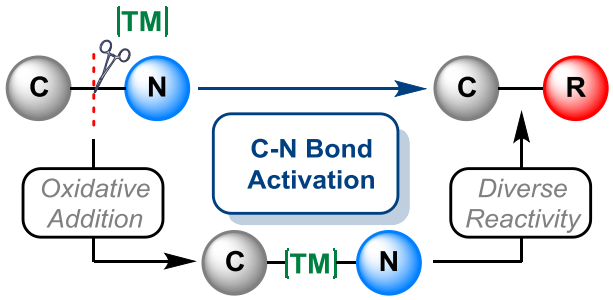


KEYWORDS: C-N bond activation, transition metal, methodology, catalysis, nitrogen-containing compounds

ABSTRACT

Transition metal bond activation is one of the most widespread methods for the synthesis of complex molecules. Within this context, C-N bond activation has emerged recently as a powerful

strategy for the preparation or utilization of nitrogen-containing compounds, due to the prevalence of C-N bonds in organic compounds. A key challenge in this area is that most C-N bonds are relatively inert, and this makes their activation a difficult task. Since the turn of the millennium the number of published articles regarding C-N bond activation has grown exponentially, providing important improvements in methodologies for such transformations. Indeed, several distinct strategies have been developed to achieve C-N bond activation. The most common have exploited either strain release or quaternization of the nitrogen-center, while other state-of-the-art strategies, such as oxidative addition of neutral C-N bonds or the use of directing groups have also appeared. Despite considerable progress, deeper insight into the mechanisms of activation and improvements in atom economy are still required for the field to advance. In this Perspective we give an overview of key advances in catalytic methodologies where C-N bond activation is achieved by oxidative addition to transition metals.

1. INTRODUCTION

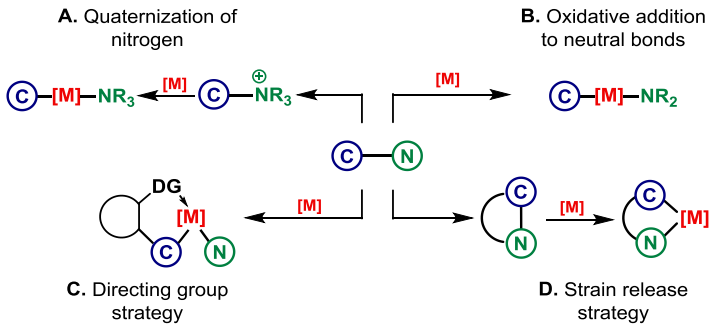
The use of transition metals (TMs) for bond activation is one of the most important strategies for the preparation of complex molecules. Mainly due to its statistical abundance, C-H activation was the first area to gain traction and contemporary C-H activation-based methodologies are abundant and widely used.[1-2] Great strides have also been made in the areas of C-C[3-5] and C-O[6-7] activation. Surprisingly, progress in C-N bond activation has lagged until very recently; this can in part be attributed to the usually high C-N bond dissociation energy[8] and the general stability of unactivated nitrogen-containing compounds. There is a vast number of chemical structures (e.g., natural products, synthetic drugs) that bear a C-N bond. Unsurprisingly, therefore, the formation

and transformation of C-N bonds is of fundamental importance to organic synthesis,[9] and enzymatic processes that achieve this, such as protein synthesis, metabolism (e.g. urea synthesis) and nucleotide biosynthesis, are essential to life. Thus, new methods for the activation of C-N bonds would open the door for novel methodologies that might allow the preparation of a great number of complex scaffolds and building blocks.

As a result of its increasing popularity in recent years, several notable reviews on C-N bond activation have been published.[10] Since 2010, the activation of C-N single bonds has received substantial attention from several groups, and the number of published articles regarding C-N cleavage has grown exponentially. Understanding the different strategies for C-N bond activation will assist in the development of new disconnection strategies for the preparation of synthetically challenging scaffolds or in the optimization of routes to existing ones.

The aim of this Perspective is to summarize recent progress made in catalytic C-N bond activation by TM oxidative addition (termed "C-N bond activation"). The methods discussed are categorized according to the strategy employed: A) C-N bond activation *via* quaternization of the nitrogen; B) oxidative addition of neutral C-N bonds; C) C-N bond activation using a directing group (DG); D) C-N bond activation *via* strain release (Scheme 1). There are many reports that detail stoichiometric metal-promoted C-N bond activation,[11-25] but these will not be discussed in this Perspective, which will instead focus on TM-catalyzed methodologies. Although outside the primary focus of this Perspective, there are a number of powerful strategies where C-N bonds are cleaved in the presence of a transition metal, but where an oxidative addition step is not involved; strategies of this type have been covered in a recent, comprehensive review.[10a] Recent advances in such TM-catalyzed C-N bond cleavage strategies include the use of Katritzky salts for activation of primary amines,[26] copper-catalyzed substitution of ammonium salts,[27] and

synthesis of amides by dealkylative N-acylation of tertiary amines with carboxylic acids[28] or by dealkylative carbonylation of amines.[29]



Scheme 1. Strategies for oxidative addition triggered TM-catalyzed C-N bond activation.

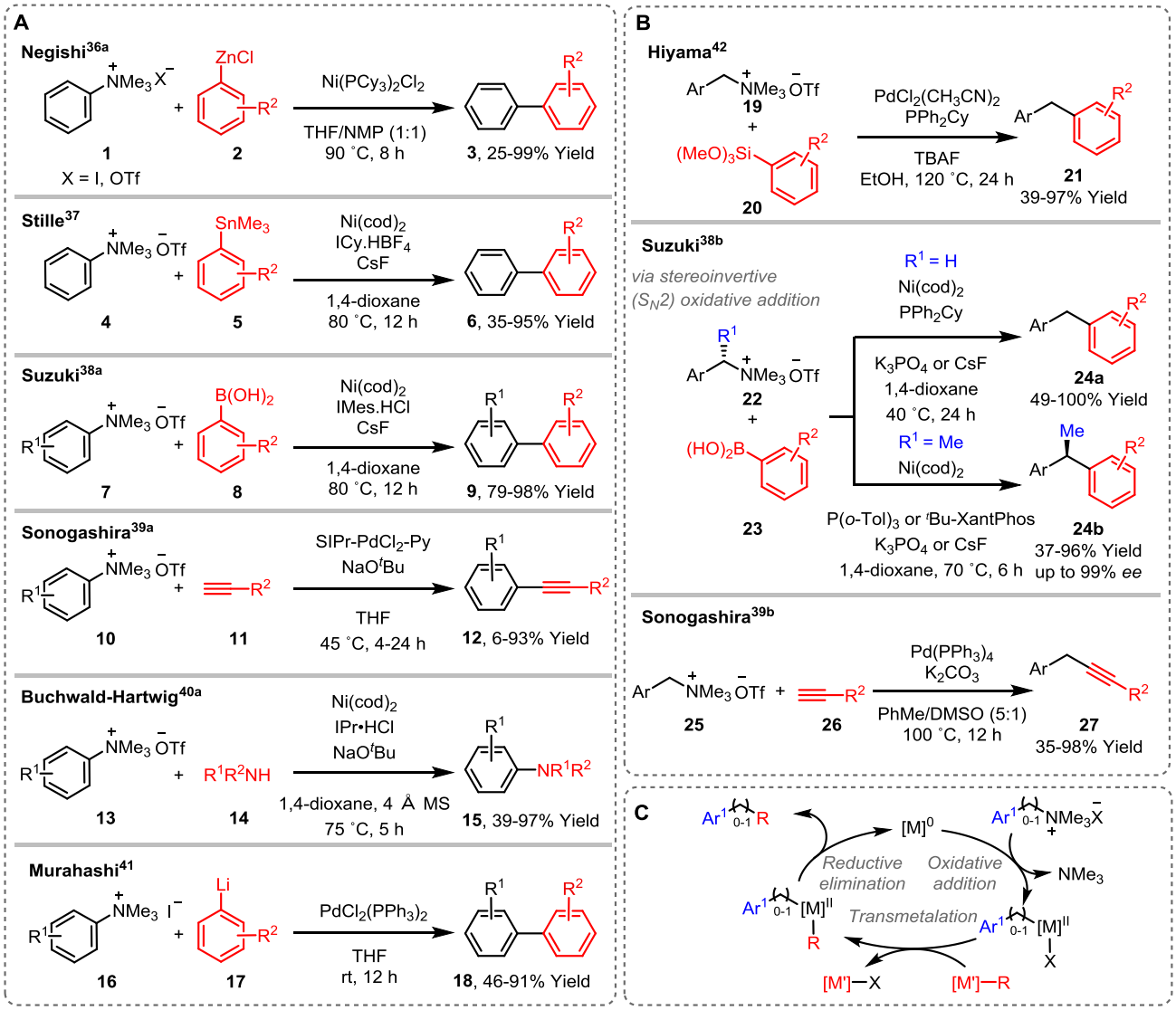
2. C-N BOND ACTIVATION VIA QUATERNIZATION OF THE NITROGEN

One of the reasons why C-N bond activation is challenging is because of the typically high bond dissociation energy of this moiety. To overcome this, an increasingly common strategy has been to quaternize the nitrogen center, thus weakening the C-N bond. Aryl diazonium salts are classical substrates in organic synthesis that have been studied extensively since the late 19th century; initially confined to electrophilic substitution reactions,[30] and more recently in TM-catalyzed processes by C-N bond activation. Reactions employing these substrates are not covered in this Perspective and the reader is instead directed to a recent review that covers these classes of compound in TM-catalyzed reactions.[31] Contemporary methods now allow simple quaternary aryl- and alkyl-ammonium salts to be used for a number of important transformations, including cross-coupling reactions, nucleophilic substitution, carboxylation (with CO_2) and carbonylation (with CO).[32]

Cross-coupling reactions that employ a discrete quaternization event have been studied extensively since the late 1980s. Quaternary ammonium salts are readily prepared from the corresponding amines, which are often commercially available at reasonable cost. Wenkert reported the first nickel-catalyzed Kumada coupling of aryltrimethylammonium iodides with aryl and alkyl Grignard reagents.[33] Later, this type of coupling was accomplished with aryltrimethylammonium triflates using either a palladium-[34] or an iron-based catalyst.[35] In a similar manner, quaternary aryl- or benzyl-ammonium salts have been used in Negishi,[36] Stille,[37] Suzuki-Miyaura,[38] Sonogashira,[39] Buchwald-Hartwig,[40] Murahashi,[41] and Hiyama[42] cross-coupling reactions, or with organoaluminium reagents[43] (Scheme 2). The general mechanism of these reactions typically involves: (i) oxidative addition of the C-N bond of the quaternary ammonium salt **1**, **4**, **7**, **10**, **13**, **16**, **19**, **22** or **25** to the TM, resulting in cleavage of the C-N bond; (ii) transmetallation with the organometallic compound **2**, **5**, **8**, **17**, **20**, **23,** alkyne **11**, **26**, or amine **14**; and (iii) reductive elimination to afford products **3**, **6**, **9**, **12**, **15**, **18**, **21**, **24** or **27**. Computational studies have shown that oxidative addition of aryl quaternary ammonium salts to TMs proceeds with a low activation energy barrier,[37] such that transmetalation is a more demanding step. This contrasts neutral aryl C-N bonds which typically do not undergo facile oxidative addition.[44]

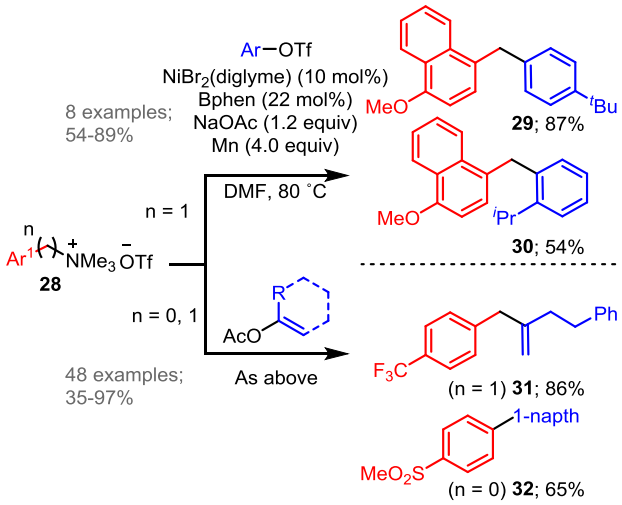
A particularly noteworthy feature for Ni-catalyzed cross coupling reactions with boronic acids is the net inversion of stereochemistry with respect to the starting benzylic ammonium salt by stereoinvertive (S_N2) oxidative addition.[32b,38b,c] In general, for the cross coupling of aryl- or benzyl-ammonium salts, a combination of a strong base and $Ni(cod)_2$, modified by either an electron rich phosphine ligand (e.g. P(*o*-Tol)$_3$) or a strongly σ-donating NHC ligand (e.g. IPr•HCl), is most effective. Cross-couplings of organolithium reagents with aryl ammonium salts

avoid unwanted lithium-halogen-exchange side reactions observed under conventional Murahashi conditions, where aryl halides are used as the electrophile.[41,45] The counterion (X = I, OTf, BF_4 etc.) can have a drastic effect on reactivity[35a,41] and, although a clear trend is not apparent between different systems, ammonium triflates are most commonly employed.



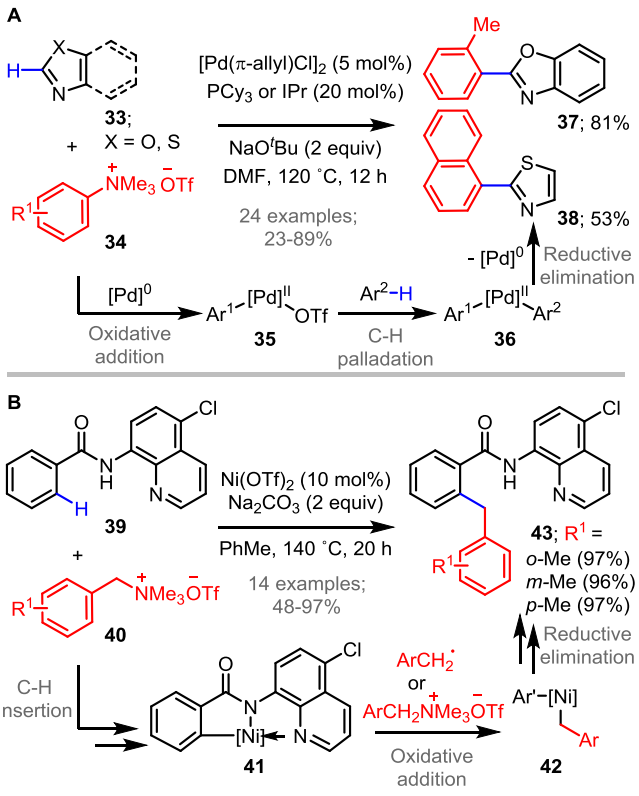
Scheme 2. Cross-coupling reactions of (A) aryl- and (B) benzyl- quaternary ammonium salts and (C) general catalytic cycle.

In general, cross-coupling reactions involve an electrophilic species (e.g., quaternary ammonium salts, halide derivatives or triflate salts) and a nucleophilic species (e.g. Mg, Zn, Sn or B derivatives), which is typically a pre-formed organometallic reagent. Such processes are redox neutral, although a discrete reduction event is usually used to prepare the organometallic reagent. To avoid this additional step, cross-coupling reactions have been developed where two electrophiles are used in the presence of a reductant. In a recent study, nickel-catalyzed reductive couplings between C-N and C-O electrophiles were described.[46] Here, using Mn as a stoichiometric reductant, benzyl- and aryltrimethylammonium triflates **28** were coupled with vinyl acetates or aryl triflates to construct C-C bonds (Scheme 3). The protocol is compatible with a wide range of functional groups, including boronic esters (albeit in a reduced yield). Radical trapping and radical clock experiments were used to support a mechanism involving the intermediacy of carbon-centered radicals which undergo capture by a Ni(I or II)-species, although the precise mechanism has yet to be elucidated.



Scheme 3. Nickel-catalyzed reductive coupling between C-N and C-O electrophiles.

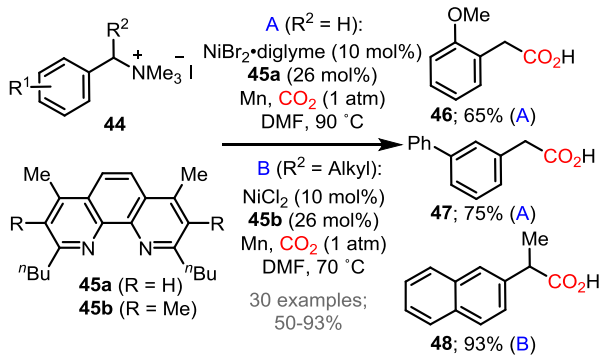
The ability to engage C-H bonds by C-H activation is a powerful strategy that has found widespread use in synthetic chemistry, particularly in late-stage functionalization of complex molecules.[47] Methods that combine C-H and C-N functionalization have emerged recently, employing benzyl- and aryltrimethylammonium salts as alkylation or arylation reagents, respectively. Wang and co-workers reported Pd-catalyzed C-H arylations (Scheme 4A)[48] and C-H benzylations[49] of oxazoles and thiazoles. Related Ni-catalyzed, directing group-assisted *ortho*-C-H functionalizations have also been reported for the benzylation of aromatic amides (Scheme 4B).[50] Mechanistically these reactions differ; the reported Pd-catalyzed benzylations and arylations likely proceed via oxidative addition of ammonium salt **34** to Pd(0) to give **35**, C-H palladation (to **36**) and reductive elimination to give arylated products **37** or **38**. The reported Ni-catalyzed examples are mechanistically ambiguous, with conflicting reports proposing either Ni(II)/Ni(IV) or Ni(I)/Ni(III) catalytic cycles; however, in both scenarios the evidence suggests oxidative addition of ammonium salt **40** occurs after insertion of nickel into the aryl C-H bond of **39** to give **41**. From here, oxidative addition to **42** is followed by reductive elimination and protodemetalation to give benzylated products **43**.



Scheme 4. (A) Palladium- and (B) nickel-catalyzed C-H and C-N functionalization reactions of quaternary ammonium salts.

For the installation of a carbonyl, carboxylation reactions (with CO_2) and carbonylation reactions (with CO) offer atom-economical alternatives to traditional methods[29a] and incorporating these C1 units as feedstocks offers promise for alternative retrosynthetic disconnections in synthetic chemistry.[51] In 2016, Martin and co-workers reported a Ni-catalyzed reductive carboxylation of benzylic C-N bonds with CO_2 for the synthesis of carboxylic acids (Scheme 5).[52] The success of these reactions was attributed to a novel set of ligands (e.g. **45a** and **45b**), which prevented competing homodimerization or β-hydride elimination pathways. For primary benzylammonium salts **44** where R^2 = H, a combination of $NiBr_2$•diglyme and ligand **45a** was optimal; whereas for secondary benzylammonium salts **44** where R^2 = alkyl, a combination of $NiCl_2$ and ligand **45b** afforded improved yields. The mechanism of this transformation is unclear, however single-

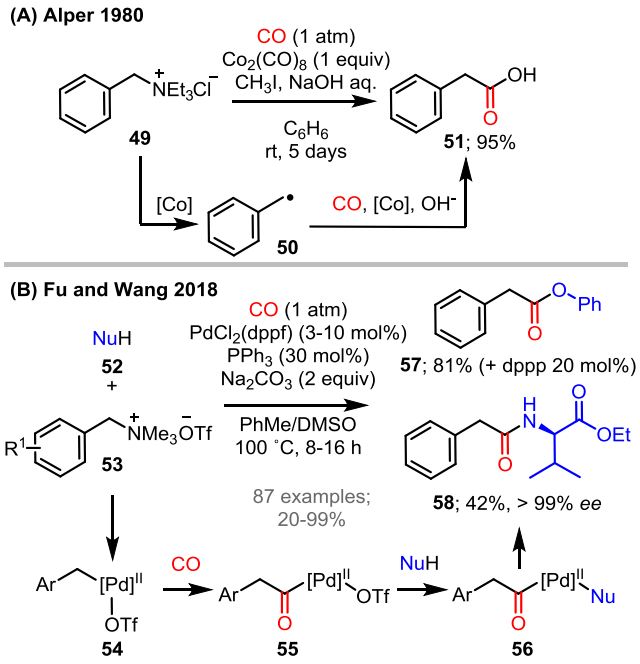
electron-transfer processes and comproportionation events via benzyl Ni(I) intermediates were suggested.[52]



Scheme 5. Nickel-catalyzed reductive carboxylation of benzylic C-N bonds.

Derivatizing C-N bonds by carbonylation with CO via C-N bond activation is a highly attractive transformation for the formation of new C-C bonds. Such transformations offer the opportunity for carbonylative coupling processes with different nucleophiles, facilitating the rapid generation of structural complexity. In a cautionary note concerning the use of phase transfer catalysts (e.g. quaternary ammonium salts) in TM-catalyzed reactions, Alper and co-workers showed that benzylammonium salts are converted into the corresponding carboxylic acid using stoichiometric amounts of $Co_2(CO)_8$, under an atmosphere of CO, in the presence of base (Scheme 6A), and indicated that a free radial mechanism may be operating (e.g. via benzyl radical **50**).[53] Soon after this, Caubere and co-workers exploited this observation and developed a catalytic variant of this reaction using visible light photostimulation for the generation of the proposed benzyl radical intermediate.[54] More recently, a Pd-catalyzed carbonylation of benzylic ammonium salts, via C-N bond activation, for the synthesis of amides and esters has been reported (Scheme 6B).[55] The method tolerates a large variety of nucleophiles, including aryl- and alkyl-amines, α-amino esters and alcohols. Mechanistically, benzyl quaternary ammonium salt **53** likely undergoes

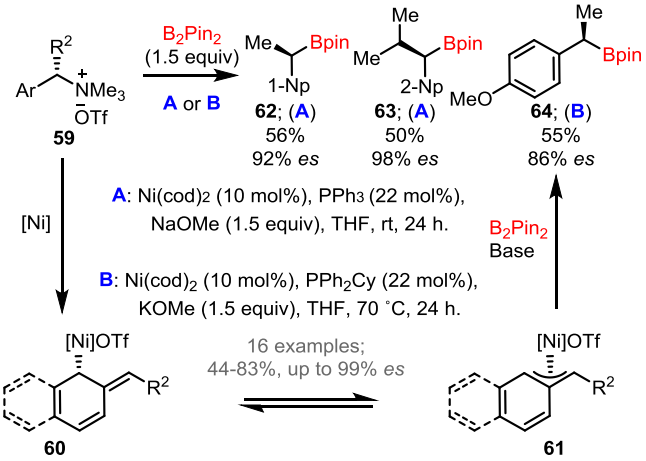
oxidative addition to Pd(0) to generate Pd(II) intermediate **54**. From here, CO insertion (to **55**), nucleophilic attack (to **56**) and reductive elimination generates the ester (e.g. **57**) or amide (e.g. **58**) product.



Scheme 6. Carbonylation reactions of benzyl ammonium salts with (A) stochiometric $Co_2(CO)_8$ and (B) $PdCl_2(dppf)$.

Further to the formation of new C-C bonds from quaternary ammonium salts via C-N bond activation, methods for the construction of new C-P,[56] C-Si,[57] C-B,[58] and bonds have also been demonstrated, providing access to important synthetic intermediates. For these transformations nickel is generally used as the TM in the presence of base (alkoxide or Cs_2CO_3), with either 1,1'-bis(diphenylphosphino)ferrocene (dppf) or N-heteterocyclic carbene (NHC) as a ligand. In a particularly significant example of Ni-catalyzed carbon-heteroatom bond formation from ammonium salts, Watson and co-workers reported a stereospecific Miyaura borylation reaction of α-alkyl substituted benzylic ammonium salts **59** (Scheme 7).[58c] Taking advantage of their

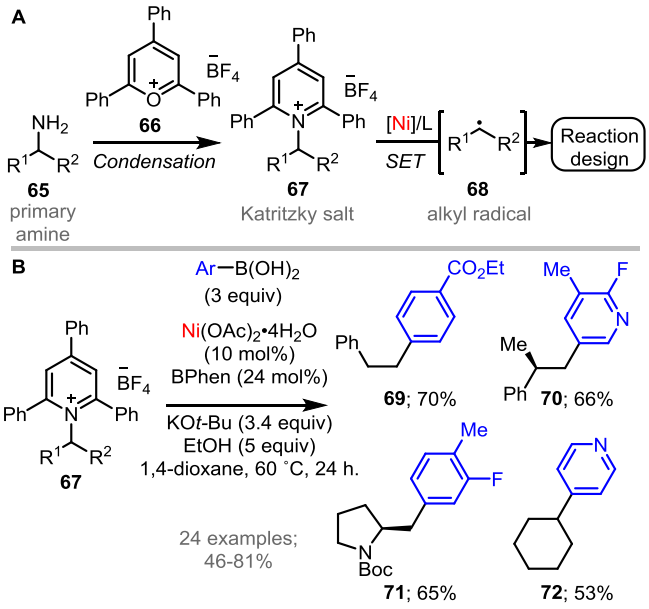
previous observations of stereospecificity in Suzuki-Miyaura-type cross coupling reactions under Ni-catalysis (see e.g. Scheme 2B),[38b] a range of benzylic boronates (e.g. **62**-**64**) were synthesized under mild conditions with inversion of stereochemistry with respect to the starting benzylic ammonium salt. The reaction worked best for aryl substituents with extended π systems (e.g. naphthyl), however, by switching the ancillary ligand from PPh_3 to PPh_2Cy, the scope of the method was extended to include some non-naphthyl substrates. A rationale for this effect was based on a hypothesis that oxidative addition of these substrates (to form **60**) would be slower, and that a more electron-rich ligand may benefit this step (as well as an increased reaction temperature and change of base).



Scheme 7. Ni-catalyzed stereospecific Miyaura borylation of benzylic ammonium salts.

Since the discovery in 2006 that pyridinium salts (e.g. Katritzky salts)[59] can be employed as electrophilic coupling partners in cross-coupling reactions,[60] this strategy for C-N bond cleavage has received an increasing amount of attention.[26b,c] Mechanistically, these processes are distinct from reactions of tetraalkyl ammonium salts discussed previously (by C-N bond oxidative addition). Pyridinium salt precursors generate an alkyl radical, which can be facilitated by three

main strategies: i) nickel catalysis, ii) photoredox catalysis, or iii) photoinduced SET to an electron-donor-acceptor complex.[26c] Significantly, Katritzky salts **67** can be prepared in a single step from the corresponding primary alkyl amine **65** by condensation with commercially available 2,4,6-triphenylpyrylium tetrafluoroborate (**66**) (Scheme 8A). Watson and co-workers first reported nickel-catalyzed Suzuki-Miyaura cross-coupling reactions of alkyl pyridinium salts (Scheme 8B),[26a] and since then a number of related (deaminative) reactions of Katritzky salts have been reported, including borylation,[61] alkynylation/alkenylation,[62] arylation,[63] alkyl-Heck type reactions,[64] allylation,[65] alkylation,[66] carbonylation,[64b,67] acylation[68] and C-heteroatom bond-forming reactions.[69]



Scheme 8. (A) Strategy for C-N bond cleavage of primary amines *via* Katritzky salts and (B) Ni-catalyzed Suzuki-Miyaura cross coupling reactions of alkylpyridinium Katritzky salts.

3. C-N BOND ACTIVATION USING DIRECTING GROUPS

Aryl C-N bonds can be formed using a range of TMs and key methods include the Ullman coupling,[70] Buchwald Hartwig amination,[71] and aryl C-H amination.[72] However, methods for the

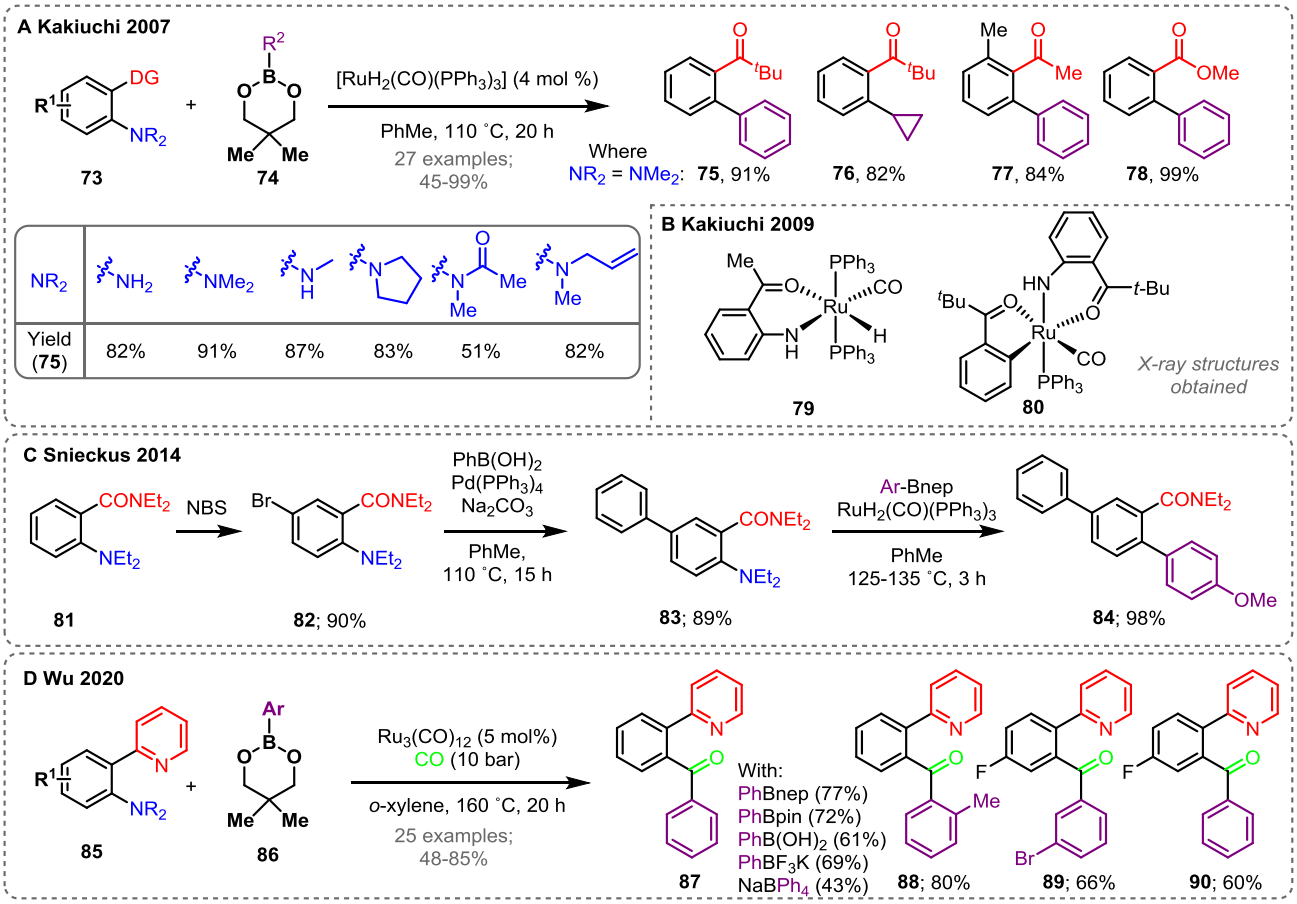
reverse disconnection (i.e. the activation of aryl C-N bonds) are much more limited, particularly for neutral aryl C-N bonds. This is largely due to two reasons: (1) the thermodynamic stability of aryl amines and (2) the strong coordination ability of their N-center.[73] One inherent challenge of TM-catalyzed (C-H, C-C, C-N) bond activation in general is achieving selectivity (i.e. controlling which bond will be activated). The use of directing groups (DGs) provides a well-established solution; in this scenario, the DG is designed to ligate the catalyst, holding it in close proximity to the target bond, thus driving kinetic and/or thermodynamic selectivity.

The first example of oxidative addition of a neutral C(sp^2)-N bond to a TM came in 1996, where Wolczanski showed that anilines undergo oxidative addition to stoichiometric Ta(OSi*t*-Bu)$_3$, without the use of a directing group.[14] However in these processes, controlling C-N vs. N-H activation was problematic, and could only be partially resolved by controlling electronic factors through variation of the aniline substituents. In 2007, Kakiuchi reported a vast improvement in controlled C-N activation of anilines and developed a ruthenium(II)-catalyzed C-N activation/C-C cross-coupling sequence by employing a directing group strategy.[74] In this study, *ortho*-ketones or esters **73** facilitated directed oxidative addition of the target C-N bond using [$RuH_2(CO)(PPh_3)_3$]. Interception of the resulting aryl-Ru species **79** or **80** with various organoboronates **74** afforded arylated or alkylated products (e.g. **75-78**) in good to excellent yield (Scheme 9A). Notably, primary anilines, *N*-substituted and *N*,*N*-disubstituted (cyclic and aliphatic) variants could all be used. X-ray structures of aryl ruthenium intermediates **79** and **80** were obtained (Scheme 9B),[75] showing the initial coordination of the *ortho*-ketone to the ruthenium catalyst and the cleavage of the C-N bond, respectively. The subsequent transmetallation is presumably driven by the coordination of the boron atom to the amino group of **80**.[74] This methodology was later extended to the use of amides,[76] imines (with subsequent

hydrolysis to form aromatic aldehyde and ketone derivatives),[77] and pyridines[78] as *ortho*-directing groups.

Orthogonality with conventional Suzuki-Miyaura cross-coupling reactions (e.g. with aryl halides) has been flagged as an advantage of ruthenium-catalyzed cross-couplings of this type; this allows the synthesis of triaryls via a bromination, Suzuki−Miyaura cross-coupling, and Ru-catalyzed C−N activation/coupling sequence (Scheme 9C).[76] Regioselective bromination of anthranilamide derivative **81** reliably gave arylbromide **82**, which was selectively coupled with phenyl boronic acid under Pd-catalysis to give biaryl **83** in good yield. A second cross-coupling reaction (via C-N bond activation) with (*p*-OMe)PhBnep, under Ru-catalysis, gave triaryl **84** in excellent yield, thus illustrating the orthogonality between C-Br and C-N bonds as electrophilic motifs in cross-coupling reactions.

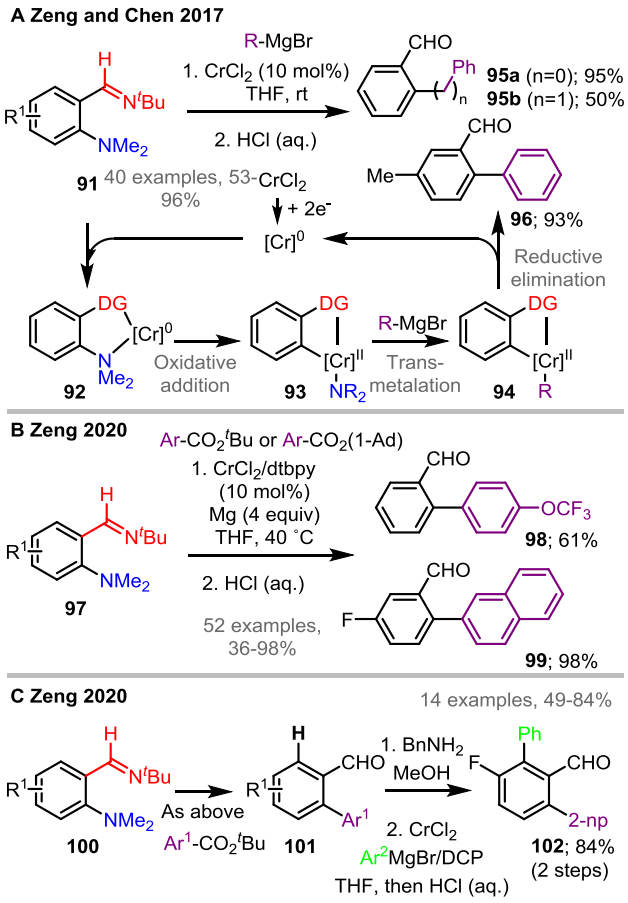
In a recent study, directed C-N bond activation has been demonstrated for *carbonylative* coupling of anilines with organoboranes, using $Ru_3(CO)_{12}$ as the catalyst (Scheme 9D).[79] In a systematic evaluation of directing groups and of boronic acid derivatives, the 2-pyridyl directing group and Bnep was found to be optimal for this system and a variety of benzophenone derivatives (e.g. **87**-**90**) were synthesized in good yields.



Scheme 9. Ruthenium-catalyzed cross coupling reactions of aniline derivatives using a directing group strategy.

Further to the use of ruthenium, DG-assisted activation of the aryl C-N bond of anilines has since been demonstrated using chromium. In 2017, Zeng, Chen and co-workers, reported that $CrCl_2$ could be employed for the imino-directed Kumada cross-coupling of various dialkylanilines **91** with Grignard reagents under mild conditions (Scheme 10A).[80] By using aryl Grignard reagents, a wide-range of *ortho*-formyl biaryls (e.g. **95**-**96**) could be obtained. Alkyl Grignard reagents also participate, albeit with generally lower yields. A series of experimental and theoretical studies suggested that a low-valent, high-spin chromium species, formed *in-situ* by two-electron reduction with excess Grignard reagent, promotes C-N cleavage, which has a relatively low activation energy barrier (13.6 kcal/mol for **95a**). This generates Cr(II) species **93**, which

undergoes transmetalation with the Grignard reagent to give **94**. From here, reductive elimination followed by imine hydrolysis generates the cross-coupled product e.g. **95-96**. In a very recent report, this method was extended to include the cross-coupling of two electrophilic partners using magnesium as a stoichiometric reductant (Scheme 10B).[81] The authors also demonstrated a series of sequential reductive and oxidative couplings of $C(sp^2)$–$N/C(sp^2)$–H bonds for the synthesis of 2,6-disubstituted benzaldehydes in an orthogonal fashion (Scheme 10C). Starting from anilines **100**, application of the standard reductive coupling conditions facilitated the synthesis of *ortho*-arylated products **101**, which were condensed with benzylamine and treated with Grignard reagents under Cr-catalysis, affording a range of 2,6-disubstituted benzaldehyde products (e.g. **102**).



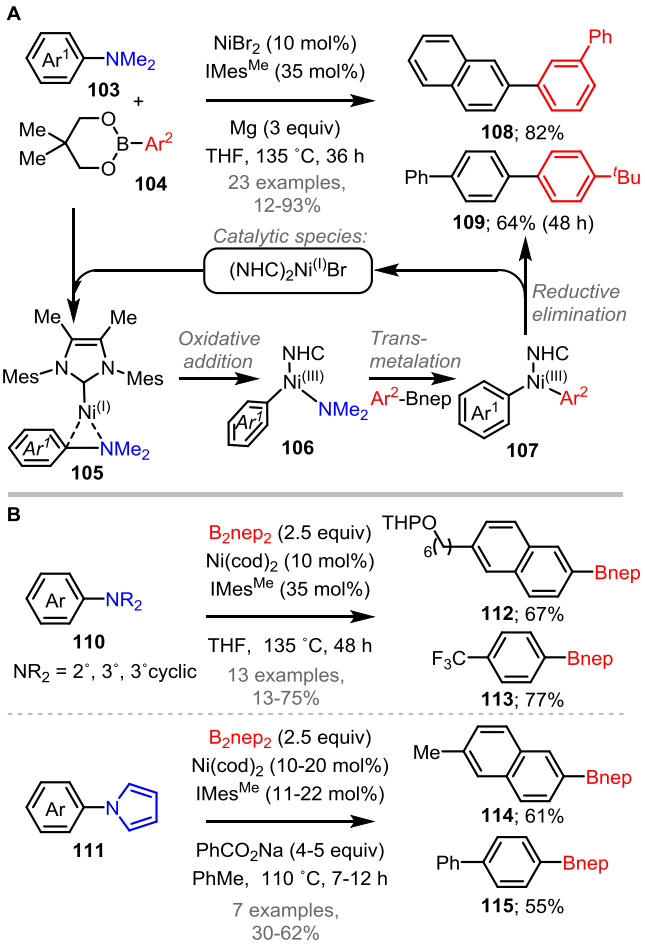
Scheme 10. (A) Chromium-catalyzed Kumada cross-coupling and (B) reductive cross-coupling reactions of aniline derivatives with aryl and alkyl Grignard reagents by directing group-assisted C-N bond activation; and (C) sequential reductive and oxidative couplings of $C(sp^2)$–N/$C(sp^2)$–H bonds.

4. NON-DIRECTED OXIDATIVE ADDITION TO NEUTRAL C-N BONDS

Despite the major advances in strategies that quaternize nitrogen or employ directing group-assistance for engaging C-N bonds in TM-catalyzed processes, neutral C-N bond activation remains underdeveloped, particularly for aryl- and alkylamines. Nevertheless, such methods are appealing because they potentially allow the valorization of biologically derived feedstocks, and the diversification of existing pharmaceutical compound libraries. The development of methods that do not require prior functionalization or highly specialized substrates would be highly desirable and would have the potential to improve the utility of such transformations in organic synthesis. There are a number of more specialized or activated substrates that have been used in C-N bond activation where the C-N bond may be classed as 'neutral'; these include cyanamides,[82] and aminals.[83] Aryl hydrazines have received an increasing amount of attention as precursors to aryldiazoniums[84] or via palladadiaziridine intermediates.[85,86] Reactions employing these substrates are not covered in this Perspective and the reader is instead directed to recent reviews that cover these classes of compound in TM-catalyzed reactions.

Recently, Shi and co-workers described the direct Suzuki-Miyaura cross-coupling reaction of dimethylarylamines **103** with aryl boronates **104**, using a Ni(I) catalyst modified by the *N*-heterocyclic carbene (NHC) ligand, $IMes^{Me}$ (Scheme 11A).[87] This is the first example where this particular transformation has been achieved without either pre-activating nitrogen or using a directing group. The addition of magnesium was critical for successful reaction, and its role likely extends beyond simply functioning as an initiating reductant because attempts use other

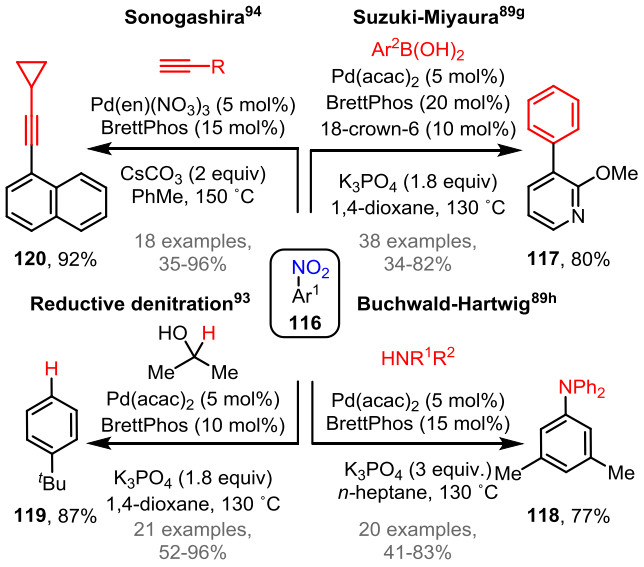
metallic reductants (e.g. Zn, Mn, Na, Al and Sn) were unsuccessful. On the basis of electron paramagnetic resonance (EPR) measurements and DFT calculations, the authors proposed a Ni(I)/Ni(III) pathway. Ligand exchange between the proposed catalytic species, $(NHC)_2Ni(I)Br$, and aniline **103** gives Ni(I) species **105**. Oxidative addition of the C-N bond to the Ni-center generates Ni(III) species **106**, from which transmetalation with aryl boronate **104** gives **107**. Reductive elimination then generates the biaryl products (e.g. **108** and **109**). The method is most effective with highly conjugated tertiary arylamines (primarily alkyl-substituted *N*,*N*-dimethyl naphthylamines) and does not extend well to phenylamines. Shi and co-workers have also demonstrated the suitability of this approach for the Miyaura borylation of arylamines **110** and *N*-arylpyrroles **111**, employing a combination of $Ni(cod)_2$ and $IMes^{Me}$, with B_2nep_2 as the borylation reagent (Scheme 11B). Interestingly, reactions of *N*-arylpyrroles **111** required the addition of base ($PhCO_2Na$) whereas for dimethylarylamines **110** the addition of base had a detrimental impact.



Scheme 11. (A) Nickel-catalyzed cross-coupling of dimethylarylamines with arylboronic esters and proposed mechanism via a Ni(I)/Ni(III) catalytic cycle; (B) nickel-catalyzed borylations of dimethylarylamines and *N*-arylpyrroles.

Nitroarenes are readily available building blocks for organic synthesis and the chemical industry.[88] The ability to employ compounds of this type as electrophilic partners in cross-coupling reactions is a relatively recent development;[89] strategically this is significant because prior modification of the nitro unit (for example, by reduction to an aniline) is no longer required, which, in turn, reduces cost, effort and waste. Nevertheless, methodologies that enable the formation of C-C and C-N bonds by C-N bond activation of nitroarenes are scarce and this

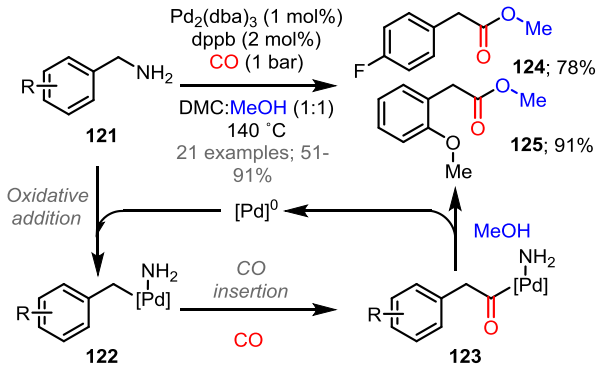
area is still underdeveloped. Nonetheless, impressive recent developments in C-N bond activation of nitroarenes **116** have been reported by the groups of Nakao and others in the context of Suzuki-Miyaura cross-couplings,[89g,90] Buchwald-Hartwig aminations,[89h,91] intramolecular C-H arylation,[92] reductive denitration,[93] and Sonogashira-type cross couplings[94] (Scheme 12). Mechanistically, these reactions are thought to proceed through the typical cross-coupling pathway initiated by oxidative addition of the C-N bond of the nitroarene.



Scheme 12. Representative examples of C-N bond activations in nitroarenes.

For direct carbonylation of neutral amine C-N bonds, methods commonly employ tertiary amines in C-N bond cleavage (dealkylative) carbonylation strategies.[29] Alternatively, there are methods that exploit strain release (see Section 5) or the thermodynamic stability of palladium π-allyl complexes derived from allylamines (see Section 6) for C-N bond activation in carbonylative reactions. Conversely, the use of primary or secondary alkyl amines for C-N bond activation is significantly more challenging.[29a] In an isolated example employing primary benzylamines as a source of neutral C-N bonds for carbonylation reactions via C-N bond activation, Wu and co-

workers showed that a variety of benzyl amines **121** can be converted into the corresponding methyl 2-arylacetates (e.g. **124** and **125**) under Pd(0) catalysis (Scheme 13).[95] It was noted that the use of dimethyl carbonate (DMC) was essential (other solvents failed), and the reaction proceeded more efficiently with excess MeOH (as a co-solvent) – the latter may facilitate oxidative addition (to **122**) by activating the amine through hydrogen bonding. CO insertion (to give **123**), is then followed by nucleophilic attack of MeOH to generate ester products (e.g. **124** and **125**).

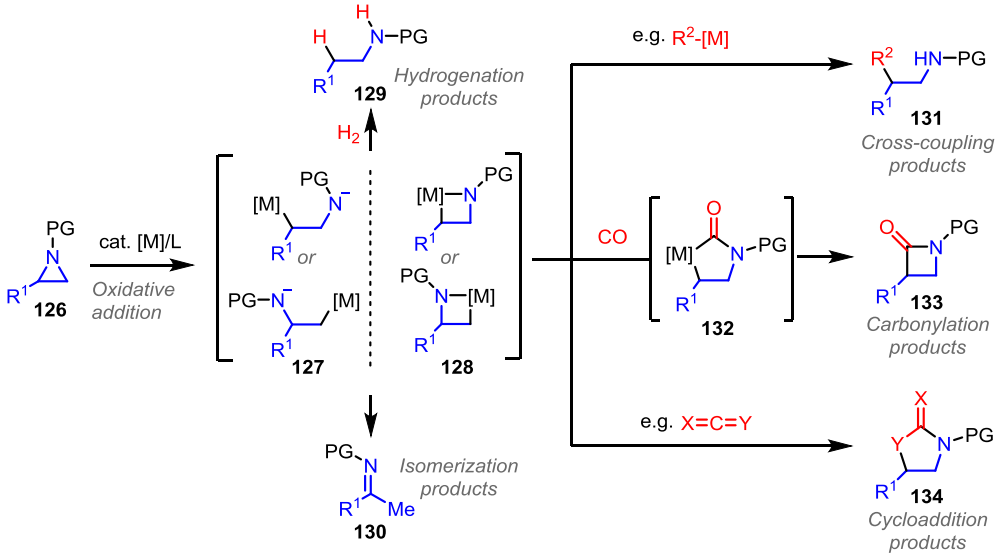


Scheme 13. Palladium-catalyzed carbonylation of primary benzylamines for the synthesis of methyl 2-arylacetates.

5. C-N BOND ACTIVATION VIA STRAIN RELEASE

Another class of "activated" C-N bonds are those found in strained *N*-heterocyclic systems. Small nitrogen-containing ring systems (i.e. aziridines, 2*H*-azirines, azetidines) are versatile intermediates, and C-N activation allows them to be used as precursors for a wide range of scaffolds (including lactams, pyrrolidines, imines, amines, pyrazines and imidazoles) that are not readily accessible through traditional methods.[96] C-N activation of such systems is driven by the release of ring strain.

Transition metal-catalyzed C-N bond activations of aziridines have received an increasing amount of attention in recent years.[96c] These precursors offer a versatile platform for reaction development, and efficient carbonylation and cross-coupling protocols are available (Scheme 14). Methods for accessing azametallacyclobutane intermediates **127** or **128** typically require strongly activating *N*-sulfonyl or bulky *N*-alkyl (e.g. *t*-butyl) substituents and require vinylic or benzylic activation of the C-N bond (R^1 = alkenyl or aryl). In cases where the aziridine is non-symmetrical, issues of C-N bond regioselectivity arise, which is partially addressed by the latter strategy, where the aziridine substituent (R^1) impacts which C-N bond undergoes cleavage.

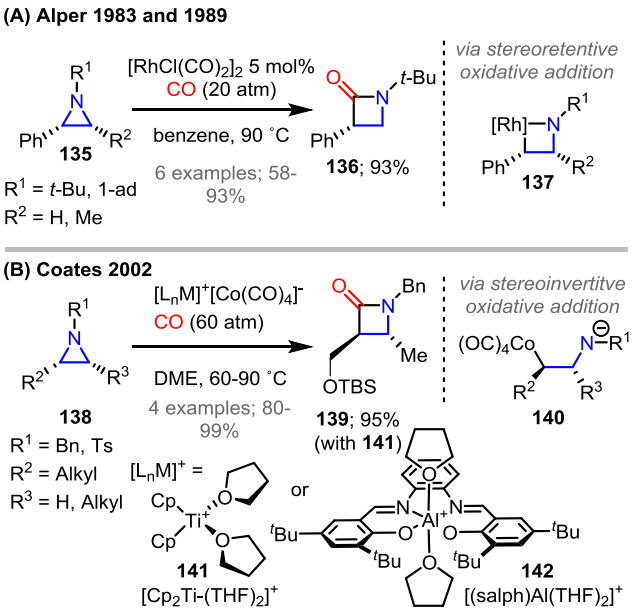


Scheme 14. C-N bond activation of aziridines.

A key milestone in aziridine C-N bond activation came in the mid-1970s when Aumann reported carbonylations of vinylaziridines *via* oxidative addition of the C-N bond to stoichiometric $Fe(CO)_5$.[97] The first catalytic carbonylation of aziridines was reported by Alper in 1983 for the ring-expansion of benzylic aziridines **135** to β-lactams **136** using $[Rh(CO)_2Cl]_2$ as a catalyst under high pressures of carbon monoxide (Scheme 15A).[98] For this system, a bulky *N*-alkyl (*t*-

butyl or 1-adamanyl) substituent was required to prevent 1,3-dipolar polymerizations and/or azametallacyclobutane collapse (by exocyclic β-hydride elimination). Further studies showed that this reaction is enantiospecific and stereoretentive, allowing enantioenriched β-lactams **136** to be prepared from enantioenriched aziridines **135**.[99] Later, catalytic carbonylations of vinylaziridines to enantiopure β-lactams were developed using palladium-based catalysts (*via* the intermediacy of π-allyl azapalladacycles, *vide infra*).[100]

Mechanistically distinct strategies for C-N cleavage of unactivated aziridines have also been developed by the Alper and Coates groups, by employing $Co_2(CO)_8$[101] or Lewis acid-cobalt catalysts $[Cp_2Ti\text{-}(THF)_2][Co(CO)_4]$ (**141**) and $[(salph)Al(THF)_2][Co(CO)_4]$ (**142**) (Scheme 15B).[102] These processes are postulated to proceed *via* Lewis acid-assisted and stereoinvertive nucleophilic attack of the $[Co(CO)_4]^-$ ion (to give **140**), followed by carbonylation and ring-closure; this mechanism has subsequently been studied and supported computationally.[103] Complementary strategies for engaging unactivated aziridine C-N bonds for the synthesis of β-lactams have been developed, such as a $Ni(CO)_4$/LiI system, reported by Pinhas and co-workers.[104] This C-N bond cleavage strategy does not proceed *via C-N* oxidative addition to the metal, but does allow retention of aziridine stereochemistry via a double inversion mechanism.

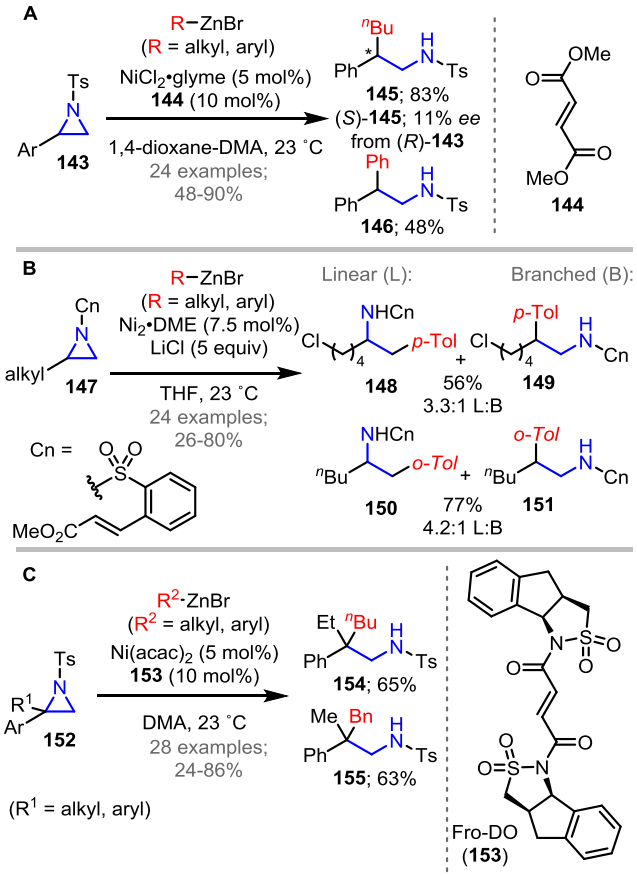


Scheme 15. Methods for carbonylative ring-expansion of aziridines *via* (A) stereoretentive oxidative addition and (B) stereoinvertive oxidative addition.

There are a number of examples that exploit aziridines as masked 1,3-dipoles for (3+2) cycloaddition chemistry (*via* C-N bond cleavage) with a variety of different dipolarophiles, including alkenes, alkynes, ketones, aldehydes, nitriles, and heterocumulenes.[105] Typically these processes employ strongly Lewis acidic (metal) catalysts to 'activate' the aziridine, there are however only a limited selection of examples that employ redox active transition metals (e.g. palladium). The exact role of the transition metal catalyst in these processes is dubious, as the metal may be serving as a Lewis acid only, without undergoing oxidative addition to the C-N bond.[96c] Catalytic hydrogenations of aziridines to form amines have also been demonstrated, typically employing either Ni or Pd heterogeneous catalysts.[106]

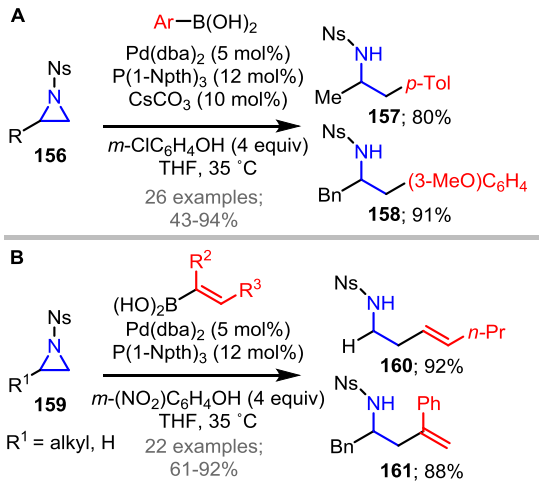
Azametallacyclobutanes **128** (Scheme 14) have also been utilized as intermediates that can be intercepted by nucleophilic organometallic species in cross-coupling reactions. This strategy opens up the possibility for catalyst-controlled selectivity and scope that is complementary to

traditional nucleophilic ring-opening processes.[96c,107] In 2002, Hillhouse demonstrated that simple (non-allylic) aziridines can undergo oxidative addition and reductive elimination using nickel complexes.[108] Subsequently, Doyle[109] and Jamison[110] showed that *N*-sulfonyl aziridines undergo Negishi cross-coupling reactions under Ni-catalyzed conditions. Doyle's protocol encompasses cross-couplings of aryl-substituted *N*-tosyl aziridines **143** with organozinc reagents at room temperature by employing $NiCl_2$•glyme as an inexpensive and air-stable nickel source and dimethyl fumarate (**144**) as an olefinic ligand (Scheme 16A).[109] In general, Ni-catalyzed cross-coupling reactions of aziridines with organozinc reagents require an electron deficient olefin ligand (e.g. **144**). This requirement has been exploited in the design of the cinsyl (Cn) N-protecting group, where the olefin is incorporated within the N-substituent (Scheme 16B).[111] This change expanded cross-coupling scope to include alkyl-substituted aziridines **147**, where modest selectivity for cleavage of the less substituted C-N bond was observed (approx. 2.5-4.9:1 linear (L):branched (B)). The development of a novel electron-deficient olefin ligand, Fro-DO (**153**), enabled the generation of quaternary carbon centers from 1,1-disubstituted styrenyl *N*-tosyl aziridines **152** (Scheme 16C).[112] Ligand **153** was required to promote C-C bond formation over β-hydride elimination pathways. For these processes, oxidative addition of the C-N bond to a low valent Ni species likely occurs via a SET pathway in most cases.



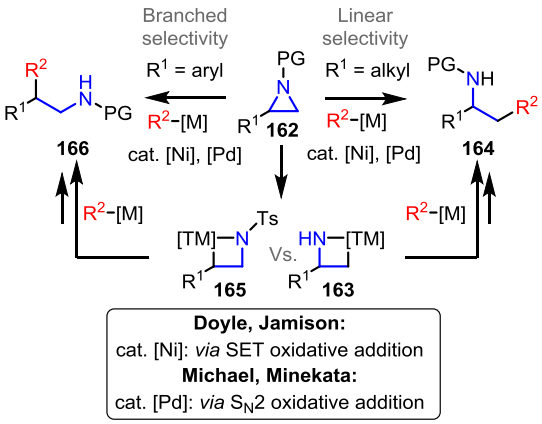
Scheme 16. Ni-catalyzed Negishi cross-coupling reactions of *N*-sulfonyl aziridines.

In a series of experiments employing *N*-tosyl aziridines, Wolfe and co-workers were able to demonstrate C-N bond oxidative addition to Pd(0), which was initially exploited for the isomerization of *N*-tosyl aziridines to ketimines.[113] Subsequently, Wolfe extended this approach to the intramolecular trapping of the azametallacyclobutane intermediate with a pendant olefin in the presence of CuI.[114] These early studies paved the way for the extension of Pd-catalyzed reactions of *N*-sulfonyl aziridines to Suzuki couplings, which was later demonstrated by Michael and co-workers in a series of highly regioselective (>20:1 L:B) couplings of alkyl-substituted *N*-nosyl aziridines **156** or **159** with both aryl- and alkenylboronic acids, using a Pd/P(1-Npth)$_3$ system (Scheme 17).[115]



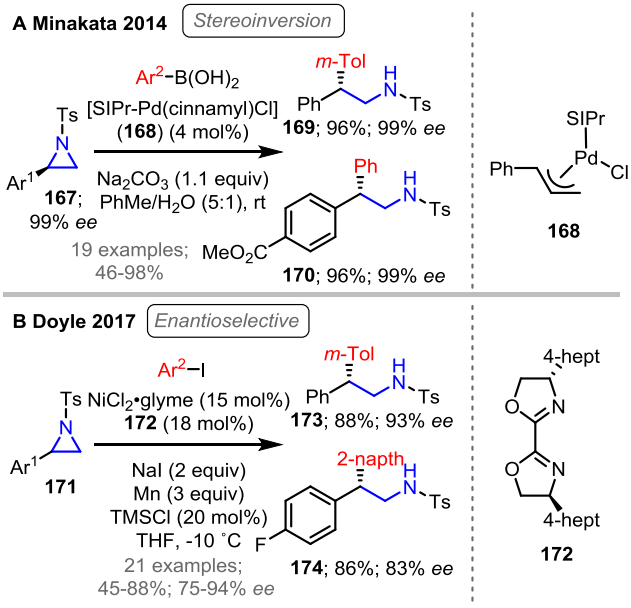
Scheme 17. Pd-catalyzed Suzuki cross-coupling reactions of *N*-sulfonyl aziridines.

In general, linear product selectivity is observed for cross-coupling reactions of alkyl-substituted aziridines, whereas branched product selectivity is observed with aryl-substituted aziridines (Scheme 18). Mechanistically, Pd- and Ni-catalyzed cross-coupling reactions of aziridines differ: Ni-catalyzed processes (Scheme 16) are proposed to proceed via a SET-oxidative addition pathway, whereas Pd-catalyzed variants (Scheme 17) occur via direct S_N2 oxidative addition.



Scheme 18. Linear vs. branched product selectivity in cross-coupling reactions of aziridines.

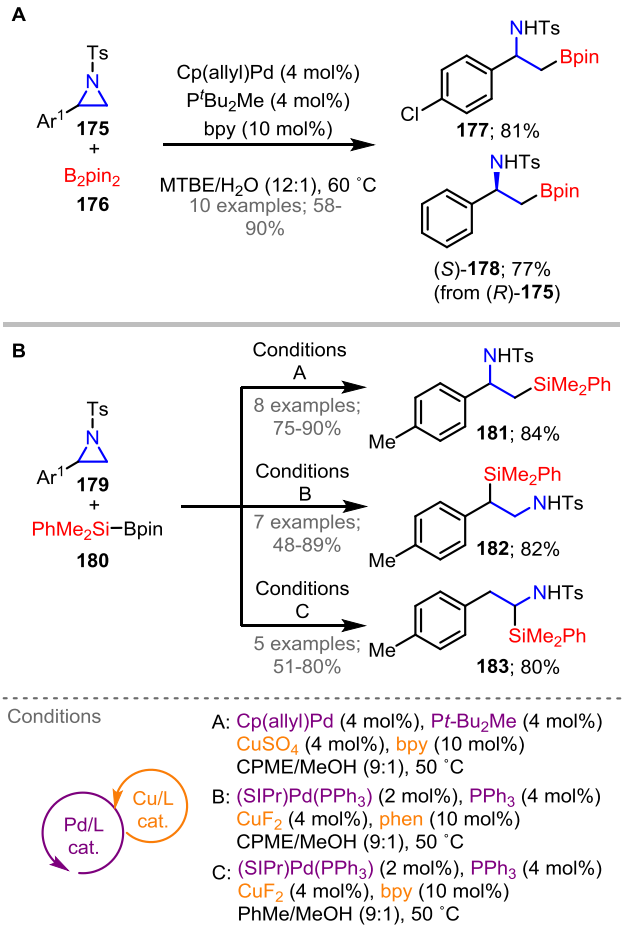
Since the observation by Doyle that reactions of enantiopure styrenyl aziridines proceeded via stereoablation,[116] (as demonstrated by the conversion of enantiopure **143** to **145** (11% *ee*); Scheme 16A),[109] there have been major advances in stereocontrolled cross-coupling reactions of styrenyl *N*-tosyl aziridines taking advantage of the differing mechanistic options.[35b] Minakata demonstrated the stereoinvertive cross-coupling of enantiopure styrenyl *N*-tosyl aziridines with arylboronic acids under mild conditions using [SIPr-Pd(cinnamyl)Cl] complex (**168**) via S_N2 oxidative addition (Scheme 19A).[117] Doyle later extended Ni-catalyzed cross-coupling reactions of racemic styrenyl *N*-tosyl aziridines **171** to include the enantioselective reductive cross-electrophile coupling with aryl iodides in a stereoconvergent fashion (Scheme 19B).[118]



Scheme 19. Stereo-controlled cross-coupling reactions of aziridines.

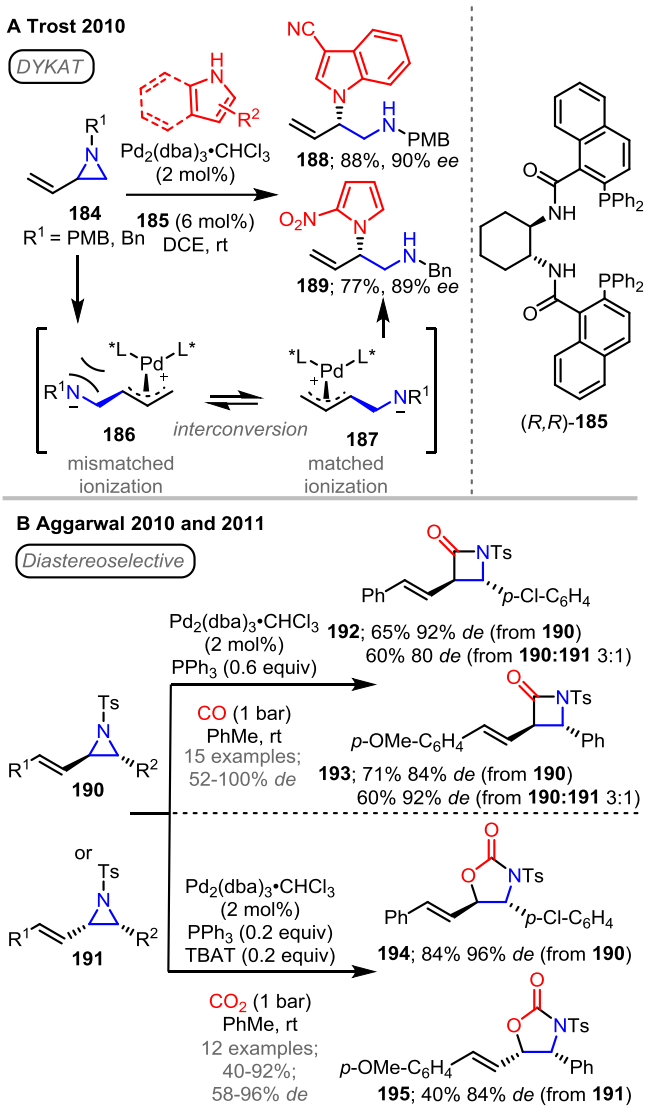
Recent advances in cross-coupling reactions of *N*-sulfonyl aziridines include directing group-assisted Pd-,[119] Rh-[120] and Co-catalyzed[121] aryl (*ortho*-) C-H insertions and dual photoredox/Ni-catalyzed reactions.[122] Further to C-C bond forming reactions, Pd-catalyzed borylation (Scheme 20A),[123] and dual Pd/Cu-catalyzed C(sp^3)-Si bond forming (Scheme 20B)[124] reactions have been

reported by Minakata and Takeda. For borylative ring-opening/cross-coupling reactions of styrenyl *N*-tosyl aziridines **175**, a combination of B_2pin_2 (**176**) with cp(allyl)Pd/phosphine/2,2'-bipyridine (bpy) system was effective. Interestingly, this reaction proceeded with switched regioselectivity (cf. Scheme 18), and the authors suggested that this was dictated by interactions between the substrate and the Pd(0) catalyst, which was supported by computational evidence.[123] For C(sp^3)-Si bond formation, Minakata, Takeda and co-workers presented a series of catalyst-controlled, regiodivergent dual Pd/Cu-catalyzed reactions with $PhMe_2Si$–Bpin (**180**). In these examples, variation of the catalyst/ligand system facilitated the synthesis of three different regioisomers (e.g. **181-183**) from a common precursor **179**.



Scheme 20. (A) C(sp^3)-B and (B) C(sp^3)-Si bond forming reactions from styrenyl N-tosyl aziridines.

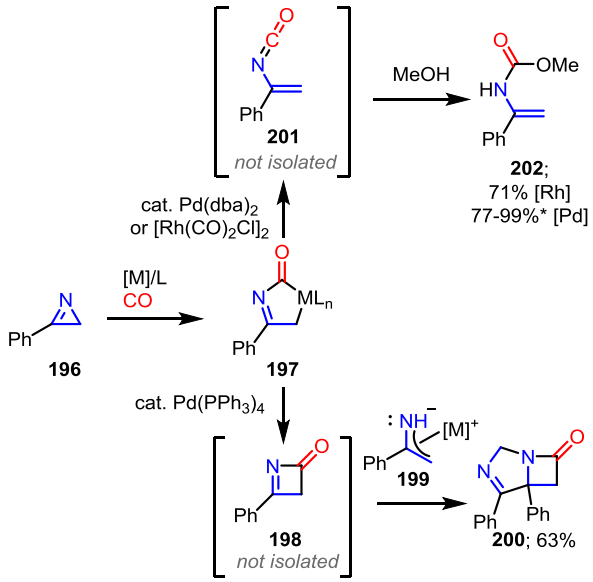
An alternative reaction pathway is available for vinyl aziridines that involves metal catalyzed ionization to generate a metal π-allyl (see Section 6). Only selected examples will be discussed herein and the reader is directed to a comprehensive review covering the synthesis and applications of vinyl aziridines.[125] In 2010, Trost reported the cross-couplings of racemic vinyl-substituted *N*-benzyl aziridines **184** with pyrroles and indoles; these processes are postulated to proceed *via* a palladium π-allyl complex (Scheme 21A).[126] Enantioenriched products (e.g. **188** and **189**) were obtained through a dynamic kinetic asymmetric transformation (DYKAT)[127] using chiral ligand (*R,R*)-**185**, where both enantiomers of the substrate were selectively converted to a single product. Contemporaneous reports by Aggarwal and co-workers demonstrated the suitability of vinyl aziridines for diastereoselective carbonylation[128] and carboxylation[129] reactions under mild conditions (Scheme 21B). Interestingly, for carbonylation, the *trans*-β-lactam products (e.g. **192** and **193**) were formed irrespective of the geometry of the starting aziridine (**190** or **191**). Whereas for carboxylation the geometry of the starting aziridine (**190** or **191**) was transferred to the 5-vinyloxazolidinone products (e.g. **194** and **195**).



Scheme 21. Stereocontrolled reactions of vinyl aziridines.

2*H*-Azirines undergo ring cleavage more easily than aziridines owing to their higher ring strain (45-48 kcal mol^{-1} for 2*H*-azirines,[130] vs. 28 kcal mol^{-1} for aziridines[130a,131]) and many reactions have been developed that exploit this.[132] Of these, some are catalyzed by transition metals (including isomerizations, cycloadditions, carbonylations, hydrogenations, reactions with carbenoids, hydrogenations, and reactions with enolates),[96c] yet, in contrast with aziridines, there are far fewer examples of TM-catalyzed process that process via oxidative addition of the C-N

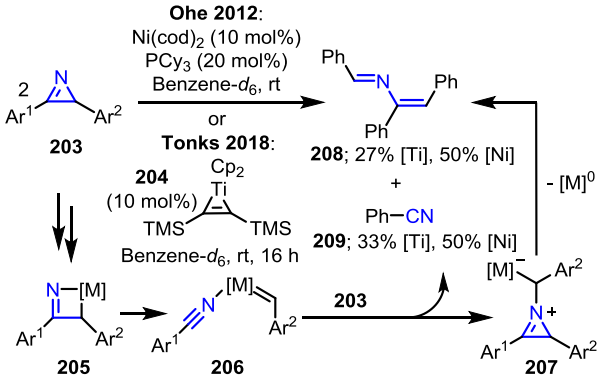
σ-bond. In 1981, Alper and co-workers reported that 2*H*-azirines undergo palladium-catalyzed oxidative ionization to generate Pd-azaallyl complexes; CO-insertion and reaction with another equivalent of azirine provided bicyclic lactams **200** (Scheme 22).[133] An earlier report had shown than C-N cleavage could be promoted by stoichiometric $[Rh(CO)_2Cl]_2$; here, mechanisms based on C-N oxidative addition (to generate a rhodacycle) or the formation of a Rh-nitrene were proposed.[134] For the process in Scheme 22, four-membered azetone **198** was not isolated, and various catalyst/ligand combinations resulted in different rearrangement processes, forming fused β-lactam products **202** or vinyl isocyanates **201** (trapped by CH_3OH to form carbamates **202**).[135] Mechanistically, these processes likely bifurcate at azametallacycle **197**.



Scheme 22. Transition metal-catalyzed carbonylation reactions of 2*H*-azirines to form carbamates and fused β-lactams. *Specific yield for **202** not reported.

Ohe and co-workers, and later Tonks and co-workers, independently observed an interesting disproportionation reaction of 2*H*-azirines in the presence of catalytic amounts of either $Ni(cod)_2$[136] or Cp_2Ti(bis(trimethylsilyl)acetylene) (**204**)[137] (Scheme 23). Mechanistically, these

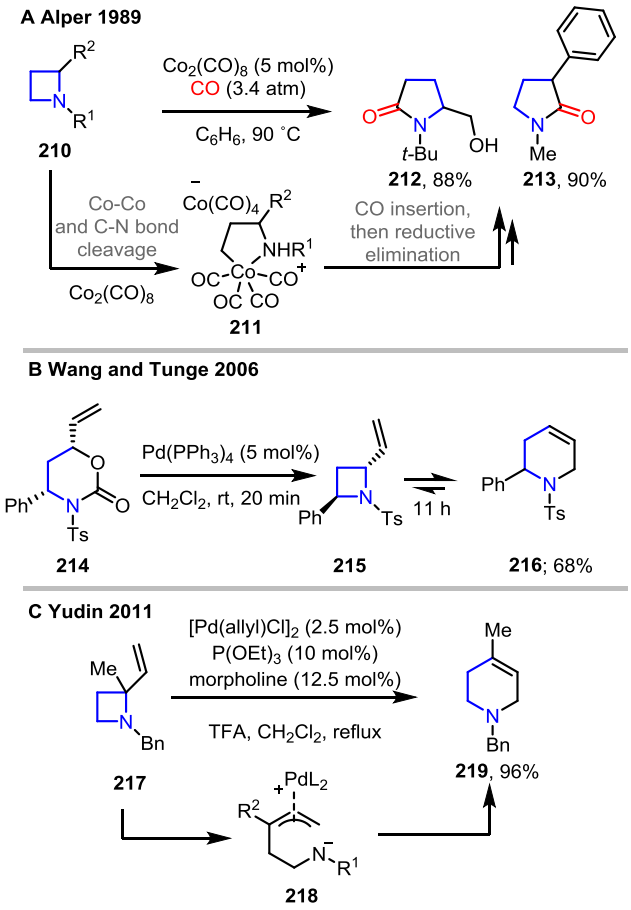
processes are proposed to proceed by oxidative addition of the C-N bond to the TM to give azametallacyclobutene **205**, which would ring-open to give metal-carbene **206**. Nucleophilic attack of another molecule of 2*H*-azirine **203** would give azirinium ylide **207** and nitrile **209** by elimination, and finally C-N bond cleavage and rearrangement of ylide **207** would give azadiene **208**. The interception of intermediates in this unique disproportionation reaction may offer novel reaction pathways. In general, 2*H*-azirines are prone to dimerization and disproportionation processes, which may offer an explanation as to why this class of compounds have found less utility for e.g. cross-coupling reactions via C-N bond activation when compared to aziridines.



Scheme 23. Transition metal-catalyzed disproportionation reactions of 2*H*-azirines.

C-N bond activations of azetidines are also considerably more challenging than aziridines and there are few reports of effective protocols. Most notably, carbonylation reactions to afford pyrrolidinones have been demonstrated by Alper and co-workers using $Co_2(CO)_8$ at high CO pressures (Scheme 24A).[138] The proposed bond activation involves heterolytic cleavage of the Co-Co bond, which enables formation of ion pair **211**. From here, migratory insertion of CO into the Co-N bond and reductive elimination provides the desired pyrrolidinone (e.g. **212** or **213**). In some cases, the regioselectivity of the CO insertion can be tuned by changing the substituent on the nitrogen atom and the reaction temperature. For vinyl azetidines, Tunge and Wang noted that

upon the synthesis of vinyl azetidine **215** from cyclic carbamate **214** under Pd(0) catalysis, that if left for prolonged reaction times, vinyl azetidine **215** is converted to tetrahydropyridine derivative **216** (68%) (Scheme 24B).[139] Later, a palladium-catalyzed protocol was reported by Yudin and co-workers for ring-contraction and ring-expansion of cyclic allylamines, where in the case of vinyl azetidine **217**, tetrahydropyridine derivative **219** (96%) was isolated (Scheme 24C).[140] Mechanistically, these rearrangement processes are driven by the release of ring-strain, resulting in the more thermodynamically stable 6-membered ring product (e.g. **216** or **219**) via the intermediacy of π-allyl complex **218**.

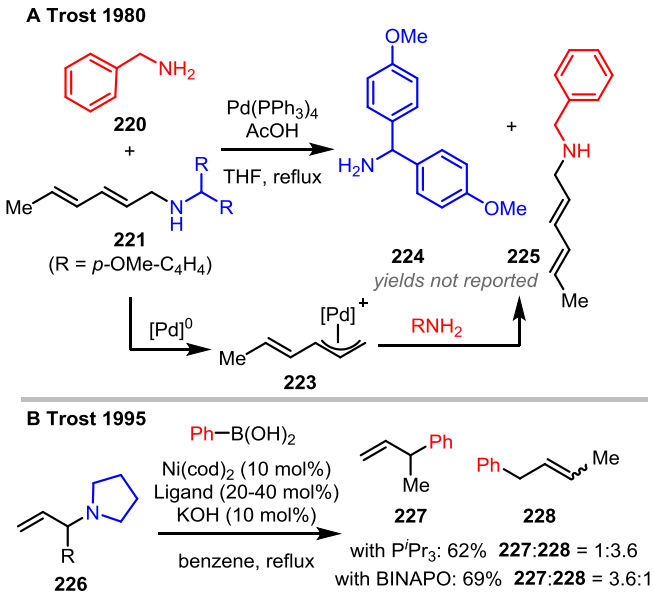


Scheme 24. (A) Carbonylative ring expansion of azetidines to afford pyrrolidinones; (B and C) Pd-catalyzed ring-expansions of vinyl azetidines to tetrahydropyridine derivatives.

6. C-N BOND ACTIVATION OF ALLYLAMINES

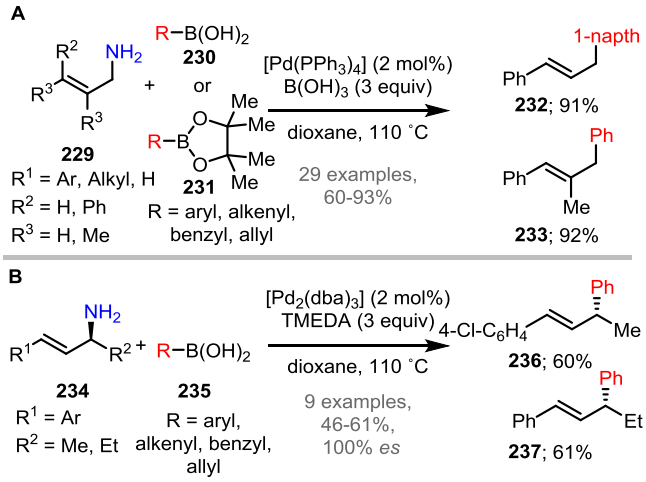
Allylic amines are suitable for C-N bond activation because the energetic penalty of C-N bond cleavage is offset by the stability of the resulting metal π-allyl complex. The most common strategy for achieving C-N bond activation of allyl amines is through prior protonation (quaternization) of the nitrogen atom.

An important observation was made by Trost in 1980 who noted that 'amine exchange' occurred in a reaction between benzylamine (**220**) and secondary allylamine **221** and under Pd(0)-catalysis, but only in the presence of stochiometric amounts acetic acid, and this led Trost to propose the intermediacy of a π-allyl complex **223** (Scheme 25A).[141] Following this important discovery, it was later reported that tertiary allylamines can be coupled with boronic acids in nickel-catalyzed Tsuji-Trost-type allylations, where the boronic acid may also act as a Lewis acid, thus activating the amine in an analogous fashion (Scheme 25B).[142] It was noted that regioselectivity with respect to the electrophile could be controlled by judicious selection of ligand: sterically bulky phosphine ligands (e.g. triisopropyl phosphine) promoted alkylation at the terminus, whereas bidentate phospinite ligands (e.g. 1,l'- binaphthyl-2,2'-ylbis(diphenylphosphinite), BINAPO) promoted alkylation at the more substituted position.



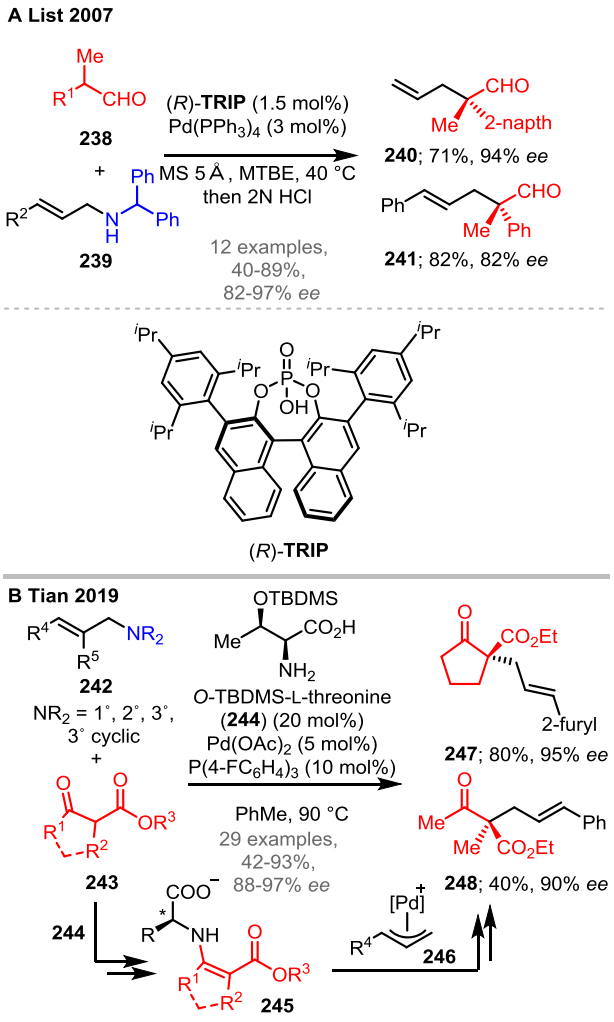
Scheme 25. (A) Pd-catalyzed amine exchange and (B) Ni-catalyzed cross-coupling reactions of allylamines.

Tian later reported an important extension of this strategy to the coupling of primary allylamines **229** with boronic acids **230** and boronates **231** in a regiospecific and stereospecific fashion under palladium catalysis (Scheme 26).[143] Here it was observed that the yield of the reaction was improved by the addition of inexpensive $B(OH)_3$ and the reaction was exemplified with a variety of different aryl-, alkenyl-, allyl- and benzyl-nucleophiles in moderate to excellent yields. For chiral allylamines **234**, the reaction proceeded with inversion (100% *es*) and benefitted from the addition of TMEDA as a ligand whereas additive $B(OH)_3$ had a detrimental impact. Since Trost's initial observation, there have been numerous reports of Tsuji-Trost-type allylations whereby the electrophilic component is a (Brønsted or Lewis acid-activated) allylamine, primarily under Pd(0) catalysis, with a variety of nucleophiles, including those based on carbon,[144] nitrogen (intramolecular),[145] phosphorus,[146] and sulfur.[147]



Scheme 26. Tsuji-Trost-type allylations of boronic acids and boronates with (A) primary allylamines (B) chiral primary allylamines.

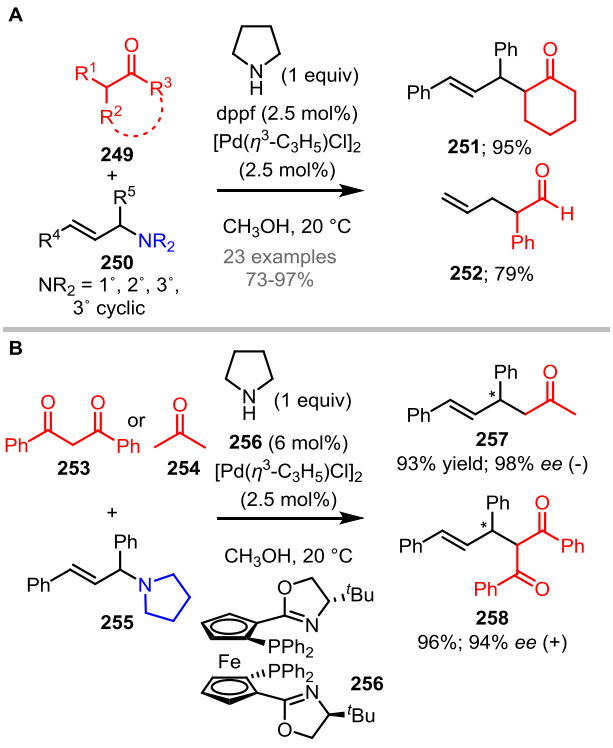
Important advances towards catalytic enantio- and regioselective selective allylations starting from allylamines have emerged, including a selected example of enantioselective α-allylation of branched aldehydes by List (Scheme 27A)[148] and a recent example of enantioselective *α*-allylation of *β*-ketoesters reported by Tian (Scheme 27B).[149] For α-allylation of branched aldehydes, chiral phosphoric acid (*R*)-**TRIP** was essential for reactivity, where a dual role was proposed: as a ligand, and as Brønsted acid (for amine activation). For *α*-allylation of β-ketoesters, L-threonine derivative **244** was employed as a ligand and also likely served a dual role; the authors indicated that the reaction was designed such that **244** would condense with β-ketoester **243** to give enamine **245**, which then undergoes enantioselective allylation by π-allyl complex **246** to give α,α-disubstituted β-ketoesters **247** and **248**. These reactions are significant as they allow for the generation of all-carbon quaternary stereogenic centers.



Scheme 27. Enantioselective Tsuji-Trost-type *α*-allylation of carbonyl compounds with allylamines.

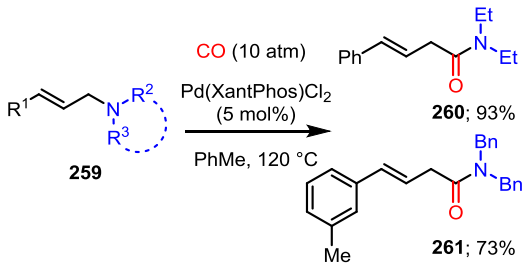
In addition to Tsuji-Trost-type allylations, the activation of allylamines with Brønsted or Lewis acids is a strategy that has been successfully employed for a variety of other related noteworthy transformations including deallylations,[150] finding most utility as a deprotection strategy for *N*-allyl derivatives; cyclic allylamine isomerisations,[140] for the synthesis of complex cyclic allyl amines; and 3-aza-cope reactions,[151] for the synthesis of δ,ε-unsaturated imines or γ,δ-unsaturated carbonyls as important synthetic intermediates.

Related processes involving insertion of a metal into the C-N bond of non-quaternized allylic amines have also been achieved. One of the first reports in this area was by Montreux,[152] who outlined efficient reactions between allylic amines and soft nucleophiles, such as malonates, β-ketoesters and 1,3-diketones, using $Ni(dppb)_2$ as a catalyst. In a selected example, Zhang later reported palladium-catalyzed C-N bond activations of allylic amines **250** for the allylation of carbonyl compounds **249** in a Tsuji-Trost-type process using dppf as a ligand (Scheme 28A).[153] In this case, the formation of the π-allyl intermediate is facilitated by hydrogen bonding of an alcoholic solvent to the nitrogen center. Zhang also demonstrated a prototype enantioselective version of this method by employing chiral ferrocene-based ligand **256** (Scheme 28B).[153]



Scheme 28. Enantioselective Tsuji-Trost-type *α*-allylation of carbonyl compounds with allylamines in alcohol solvent.

Carbonylation of allylamines as a method for the construction of β,γ-unsaturated amides was first reported by Murahashi and co-workers.[154] This method employed $Pd(OAc)_2$ as a catalyst and dppp as a ligand, under high pressures (50 atm) at high temperature (110-130 ˚C). Two decades later, in 2014, Huang and co-workers reported an improvement by the use of $Pd(XantPhos)Cl_2$ as a catalyst, allowing the required pressures of CO to be dropped (10 atm) (Scheme 29).[155] Despite the requirement for high temperatures (120 ˚C), this result is significant as it illustrates that allyamine C-N bonds are able to undergo oxidative addition to palladium in the absence of an additive (e.g. Brønsted or Lewis acid).

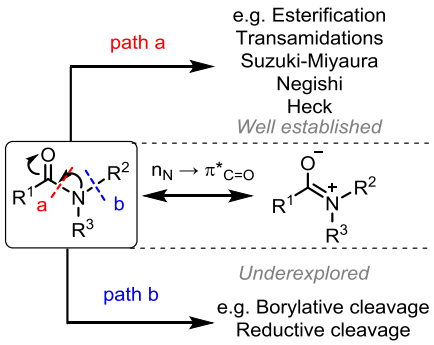


Scheme 29. Pd-catalyzed carbonylation of allylamines.

7. C-N BOND ACTIVATION OF AMIDE DERIVATIVES

Amide bonds are ubiquitous in both in organic synthesis and biology.[156] Despite their prevalence, the engagement of amide C-N bonds as the electrophile in cross-coupling reactions is hampered by amide resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation), resulting in a shorter (1.47 Å [amine] vs 1.34 Å [amide])[157] and stronger (15–20 kcal/mol)[158] C-N bond (Scheme 30). Additionally, there are two options for the site of bond cleavage: the acyl C-N bond (Scheme 30, path a) and the non-acyl C-N bond (Scheme 30, path b). Transition metal-based catalysts have shown promise for cleaving these types of bond; reactions of these types have been the subject of extensive investigations in recent years and the subject of many reviews.[159] These findings are of great

interest, since the amide functional group can now be exploited as a redox active handle for the construction of new bonds. Key milestones and selected reactivity points in the context of C-N bond activation will be discussed herein.



Scheme 30. Amides as coupling partners in cross-coupling reactions by cleavage of acyl (path a) and non-acyl (path b) C-N bonds.

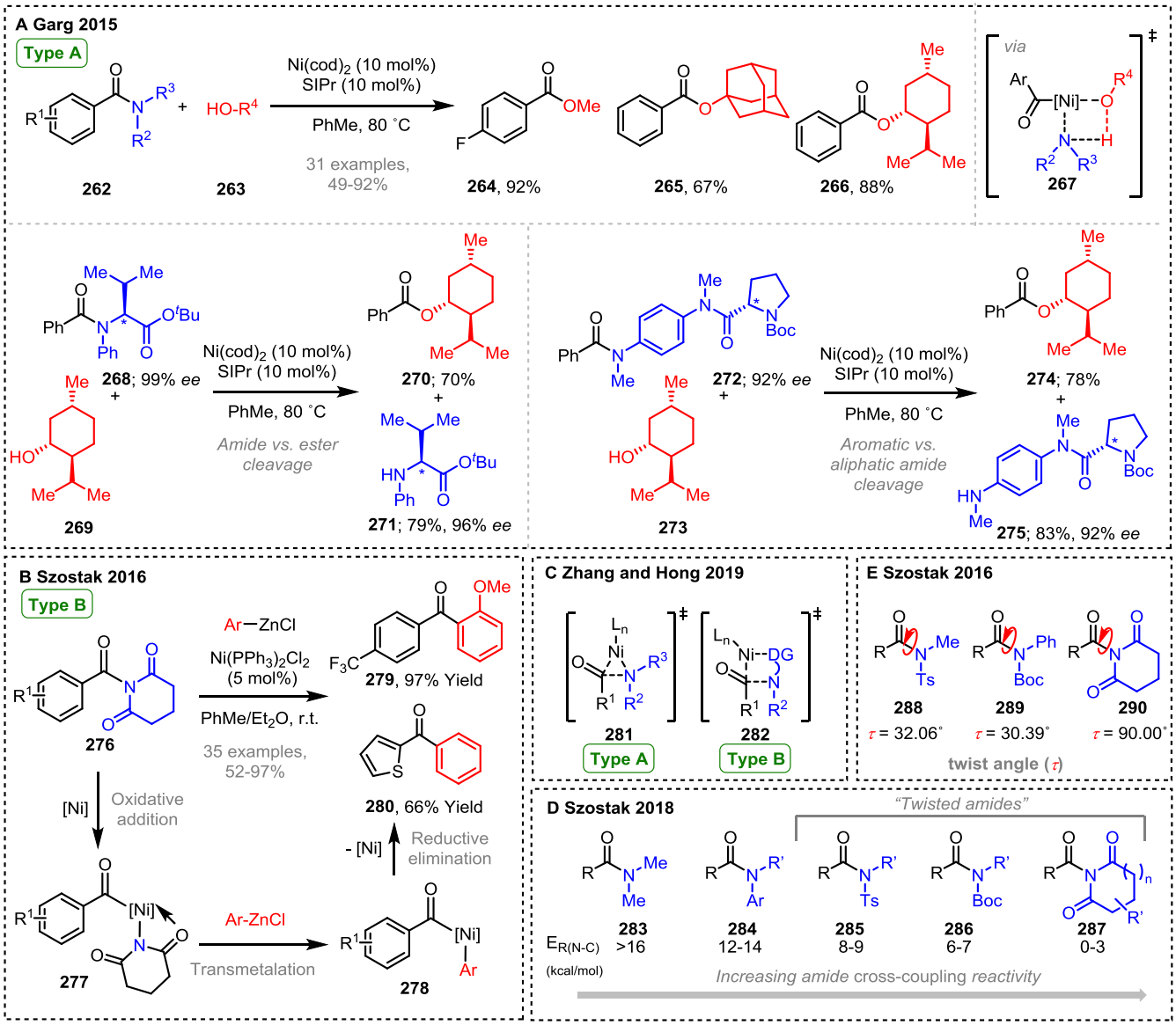
Regarding acyl C-N bond activation, early examples by Matsubara and Kurahashi include the preparation of isoquinolin-1(*2H*)-one derivatives via decarbonylative carboamination of alkynes with *N*-arylphthalimides,[160] and decarboxylative carboamination of alkynes with isatoic anhydrides[161] under Ni-catalysis. The first direct metal-catalyzed activation of C-N bonds of amides was reported in 2015 by Garg and co-workers who described a mild method for the transformation of amides into esters;[162] typically, esterification of amides requires harsh conditions and a large excess of alcohol.[158] Garg's report outlined an alternative approach where the acyl C-N bond of amides **262** is cleaved under reasonably mild conditions via oxidative addition using a nickel catalyst (Scheme 31A),[162] and this allows transacylation using only a slight excess of alcohol **263** (1.2 equiv). Chemoselective cleavage of electronically differentiated amides (e.g. aliphatic vs. aromatic amide systems) was demonstrated, as well as the cleavage of amides in the presence of ester functionality. For transacylation of valine-derived amide **268**, no

epimerization of the α-stereocenter center was observed, highlighting the mildness of the method. DFT calculations indicate that, following C-N oxidative addition, the reactant alcohol drives exchange of the amide ligand through hydrogen bonding (via transition state **267**), and this is followed by C-O bond forming reductive elimination.

Subsequently, examples of nickel-, palladium-, rhodium- and cobalt-catalyzed C-C bond forming cross-couplings of amide-based systems have been reported, including Negishi,[163] Suzuki-Miyaura,[164] Sonogashira,[165] Heck,[166] dual C-H/C-N bond activation[167] and reductive coupling[168] reactions. In particular, Szostak disclosed the first Negishi coupling of *N*-acyl-glutarimides **276** using $[Ni(PPh_3)_2Cl_2]$ as an inexpensive and air-stable catalyst.[163] This provided access to diaryl ketones (e.g. **279** and **280**) under mild conditions, with the protocol exhibiting excellent functional group tolerance and chemoselectivity (Scheme 31B). Key to the success of this strategy was the choice of substrate; amide bonds distorted from planarity, termed 'twisted amides', have been shown to undergo facile bond activation.[169] Twisted amides possess remarkable reactivity due to disruption of $n_N \rightarrow \pi^*_{C=O}$ conjugation and have attracted much attention in recent years.[170] Furthermore, such amides are able to engage and direct the TM via chelation assistance (vide infra). Mechanistically, (chelation-assisted) oxidative addition to the TM gives **277**. Transmetalation with the aryl zinc reagent gives intermediate **278**, which undergoes reductive elimination to form ketone products (e.g. **279** and **230**).

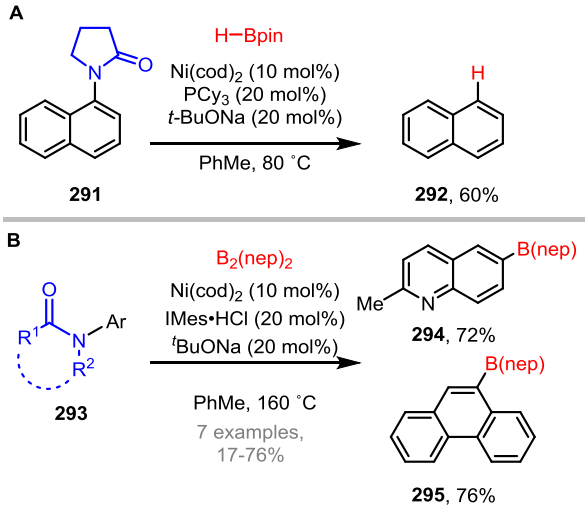
A recent review of computational studies offers further insight into the mechanism of Ni-driven amide C-N bond activations.[171] Two principal mechanistic models have been proposed, depending on the substrate: i) a three-membered ring oxidative addition transition state (Type A, **281**), or ii) a chelation-assisted bond activation process (Type B, **282**) (Scheme 31C). The most

prevalent mode of activation is Type A, which encompasses *N*-alkyl and *N*-aryl amide systems, whereas Type B is available for *N*-acyl amides systems (e.g. in twisted amides). In both scenarios, π-coordination of the amide carbonyl to nickel also appears to be important for destabilization of the amide C-N bond in advance of C-N bond activation. To elucidate further the origins of extraordinarily high reactivity of twisted amides, resonance energies[172] (Scheme 31D) and ground-state distortions (Scheme 31E)[173] for various amides were calculated computationally, allowing a trend in reactivity for various amides towards C-N bond activation to be established.



Scheme 31. Ni-catalyzed reactions of amides via C-N bond activation: (A) Esterification and (B) Negishi cross-coupling; (C) Calculated mechanistic models of Ni(0)-catalysed amide C-N bond activation; (D) Calculated resonance energies of various amides; and (E) Twist angles (τ) for twisted amides.

In contrast to TM-catalyzed amide C(acyl)-N bond activation, the catalytic cleavage of amide C(alkyl/aryl)-N bonds remains underexplored. In a selected example of non-acyl amide bond cleavage (Scheme 30, path b), studies by Tobisu and Chatani demonstrated nickel-catalyzed reductive (Scheme 32A) and borylative (Scheme 32B) cleavage *N*-aryl amides and carbamates.[174] These examples are significant as they represent the first time this bond disconnection has been successfully achieved by C-N activation. In this study, HBPin was used for reductive cleavage of primarily carbamates, with a single example of *N*-aryl amide reductive cleavage for the synthesis of arene **292** from lactam **291**. $B_2(nep)_2$ was used for borylative cleavage of *N*-aryl amides **293** to give aryl boronates (e.g. **294** and **295**). The method is limited to highly conjugated *N*-aryl amides and both lactam and acyclic substrates were tolerated.



Scheme 32. Ni-catalyzed (A) reductive and (B) borylative cleavages of amide N-C(aryl) bonds.

8. CONCLUDING REMARKS

The development of new reaction initiation processes is the key to unlocking new or improved synthetic methodologies. This Perspective outlines key developments in the field of C-N bond activation via oxidative addition to transition metals. As can be seen, strategies have been developed that enable the activation of increasingly challenging C-N bonds. For example, in the field of aryl C-N bond activation, the range of suitable substrates has progressed from aryl diazonium salts, through to aryl trialkylammonium salts and finally to processes that encompass anilines and aryl nitro compounds. This progression of utilizable C-N bonds allows chemists to harness functionality that can be installed more directly from feedstock precursors, thereby minimizing "concession" steps. C-N bonds are present in many organic compounds and so the ability to use them as functional handles opens new possibilities for e.g. route design or scaffold diversification. For example, amide C-N bond activation might enable amino acid derivatives to function as enantiopure units for cross-coupling; however, challenges remain in effecting the direct activation of "simple" amides. Perhaps the most appealing area for further development are processes based on the C-N bond activation of aziridines. Here, the substrates are easily accessed in a stereodefined manner and they are automatically pre-activated for C-N cleavage. Clearly, more sophisticated catalyst designs will be required to develop the field of C-N bond activation further. The strategies and mechanistic considerations outlined in this Perspective might provide inspiration towards this endeavor.

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All authors have given approval to the final version of the manuscript.

Notes

Any additional relevant notes should be placed here.

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