Direct sp^3 C–H bond activation adjacent to nitrogen in heterocycles

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Activation of sp^3 C–H bonds adjacent to nitrogen in heterocycles is an attractive transformation that is emerging as a practical method in organic synthesis. This *tutorial review* aims to summarize the key examples of direct functionalization of nitrogen-containing heterocycles *via* metal-mediated and metal-catalyzed processes, which is meant to serve as a foundation for future investigations into this rapidly developing area of research. The review covers functionalization of N-heterocycles *via* α-lithiation with alkyllithium/diamine complexes, α-amino radical formation, metal-catalyzed direct C–H activation, C–H oxidations and oxidative couplings, and metal-catalyzed carbene insertions.

1. Introduction

Functionalized, nitrogen-containing heterocycles constitute a widespread structural motif in biologically active compounds and an invaluable template for chiral auxiliaries in asymmetric synthesis. Several methods exist for the synthesis of heterocycles possessing functionalization adjacent to nitrogen; however, most require long, impractical synthetic sequences. The most efficient construction of 2-substituted heterocycles would rely on direct sp^3 C–H bond activation adjacent to nitrogen followed by C–C bond formation. In recent years, some limited examples of this powerful approach have been reported in the literature; however, very few have been enantioselective. This review is intended to enlighten the reader to the various methods which have been reported for the direct functionalization of sp^3 C–H bonds adjacent to nitrogen in heterocycles, which will hopefully provide a platform for new and innovative methods in the future. The ability of nitrogen-containing heterocycles to act as either nucleophilic (Section 2) or electrophilic (Section 5) coupling partner under appropriate conditions is astounding. As a result this review is divided into Sections 2 through 6, each describing a different mechanism of functionalization including α-lithiation with alkyllithium/diamine complexes, α-amino radical formation, metal-catalyzed direct C–H activation, C–H oxidations and oxidative couplings, and metal-catalyzed carbene insertions respectively.

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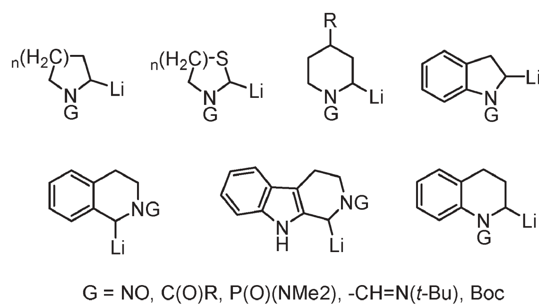
Kevin Campos, born in 1971, received his Bachelor of Science in Chemistry in 1993 from Virginia Polytechnic Institute and State University (Blacksburg, Virgina). In 1999, he received his PhD from Harvard University under the guidance of Professor David A. Evans regarding the development of chiral mixed phosphorus/sulfur ligands in late transition metal-catalyzed reactions. More recently, he reported the enantioselective α-arylation of N-Boc-pyrrolidine in the Journal of the American Chemical Society, which was highlighted in C&E News. He is currently a Senior Investigator in the Department of Process Research at Merck & Co in Rahway, New Jersey.

2. α-Lithiation with alkyllithium/diamine

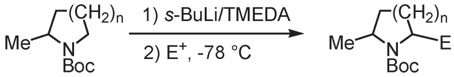
By far the oldest reported method for the direct functionalization of nitrogen-containing heterocycles is α-lithiation with alkyllithium/diamine complexes, producing a dipole-stabilized carbanion, followed by electrophilic substitution.[1] Several dipole-stabilizing groups, including amide, phosphoramide, formadine, oxazoline, nitroso, and carbamate functionalities, were effective at directed metalation adjacent to nitrogen in heterocycles. Of these, the *tert*-butyl carbamate (Boc) protecting group was most common due to availability, practicality, and ease of removal. Although this area has been extensively reviewed, Scheme 1 depicts several α-lithio-nitrogen heterocycles that have been formed *via* selective deprotonation with alkyllithium/TMEDA.

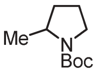
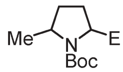
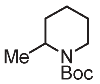
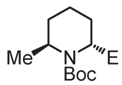
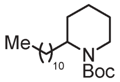
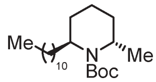
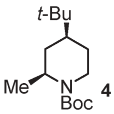
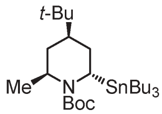
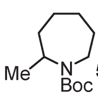
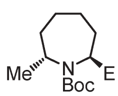
Lithiation of 2-alkyl-*N*-Boc-pyrrolidines such as **1** occurred selectively at the 5-position; however, the 2,5-disubstituted products **6–8** were often mixtures of both *cis* and *trans* isomers



Scheme 1

Table 1 Alkyllithium/TMEDA deprotonation/substitution of functionalized heterocycles

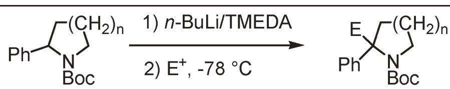


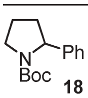
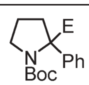
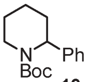
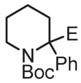
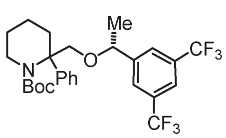
Substrate	Major product	E, % Yield
 1		Me, **6**, 72 TMS, **7**, 93 D, **8**, 81
 2		Me, **9**, 71 PhCH(OH), **10**, 96 D, **11**, 90 CHO, **12** 87
 3		**13**, 83
 4		**14**, 83
 5		Me, **15**, 41 TMS, **16**, 67 CHO, **17**, 63

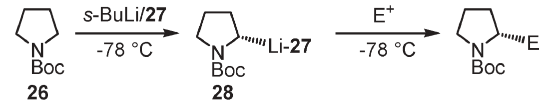
(Table 1).[2] Metalation of 2-substituted piperidines, and perhydroazepines **2–5** also occurred at the 6-, and 7-positions respectively; however, the resulting disubstituted products strongly favored the *trans* isomer. For example, selective metalation of **3** followed by treatment with dimethyl sulfate afforded **13** with near complete diastereoselectivity. Deprotection of **13** afforded the natural product (±)-Solenopsin.

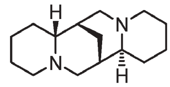
In contrast to the results reported in Table 1, Xiao and co-workers at Schering-Plough showed that metalation of 2-phenyl-*N*-Boc-pyrrolidine (**18**) and piperidine **19** with *n*-butyllithium/TMEDA, resulted in selective lithiation at C-2 instead of C-5.[3] Treatment of the resulting tertiary carbanions with a variety of electrophiles resulted in the formation of *gem*-disubstituted pyrrolidines and piperidines (Table 2). This methodology was used to synthesize NK_1-antagonist **25**.

Table 2 Alkylation of 2-phenyl-substituted heterocycles

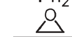


Substrate	Major product	E, % Yield
 18		Me, **20**, 44 Et, **21**, 33
 19		Me, **22**, 51 allyl, **23**, 43 CHO, **24**, 52
19		**25**, 61





(-)-Sparteine, **27**

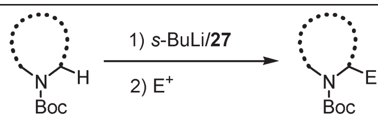
E	Product, % Yield (er)
TMS	**29**, 71, (97:3)
CH_3	**30**, 76, (98:2)
Bu_3Sn	**31**, 70, (97:3)
CO_2H	**32**, 55, (94:6)
$Ph_2C(OH)$	**33**, 75, (95:5)
 , BF_3	**34**, 83, (91:9)

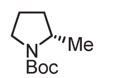
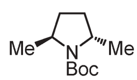
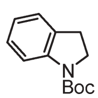
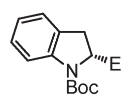
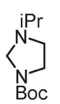
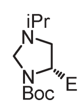
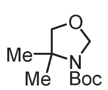
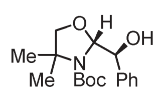
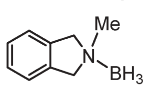
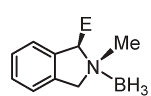
Scheme 2

Beak and co-workers discovered that deprotonation of *N*-Boc-pyrrolidine (**26**) with *s*-BuLi in the presence of the chiral diamine (−)-sparteine (**27**), instead of *N,N*-tetramethylethylenediamine (TMEDA), resulted in the formation of the chiral organolithium complex **28**, which was trapped with electrophiles at low temperatures to give enantioenriched products in good yield and high enantioselectivity (Scheme 2).[4]

Significant mechanistic investigation has been performed on this remarkable transformation, and all experimental evidence supported a kinetically-controlled deprotonation of the *pro-S* hydrogen to yield **28**, which was configurationally stable at temperatures below −50 °C.[5] Reaction of **28** with electrophiles occurred stereospecifically with retention of configuration. As shown in Table 3, the asymmetric deprotonation/substitution sequence was also performed on 2-substituted-*N*-Boc-pyrrolidines such as **30** to produce 2,5-disubstituted pyrrolidines with not only high enantioselectivity, but also high

Table 3 Asymmetric deprotonation of nitrogen-containing heterocycles



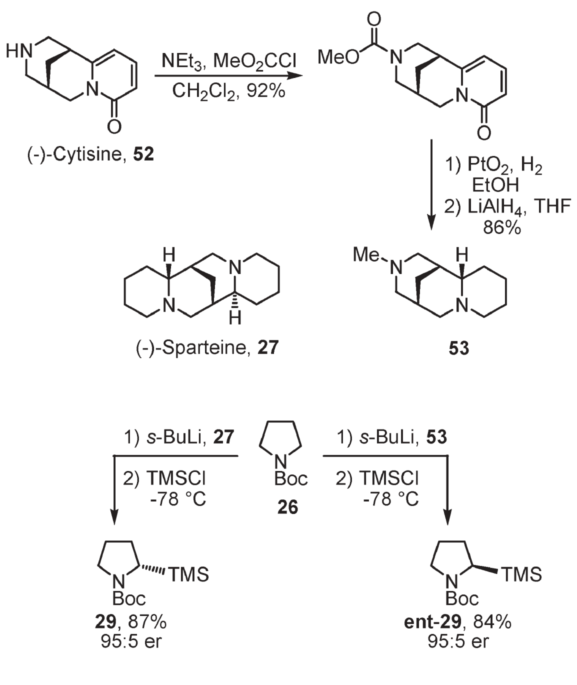
Substrate	Major product	E, % Yield, (er)
 **30**, 95:5 er		**39**, 50, (99 : 1) dr = 92 : 8
 35		$SnBu_3$, **40**, 70, (99 : 1) CO_2, **41**, 65, (99 : 1) Me, **42**, 52, (98 : 2) TMS, **43**, 70, (98 : 2)
 36		$SnBu_3$, **44**, 40, (94 : 6) TMS, **45**, 40, (93 : 7) $Ph_2C(OH)$, **46**, 50, (92 : 8) Me, **47**, 44, (92 : 8)
 37		**48**, 71, (93 : 7) dr = 90 : 10
 38		Bu_3Sn, **49**, 95, (94 : 6) dr = 95 : 5 TMS, **50**, 84, (92 : 8) dr = 93 : 7 Et, **51**, 71, (88 : 12) dr = 9 : 91

diastereoselectivity, which was in contrast to the selectivity observed when TMEDA was used.[4] The sparteine-mediated asymmetric deprotonation was also successfully demonstrated on several other nitrogen-containing heterocycles (Table 3);[6–9] however, the reaction did not proceed efficiently with *N*-Boc-piperidine, which has been explained computationally.[10] It is notable that the (−)-sparteine-mediated deprotonation of amine-borane **38** was achieved with good yield and high enantio- and diastereoselectivity. Surprisingly, a complete turnover in diastereoselectivity occurred when the electrophile was EtI.

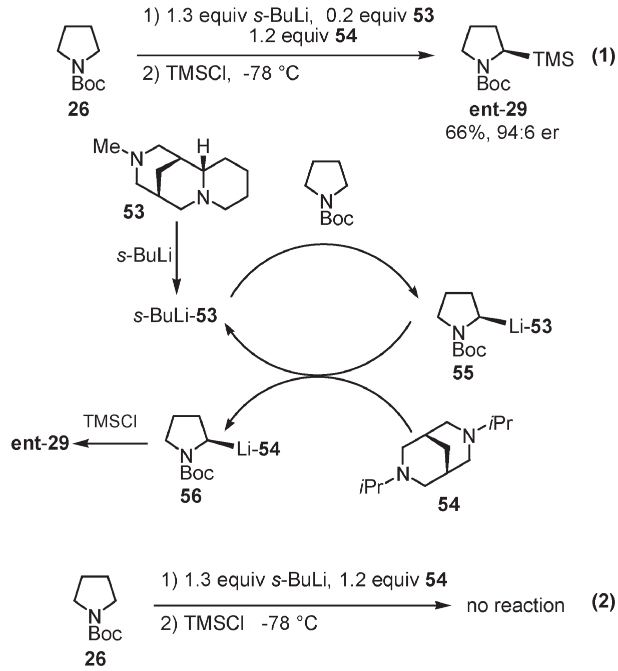
Despite its remarkable versatility, the primary liability of (−)-sparteine as a practical chiral ligand is the lack of availability of its enantiomer, which limits the range of any sparteine-related methodology to only one enantiomer. Several research groups have attempted to identify a chiral bidentate ligand which was readily synthesized in both enantiomeric forms to serve as a convenient surrogate of sparteine; however, successful application has been limited.[11,12]

O'Brien and co-workers recently reported that chiral diamine ligand **53** performed equally well as (−)-sparteine in the asymmetric deprotonation of **26**, but provided optically-enriched substitution products with the *opposite* sense of enantioselectivity.[13] Sparteine surrogate **53** was readily synthesized from (−)-cytisine (**52**) in excellent overall yield (Scheme 3).[14]

Even more remarkable was O'Brien's recent disclosure that the enantioselective deprotonation of *N*-Boc-pyrrolidine could be accomplished using only *catalytic* amounts of sparteine surrogate **53** when performed in presence of a "dummy ligand" such as bispidine **54** (Scheme 4, eqn. (1)). The authors suggested that deprotonation of *N*-Boc-pyrrolidine with alkyllithium/**54** was significantly slower than with alkyllithium/**53**; however, ligand exchange was rapid (Scheme 4). This extraordinary discovery not only provided convenient access to both enantiomers of substituted heterocycles using substoichiometric amounts of either (−)-sparteine or O'Brien's (+)-sparteine surrogate **53**, but also significantly expanded the scope of this ever-emerging area of research.



Scheme 3

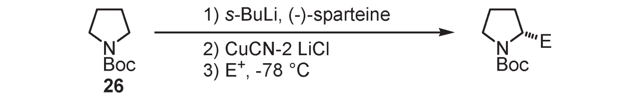


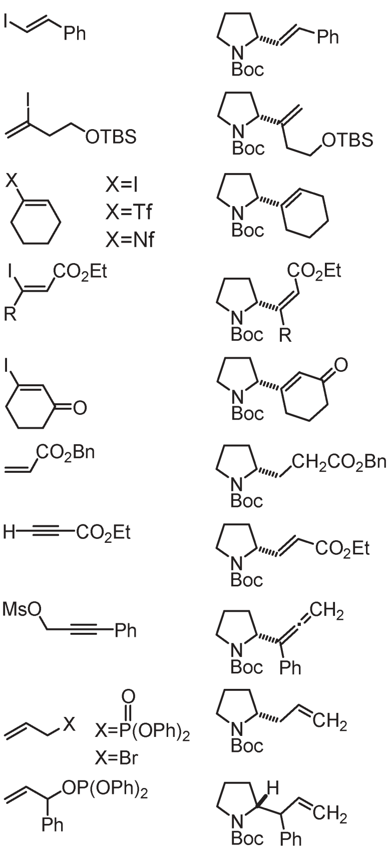
Scheme 4

Due to the configurational lability of α-aminocarbanions, such as **28**, **55**, and **56**, at temperatures above −50 °C, substitution reactions were limited to only the most reactive electrophiles such as TMSCl, Bu_3SnCl, CO_2, benzophenone and Me_2SO_4, as illustrated by the limited number of substituted products presented in Scheme 2 and Table 3. Dieter and co-workers expanded the scope of coupling partners that were compatible with this methodology through the transmetalation of **28** with copper.[15] As shown in Table 4, good yields and enantioselectivities were observed in coupling reactions with vinyl iodides, α,β-unsaturated ketones, propriolates, and propargyl mesylates; however, less reactive substrates such as acrylates afforded products in good yield, albeit with no enantioselectivity. Acid chlorides, enol triflates derived from β-ketoesters, and propargyl epoxides also have been effectively coupled *via* this method, but in racemic form.[16–18]

It is notable that allylic halides and phosphonates were effectively displaced in an S_N2 fashion to afford adduct **67** in high yield and good enantioselectivity.[19] Although the absence of diastereoselectivity in the displacement reflected the use of the racemic allylic phosphonate, employment of an enantiomerically enriched coupling partner could show increased selectivity. This methodology has also proven to be an effective method to α-aminoallenes such as **65**, which have recently been transformed into Δ^3-pyrrolines in good yield using $AgNO_3$ or $Ru_3(CO)_{12}$.[20] Dieter's demonstration that vinyl iodides can be coupled in an enantioselective manner to produce products **57**–**59** has been recently utilized in the synthesis of a variety of natural products including (−)-pyrrolam A (**68**),[21] pyrrolizidine and indolizidine alkaloids **73**–**75**,[22] and (+)-elaeokanine A (**78**, Scheme 5).[23]

Table 4 Asymmetric reaction of chiral α-(*N*-carbamoyl)alkylcuprates

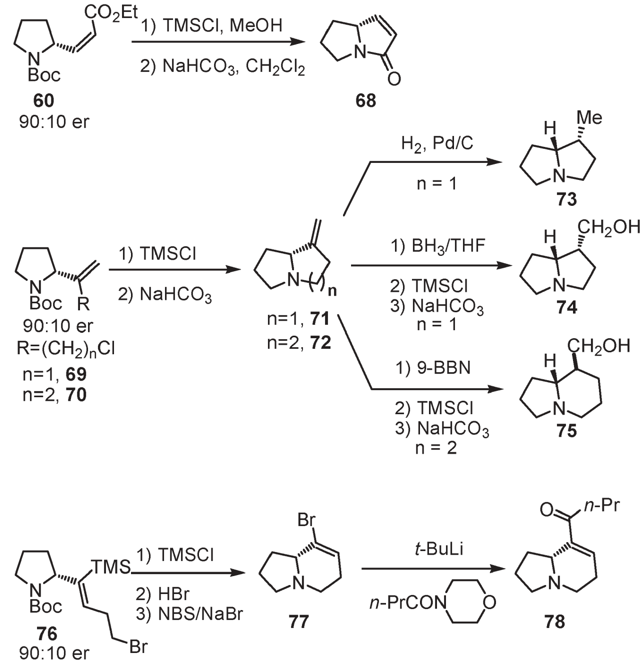




E^+	Product	% Yield (er)
I–CH=CH–Ph		**57**, 85 (90 : 10)
OTBS vinyl iodide		**58**, 84 (94 : 6)
X=I		**59**, 56 (72 : 28)
X=Tf		**59**, 65 (94 : 6)
X=Nf		**59**, 50 (92 : 8)
R = H		R = H, **60**, 89 (95 : 5)
R = *n*-Bu		R = *n*-Bu, **61**, 53 (91 : 9)
		62, 79 (80 : 20)
CO_2Bn	CH_2CO_2Bn	**63**, 95 (50 : 50)
H–≡–CO_2Et		**64**, 56 (72 : 28)
MsO, Ph	CH_2, Ph	**65**, 57 (65 : 35)
X=P(O)(OPh)$_2$	CH_2	**66**, 57 (90 : 10)
X=Br		**66**, 100 (89 : 11)
OP(OPh)$_2$, Ph	CH_2, Ph	**67**, 87 (85 : 15) dr = 56 : 44

Although transmetalation with copper did allow reaction with coupling partners that were not compatible with α-aminoorganolithium reagent **28**, the enantioselective variants of this methodology did not have enantiomeric ratios that were equivalent to those observed in Scheme 2, which suggests that the organocuprate may still be configurationally labile, albeit much less so than **28**.

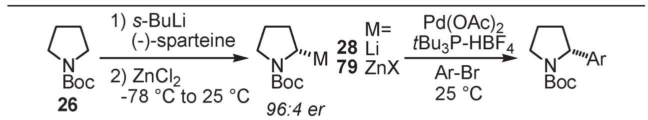
Recently, Campos and co-workers at Merck reported a configurationally stable organozinc species **79**, which was accessed *via* transmetalation of **28** with $ZnCl_2$. This species was coupled with a variety of aryl bromides using a palladium catalyst derived from *t*-Bu_3P (Table 5).[24] Reaction temperatures were as high as 60 °C, and the resulting 2-arylpyrrolidines were always obtained with an enantiomeric ratio of 96 : 4, which suggested that little to no racemization of **79** was occurring during the reaction. Moreover, the organozinc intermediate was compatible with acidic functionalities such as anilines and indoles, which would be unsuitable with the corresponding organolithium species. Since the stereogenic center adjacent to nitrogen was created during the deprotonation with s-BuLi/(−)-sparteine, the methodology consistently provides 2-arylpyrrolidines in an enantioselective manner, regardless of coupling partner. Although the configuration

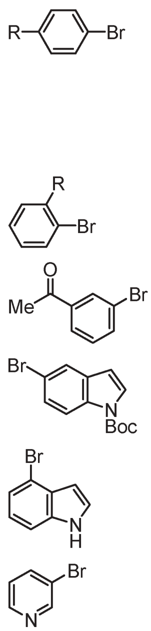


Scheme 5

stability of organozinc intermediate **79** was exploited in the enantioselective Pd-catalyzed arylation of *N*-Boc-pyrrolidine, it is likely that **79** could further expand the scope of potentially accessible 2-substituted pyrrolidines.

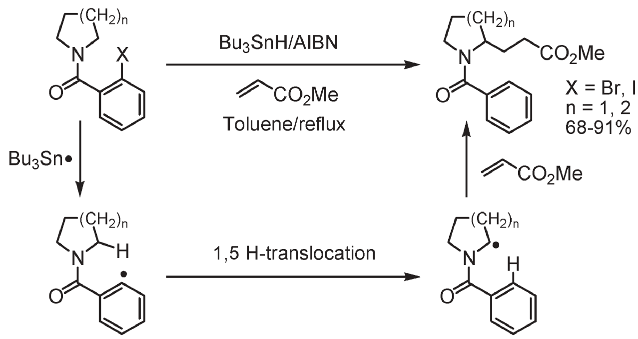
Table 5 Enantioselective, Pd-catalyzed α-arylation of **26**





Ar–Br		Product	% Yield (er)
R–C$_6$H$_4$–Br	R = H	**80**	82 (96 : 4)
	F	**81**	75 (96 : 4)
	NMe$_2$	**82**	78 (96 : 4)
	CO$_2$Me	**83**	81 (96 : 4)
	SO$_2$Me	**84**	87 (97 : 3)
	CN	**85**	80 (96 : 4)
	NH$_2$	**86**	70 (96 : 4)
2-R–C$_6$H$_4$–Br	R = Me	**87**	71 (96 : 4)
	OMe	**88**	72 (96 : 4)
		89	78 (96 : 4)
		90	81 (96 : 4)
		91	77 (96 : 4)
		92	60 (96 : 4)[a]

[a] Reaction was performed at 60 °C

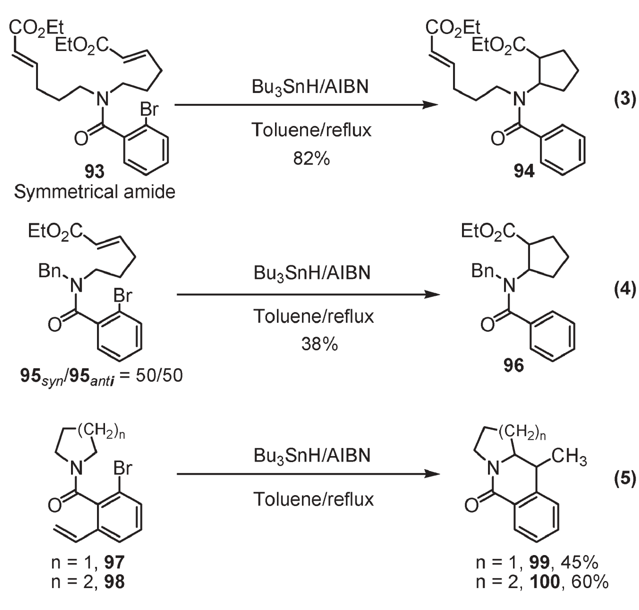


Scheme 6

3. Radical-based C–H activation

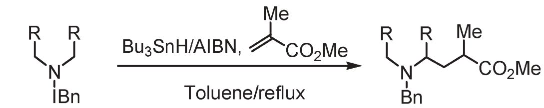
In recent years, activation of sp^3 C–H bonds has garnered much attention due to its high efficiency through the elimination of lengthy sequences to functionalize the coupling partners; however, early reports of the activation of sp^3 C–H bonds adjacent to nitrogen in heterocycles were accomplished through a clever prefunctionalization. Curran and Snieckus reported that radicals generated from *ortho*-halobenzamides undergo a 1,5-hydrogen atom transfer, cleanly producing an α-amino radical, which could be subsequently coupled to electrophiles such as methyl acrylate (Scheme 6).[25] The elegance of generating a carbon-centered radical at a remote position, in this case on a benzamide protecting group, and translocating it *via* 1,5-hydrogen atom transfer prior to the desired reaction constitutes an ingenious method to access α-amino radicals in nitrogen-containing heterocycles.

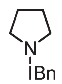
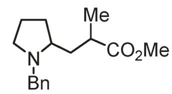
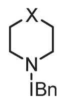
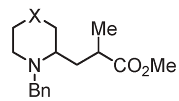
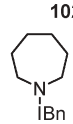
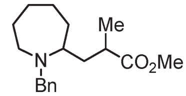
Intramolecular trapping of the resultant α-amido radical was also achieved when suitable electrophiles were appended to the termini of the amide (Scheme 7, eqn. (3)); however, due to the short solution lifetime of the carbon-centered radicals relative to amide rotamer interconversion (10^{-5} s *vs* 10^{-1}s), the ratio of amide rotamers in solution dictated the regioselectivity in non-symmetrical amide substrates such as **95** (Scheme 7, eqn. (4)). In contrast, intramolecular cyclizations were very effective for symmetrical benzamides possessing an appropriate electrophile on the aromatic ring such as **97** and **98** (Scheme 7, eqn. (5)). In these substrates, rapid rotation of the aromatic ring facilitated the capture of the α-amido radical before its demise, providing benzoindolizidinone **99** and benzoquinolizidinone **100** in good yield.



Scheme 7

Table 6 Radical homologation of nitrogen heterocycles

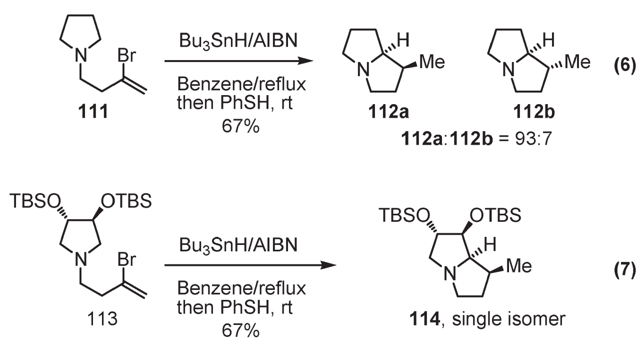


Precursor^a	Product		% Yield
 **101**		**104**	66
 **102a-e**		X = CH_2, **105** X = O, **106** X = S, **107** X = NCHO, **108** X = NMe, **109**	65 55 23 41 29
 **103**		**110**	55

^{a} IBN = 2-iodobenzyl

Undheim and co-workers applied this approach to *o*-iodobenzyl-protected amine heterocycles (Table 6), which not only eliminated the issue of hindered amide rotation, but also facilitated the mild deprotection of the resulting products *via* hydrogenolysis.[26] The 2-iodobenzylamines also generated a more reactive α-amino radical intermediate, which provided better yields and required fewer equivalents of electrophile than reactions performed with 2-iodobenzamides. Application of the methodology to more complex heterocyclic substrates led to lower yields due to competing reduction and telomerization products, which was attributed to destabilization of the α-amino radical.

Robertson and co-workers demonstrated that vinyl radicals also undergo 1,5-H atom translocation in nitrogen-containing heterocycles; however the resulting α-amino radical rapidly underwent intramolecular C–C bond formation with the pendant vinyl substituent (Scheme 8, eqn. (6), (7)).[27] This



Scheme 8

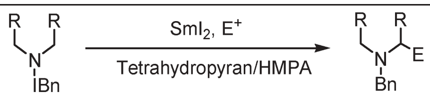
elegant cascade, radical translocation/cyclization was applied to the synthesis of pyrrolizidine alkaloids **112a** and **114** and truly displayed the power of this methodology to rapidly and efficiently build complex molecules. It is noteworthy that in the cyclization of **111**, the diastereoselectivity was remarkably high (93 : 7), and in the cyclization of **113**, only one isomer was observed.

Ito and co-workers have also developed a similar process to functionalize nitrogen heterocycles directly *via* 1,5-hydrogen atom translocation; however their method employed samarium diiodide as the reducing agent (Table 7).[28] The samarium and tin hydride approaches are complementary, affording direct functionalization adjacent to nitrogen *via* reaction with either carbonyl compounds or alkenes respectively. The authors proposed that the samarium-mediated mechanism proceeded *via* (i) deiodination of the 2-iodobenzyl group by SmI_2 to provide the aryl radical, (ii) intramolecular 1,5-hydrogen atom transfer to produce the α-amino radical, and (iii) single electron transfer of the α-amino radical by SmI_2 to afford the α-aminoorganosamarium anion. Nucleophilic addition of the α-amino organosamarium to a variety of different electrophiles, such as enolizable ketones, isocyanates, and isocyanides, delivered the expected products in good yield. The value of this chemistry is exhibited in the 3-component coupling of pyrrolidine **101** with 2,6-xylylisocyanide and cyclohexanone, delivering **118** in excellent yield (Table 7, entry 3). These conditions provide an alternative procedure for the metalation of nitrogen-containing heterocycles, which is typically carried out by deprotonation with alkyllithium/TMEDA as discussed in Section 2.

In contrast to the generation of an α-amino radical *via* 1,5-hydrogen atom transfer, two recently reported methods directly accessed the requisite N-heterocyclic radical intermediate. First, Yoshida's pioneering work in the area of "cation pool" chemistry was recently applied to radical mediated C–C bond forming reactions.[29] This process generated high concentrations of *N*-acyliminium carbocations such as **125** *via* low-temperature electrolysis of *N*-(methoxycarbonyl)pyrrolidine (**124**). Electrochemical reduction of **125** afforded α-amino radical **126**, which was readily trapped in the presence of electron-deficient olefins to produce C–C coupled products **128–131** in good yield (Table 8). This procedure was an adaptation of Yoshida's original "cation pool" coupling method, where cations such as **125** were generated and trapped directly (rather than being reduced to the radical) with variety of different nucleophiles such as allyl silanes, electron-rich aromatic rings, and 1,3- dicarbonyl compounds (Table 9).[30]

Secondly, Yoshimitsu and Nagaoka reported the direct activation of sp^3 C–H bonds to form α-amino radicals, which were trapped with aldehydes, in a variety of nitrogen-containing heterocycles (Table 10).[31] The authors proposed that an α-amino radical was produced when the substrate was subjected to BEt_3 in the presence oxygen and underwent irreversible addition to aldehydes, which was also promoted by BEt_3 (Scheme 9). In all of the examples reported, endocyclic C–H abstraction was preferred over exocyclic C–H abstraction with regioselectivities ranging from 5 : 1 to 9 : 1, presumably due to the release of steric strain as well as greater stabilization of the α-amino radical. Under a standard set of conditions, several electronically- and structurally-diverse, nitrogen-containing heterocycles provided the expected hydroxyalkylated product in good yield.

Table 7 Samarium-mediated homologation of nitrogen heterocycles



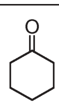
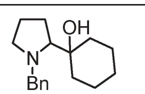
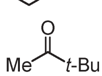
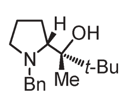
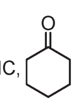
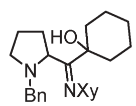
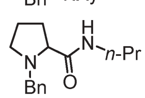
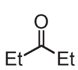
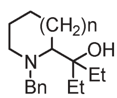
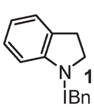
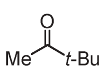
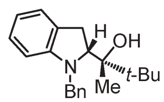
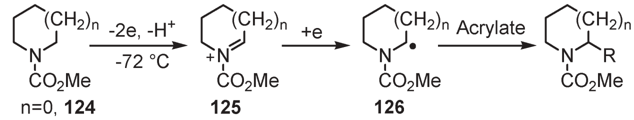
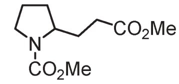
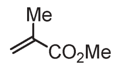
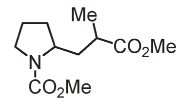
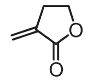
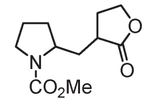
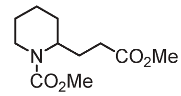
Precursor	E^+	Product		% Yield
101			**116**	63
101			**117**	87 dr = 95 : 5
101	2,6Xy-NC, 		**118**	70
101	*n*-PrNCO		**119**	67
101 **102a** **103**			*n* = 1, **120** *n* = 2, **121** *n* = 3, **122**	60 88 79
 **115**			**123**	68 dr = 95 : 5

Table 8 "Cation pool" based radical-mediated C–C bond formation

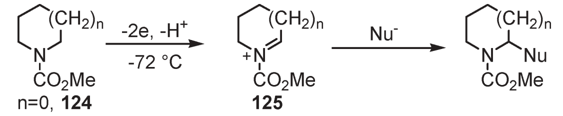


Precursor	Acrylate	Product		% Yield
124			**128**	84
124			**129**	77 dr = 59 : 41
124			**130**	78 dr = 74 : 26
127 n = 1			**131**	53

4. Transition metal-catalyzed C–H activation

Athough previous sections discussed methods which were pioneering studies in the area of sp^3 C–H bond activation of nitrogen-containing heterocycles, they all employed stoichiometric reagents to affect C–H activation (alkyllithium,

Table 9 "Cation Pool" based oxidative C–C bond formation



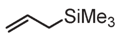
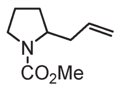
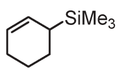
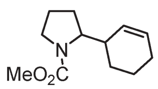
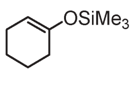
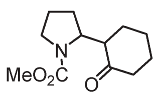
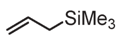
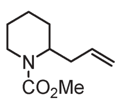
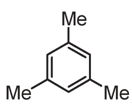
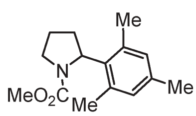
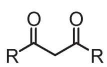
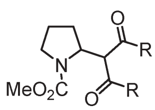
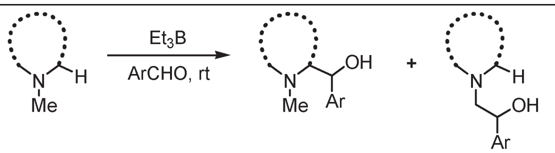
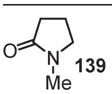
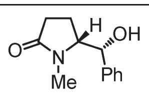
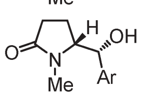
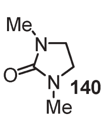
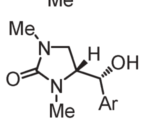
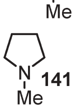
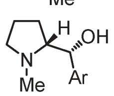
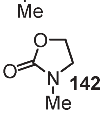
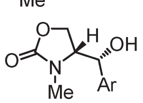
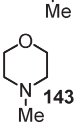
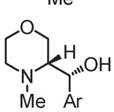
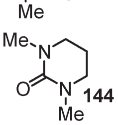
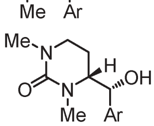
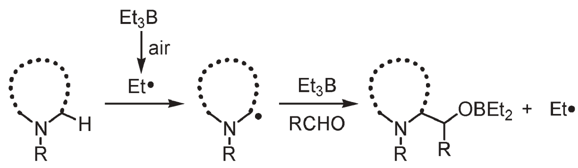
Precursor	Nu⁻	Product		% Yield
124			**132**	82
124			**133**	87
124			**134**	84
127 *n* = 1			**135**	64
124			**136**	72
124			R = Me, **137** R = OMe, **138**	71 46

Table 10 BEt_3-mediated radical hydroxyalkylation of N-heterocycles



Substrate	Aldehyde	Product		% Yield *endo* (*exo*)
	PhCHO		**145**	62 (9) dr = 67 : 33
139	4-MeOPhCHO		**146**	68 (7) dr = 68 : 32
	4-MeOPhCHO		**147**	75 (8) dr = 62 : 38
	4-MeOPhCHO		**148**	79 (5) dr = 58 : 42
	4-MeOPhCHO		**149**	38 (5) dr = 56 : 44
	4-MeOPhCHO		**150**	57 (11) dr = 52 : 48
	4-MeOPhCHO		**151**	72 (11) dr = 79 : 21

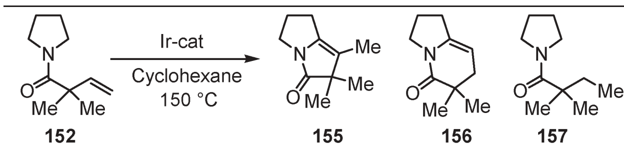


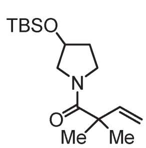
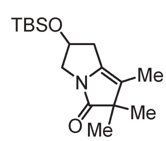
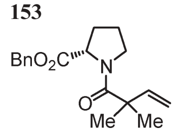
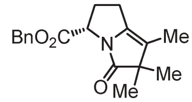
Scheme 9

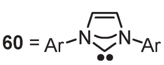
Bu_3SnH, SmI_2, or BEt_3). Despite the inherent difficulty in achieving *catalytic*, direct sp^3 C–H bond activation adjacent to nitrogen in heterocycles, several examples have been reported, which employ a variety of unique transition metal catalysts.

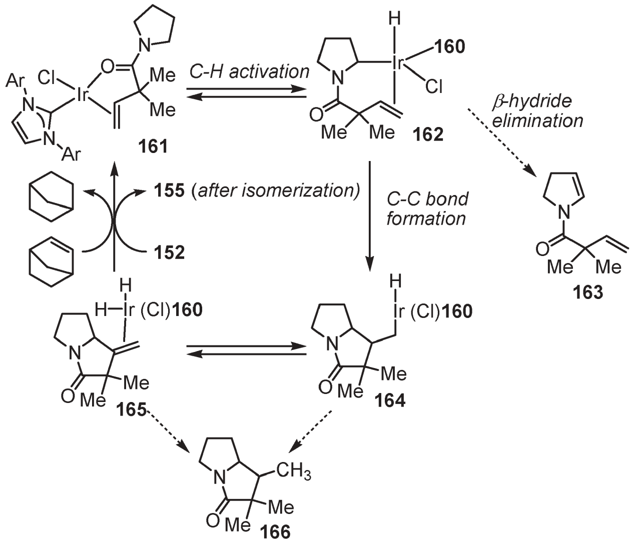
Sames and co-workers reported the iridium-catalyzed formation of pyrrolizidinone **155** from *N*-acylated pyrrolidine **152**, which relied on direct sp^3 C–H insertion adjacent to nitrogen followed by intramolecular C–C bond formation with an olefin tether.[32] Optimization studies of the iridium catalyst revealed that *N*,*N′*-bis-(2,6-diisopropylphenyl)imidazolyl carbene (**160**) provided the best yield and selectivity for the 5-*exo* cyclized product (**155**) over the 6-*endo* cyclized product (**156**, Table 11). Addition of norbornene to the reaction as a hydrogen acceptor further increased the yield by minimizing the formation of reduction side product **157**. Functionalized substrates **153** and **154** were also tolerated in the reaction, providing cyclized products **158** and **159** respectively in good yield. It is noteworthy that the stereogenic center in proline-derived substrate **154** was completely preserved during the its cyclization to **159**.

Table 11 Ir-catalyzed cyclization of alkene-amide substrates



Substrate	Catalyst	% Yield **155** : **156** : **157**
152	10 mol% $[Ir(COE)_2Cl]_2$ 20 mol% PCy_3	26 : 11 : 25
152	10 mol% $[Ir(COE)_2Cl]_2$ 20 mol% **160**[a]	41 : 4 : 41
152	10 mol% $[Ir(COE)_2Cl]_2$ 20 mol% **160** 4 equiv. norbornene	66 : 17 : 10
 **153**	5 mol% $[Ir(COE)_2Cl]_2$ 10 mol% **160** 3 equiv. norbornene	 **158**, 60%
153		**158**, 60%
 **154**, 99%ee	5 mol% $[Ir(COE)_2Cl]_2$ 10 mol% **160** 3 equiv. norbornene	 **159**, 46% (99% ee)
154, 99%ee		**159**, 46% (99% ee)

[a] **160** =  (Ar = 2,6-diisopropyl)



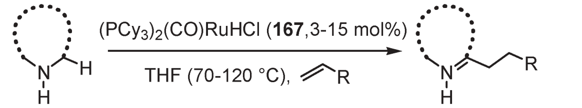
Scheme 10

The authors proposed that the catalytically-active species was [**160**–Ir–Cl]. This was supported by the synthesis and isolation of complex **161**, which was subjected to the reaction conditions to provide comparable yields and ratios of products **155**, **156**, and **157**. Moreover, **161** proved to be a competent catalyst in the reaction, delivering nearly identical yields and kinetics to that observed with the original catalyst system. Based on these results, the authors proposed the catalytic cycle presented in Scheme 10. The key intermediate in the proposed catalytic cycle is **162**, which favors alkene insertion to **164** over β-hydride elimination to **163**. One might argue that if intermediates **164** and **165** are indeed part of the catalytic cycle, one would expect to observe reduction product **166**; however no mention of its formation was reported in the manuscript.

Yi and co-workers reported a ruthenium-catalyzed dehydrogenative coupling of unprotected, secondary cyclic amines with alkenes.[33] The catalyst, $(PCy_3)_2(CO)RuHCl$ (**167**), selectively activated not only the sp^3 C–H bond adjacent to nitrogen but also the N–H bond, ultimately transforming the cyclic amines into 2-substituted cyclic imines (Table 12). When vinylsilanes were used, the *N*-silylated product was produced, and when piperidines were used, no reaction was observed.

Preliminary mechanistic investigations suggested that the key reaction intermediate was **179**, which underwent either C–H or N–H bond activation (Scheme 11). The authors proposed a catalytic cycle involving first an sp^3 C–H bond activation to form **180** followed by β-hydride elimination, to deliver cyclic imine **182**. Subsequent, imine-directed sp^2 C–H bond activation afforded **183**, which underwent alkene insertion to deliver the functionalized imine, **172**. Interestingly, in reactions performed with ethylene, which favor C–H activation over N–H activation of complex **179**, the evolution of ethane gas was detected. In contrast, reactions performed with vinylsilanes evolved ethylene gas, which was consistent with the proposed mechanism. The authors suggested that sterically demanding amines such as **169** experienced competitive reductive elimination *versus* N–H activation of intermediate **180**, which explained

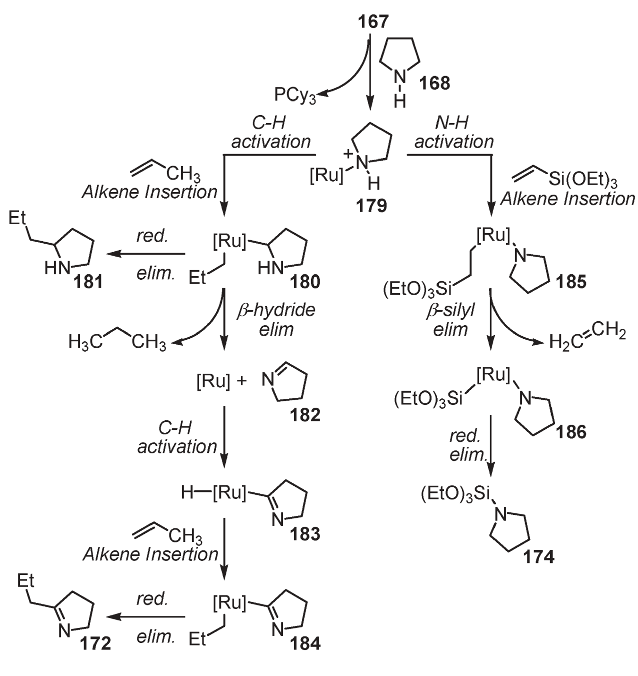
Table 12 Ru-catalyzed dehydrogenative coupling of cyclic amines and alkenes



Substrate	R	Product	% Yield
168	H CH_3 *t*Bu		**171**, 86 **172**, 51 **173**, 29
168	$Si(OEt)_3$		**174**, 88
169	H		**175/176**, 87 60 : 40
169	$Si(OEt)_3$		**177**, 88
170	H		**178**, 84

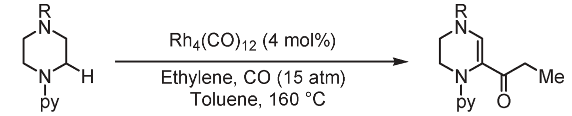
the observation of formal C–H insertion product **181**. This exciting discovery is one of a select few examples of direct C–H functionalization that do not require any directing group to affect the reaction.

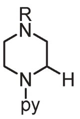
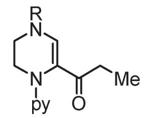
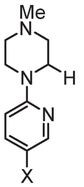
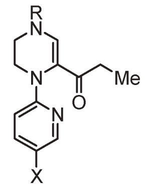
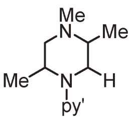
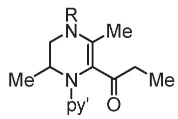
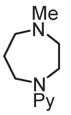
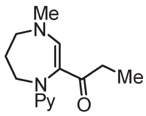
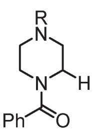
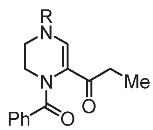
Murai has contributed extensively to the general area of transition metal-catalyzed C–H activation, and in 1997, first reported the rhodium-catalyzed carbonylation of *N*-(2-pyridinyl)piperazine (**187**) *via* sp^3 C–H bond activation to produce **197** (Table 13).[34] Several factors were found to be critical to the success of the reaction. First, the 1,4-relationship of the



Scheme 11

Table 13 Rh-catalyzed carbonylative coupling of piperazines with olefins



Substrate	R	Product	% Yield
	Me, **187** Bn, **188** Ph, **189** 4-MeOPh, **190**		**197**, 85 **198**, 44 **199**, 0 **200**, 37
	X = CO_2Me **191** X = CF_3 **192**		**201**, 93 **202**, 95
	**193**[a]		**203**, 52
	**194**		**204**, 65
	Me, **195** Bn, **196**		**205**, 89 **206**, 79

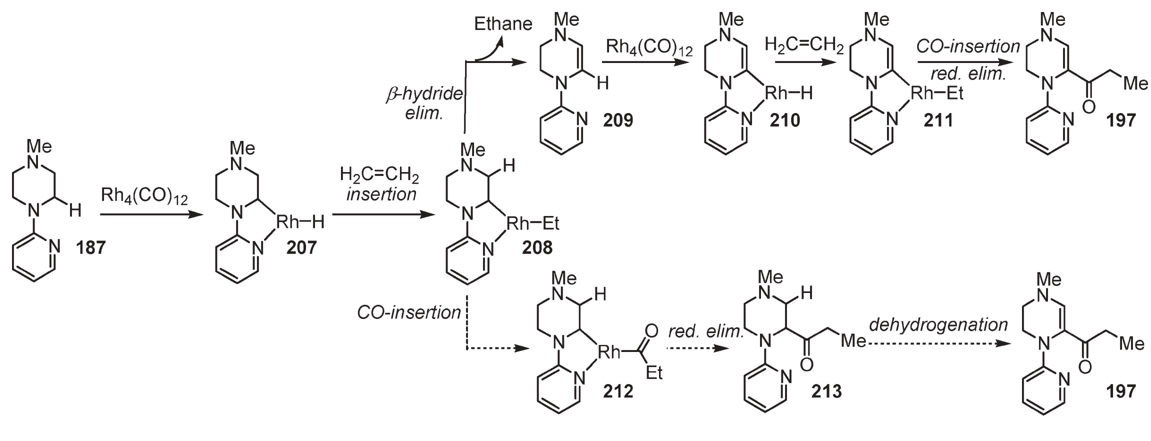
[a] py′ = 2-[5-(CO_2Me)pyridinyl]

amines in the piperazine core was essential for the reaction to proceed. Second, the reaction was strongly influenced by electronic perturbation of the substituents at both nitrogen termini: electronic donating groups were favored at the distal piperazine nitrogen, while electron-withdrawing groups on the pyridine enhanced reactivity. Finally, the 2-pyridinyl group was crucial to the success of the reaction; however Murai and co-workers have also accomplished the same transformation on *N*-acylpiperazines **195** and **196**, suggesting that other directing groups may also be effective.[35] Catalysts derived from other transition metals such as Co, Ru, and Ir were completely inactive.

The scope of the reaction was limited with respect to olefin coupling partner, affording good yields solely with ethylene. Mechanistic investigations revealed that ethylene was crucial for the conversion of **187** to the unsaturated tetrahydropyrazine **209**, which suggested that the process involved two steps: (i) Rh-catalyzed, pyridine-directed *dehydrogenation* of the piperazine *via* sp^3 C–H activation adjacent to nitrogen to form tetrahydropyrazine **209**, and (ii) Rh-catalyzed, pyridine-directed *carbonylation* of **209** *via* sp^2 C–H activation adjacent to nitrogen to produce **197** (Scheme 12). Alternatively, carbonylation would occur first to produce acyl piperazine **213**, and dehydrogenation would follow. In order to identify the correct mechanistic pathway, both **209** and **213** were independently synthesized and subjected to the reaction conditions. Reaction of **209** delivered **197** in 93% yield; however when **213** was subjected to identical conditions, a complex mixture of products was obtained, providing further evidence that **209** is likely an intermediate on the major mechanistic pathway.

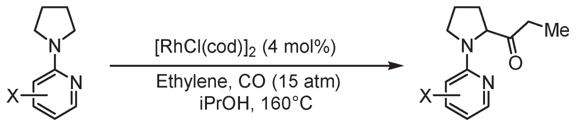
Murai also discovered a rhodium catalyst for the direct carbonylation at sp^3 C–H bonds adjacent to nitrogen in *N*-pyridyl pyrrolidines and related heterocycles (Table 14).[36] The initiation of this catalytic cycle was similar to that observed in Scheme 12; however in these examples, the CO-insertion pathway predominated over the β-hydride elimination pathway, which displayed the sensitivity of these types of reactions to the nature of the catalyst and substrate. Nevertheless, this report constituted the first effective example of carbonylation at sp^3 C–H bonds adjacent to nitrogen.

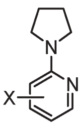
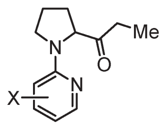
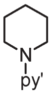
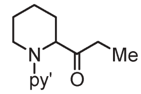
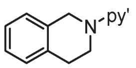
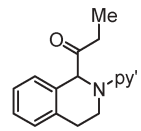
Lastly Murai disclosed a non-carbonylative coupling of sp^3 C–H bonds adjacent to nitrogen with alkenes using $Ru_3(CO)_{12}$.[37] Interestingly, this discovery was the result of an attempt at a Ru-catalyzed carbonylative coupling identical to the Rh-catalyzed version presented in Table 14. When carbonylative coupling of **214** was attempted with $Ru_3(CO)_{12}$ instead of $[Rh(cod)Cl]_2$, none of the desired carbonylated product **221** was observed; however, a new product was formed, which was identified as 2,5-dialkylated pyrrolidine **233**, isolated as a mixture of diastereomers (dr = 54 : 46). These conditions were found to be applicable to a variety of cyclic amines and alkenes, producing a range of disubstituted



Scheme 12

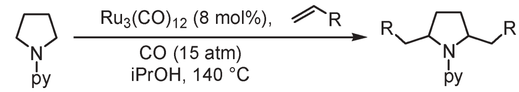
Table 14 Rh-catalyzed carbonylative coupling of heterocycles

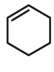
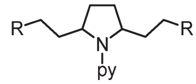
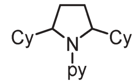
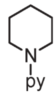
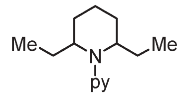
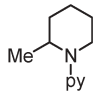
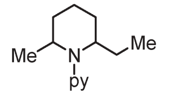
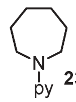
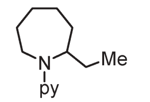
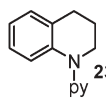
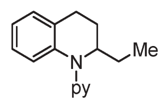
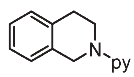
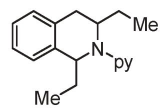
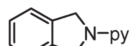
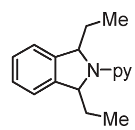


Substrate	R	Product	% Yield
	H, **214** 3-Me, **215** 5-Me, **216** 6-Me, **217** 5-CF$_3$, **218**		**221**, 68 **222**, 73 **223**, 84 **224**, 12 **225**, 15
	**219**[a]		**226**, 54
	**220**[a]		**227**, 73

[a] py′ = 2-[5-Me-pyridinyl]

Table 15 Ru-catalyzed coupling of cyclic amines with olefins[a]

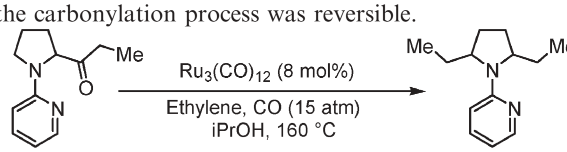


Substrate	R	Product	% Yield (dr)
214 **214** **214** **214** **214**	H *n*-Bu *t*-Bu Ph 	 	**233**, 92, (55 : 46) **234**, 53, (52 : 48) **235**, 73, (51 : 49) **236**, 58, (50 : 50) **237**, 33, (60 : 40) 39% mono
 **228**	H		**238**, 73, (60 : 40)
 **229**	H		**239**, 73, (63 : 37)
 **230**	H		**240**, 47 14% bis, (52 : 48)
 **231**	H		**241**, 73
 **220**	H		**242**, 85, (76 : 24)
 **232**	H		**243**, 90, (80 : 20)

[a] py = 2-pyridinyl

heterocycles; however when the steric bulk of either coupling partner was increased, the monosubstituted products predominated (Table 15, entries 5,8)

Although the precise mechanism of reaction was unclear, the authors proposed a similar mechanism very similar to that presented in Scheme 12; however with $Ru_3(CO)_{12}$ as catalyst, reductive elimination was preferred over either β-hydride elimination or CO-insertion. In an effort to understand why carbonylative coupling was not observed with $Ru_3(CO)_{12}$, 2-acylpyrrolidine **221**, which was produced using the Rh-catalyzed carbonylative coupling (Table 14), was subjected to the Ru-catalyzed reaction conditions (eqn. (8)). Remarkably, the major product from this reaction was **233**, indicating that the carbonylation process was reversible.



221 → **233**, 81% dr=66:34 (8)

5. C–H oxidations/oxidative couplings

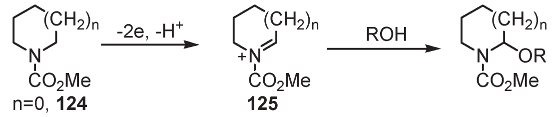
The transformations discussed in sections 1 through 4 of this review have covered methodologies in which the N-heterocycle participates primarily as the nucleophilic coupling partner. In contrast, in oxidative couplings the N-heterocycle acts as an electrophile. This section will cover the advances in direct C–H oxidation as well as C–H oxidative couplings.

One of the earliest methods was disclosed by Shono, which utilizes electrochemical, anodic oxidation of N-heterocycles to deliver the corresponding α-aminals in good yield (Table 16).[38,39] The mechanism is very similar to the anodic oxidation described in Section 3 (Table 9), which involves oxidation of **124** to *N*-acyliminium ion **125** and subsequent trapping with solvent. The most common application of this methodology has been towards the practical synthesis of 2-alkoxy-N-heterocycles (**244–249**), which are stable precursors to *N*-acyliminium ions and well-established as valuable synthons in organic chemistry.[40] Comprehensive reviews of the application of 2-alkoxy-N-heterocycles in organic synthesis have been reported.[41–43]

Weinreb and co-workers have developed a practical alternative to the electrochemical oxidation developed by Shono, which takes advantage of the 1,5-hydrogen atom transfer reviewed in Section 3.[44] Weinreb prepared a variety of 2-aminobenzamidyl heterocycles, and subjected them to sodium nitrite in the presence of copper(I) chloride in methanol, which consistently produced α-methoxybenzamides in good yield (Table 17). It was proposed that diazotization of the aniline, in the presence of copper(I), generated radical **259**, which underwent 1,5-hydrogen atom transfer (Scheme 13). The resulting α-amidylradical (**260**) was oxidized to the *N*-acyliminium ion **261** by copper(II), which was captured by methanol to provide α-methoxybenzamide **262**. This methodology has proven to be quite general, and was recently employed in a key transformation in the synthesis of Lepadiformine (**266**, Scheme 14).[45]

Katsuki and co-workers have recently reported an enantioselective sp^3 C–H oxidation of *meso*-pyrrolidine carbamates,

Table 16 Electrochemical oxidation of N-heterocycles



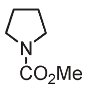
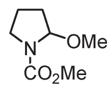
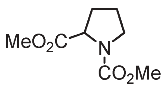
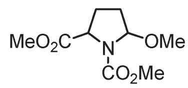
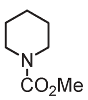
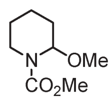
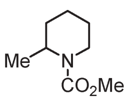
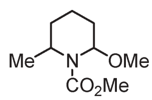
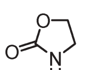
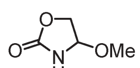
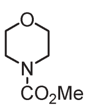
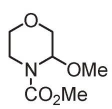
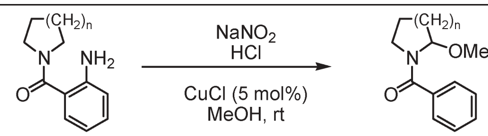
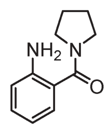
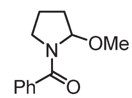
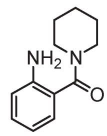
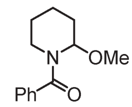
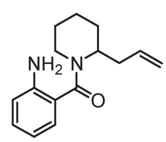
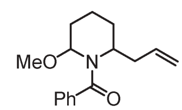
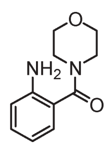
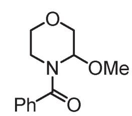
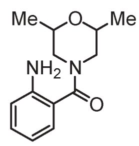
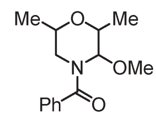
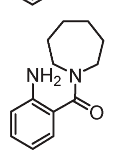
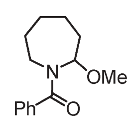
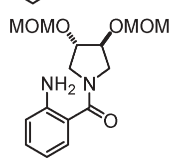
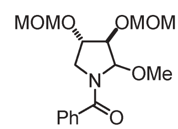
Precursor	Product		% Yield
		**244**	78
		**245**	87
		**246**	86
		**247**	69
		**248**	89
		**249**	55

Table 17 α-Methoxylation of cyclic secondary amides

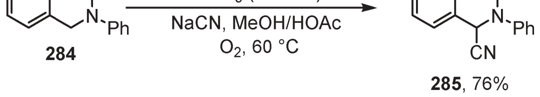


Precursor	Product		% Yield
		**250**	43
		**251**	69
		**252**	86
		**253**	68
		**254**	71
		**255**	73
		**256**	73

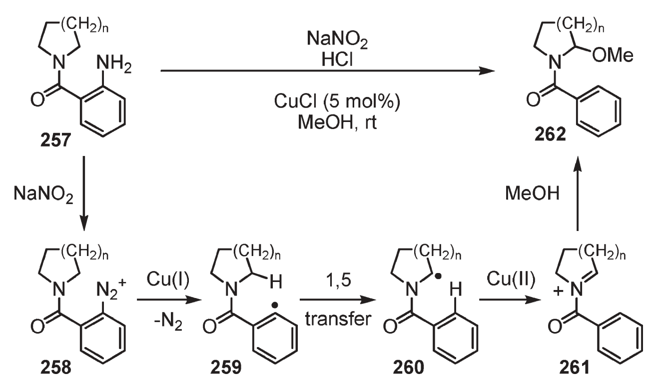
which employs manganese–Salen complex **266** (Table 18).[46] The intermediate aminals were oxidized to the corresponding amides *via* Jones oxidation, providing convenient access to several 2,3-disubstituted pyrrolidinones in good yield and enantioselectivity. Although no mechanistic insight was provided by the authors, the methodology was employed in the enantioselective synthesis of the natural product Swainsonine (**283**, Scheme 15).[47]

In all of the examples of C–H oxidation discussed so far, C–H activations of heterocyclic substrates have proceeded *via* an *N*-acyliminium ion, which was trapped by either methanol or water. The resulting stable intermediates have then been subjected to C–C bond forming reactions in a separate step. More recently, research groups have attempted to *directly* trap *N*-acyliminium ion intermediates with carbon nucleophiles, eliminating the isolation of the α-alkoxy intermediate. This oxidative coupling approach has been very successful with a variety of nucleophilic coupling partners, even in transition metal-catalyzed transformations.

In 2003, Murahashi and co-workers reported an oxidative cyanation of tertiary amines which employed $RuCl_3 \cdot nH_2O$ as the catalyst and oxygen as the stoichiometric oxidant.[48] Although most of the examples reported in this article were acyclic tertiary amines, of notable interest to this review was the effective oxidative cyanation of tetrahydroisoquinoline **284** to **285** under relatively mild conditions (eqn. 9).

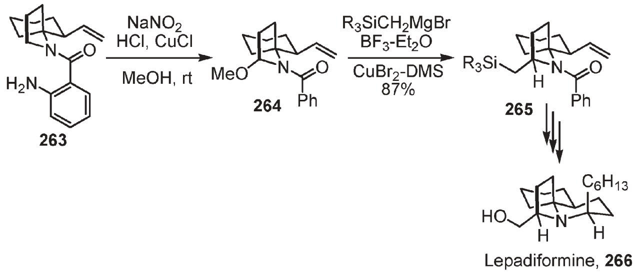


(9)



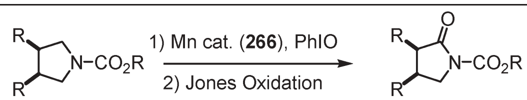
Scheme 13

Li and co-workers broadened the scope of this process, employing copper catalysts to affect the coupling of cyclic



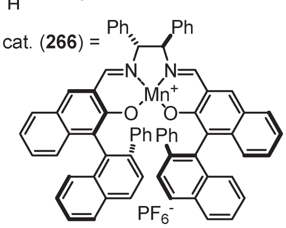
Scheme 14

Table 18 Enantioselective desymmetrization of *meso*-pyrrolidines

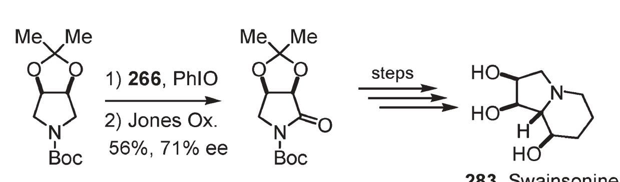


Substrate	% Yield (Product), % ee
267	29 (**274**), 64
268	70 (**275**), 88
269	51 (**276**), 63
270	57 (**277**), 82
271	48 (**278**), 75
272	35 (**279**), 79
273	68 (**280**), 76

[a] Mn cat. (**266**) =

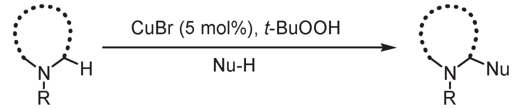


tertiary amines with a vast array of nucleophilic partners including alkynes,[49] nitromethane,[50] malonates and malononitrile,[51] indoles,[52] naphthols, and Morita–Baylis–Hillman (MBH) adducts (Table 19).[53] Although tetrahydroisoquinoline **284** was used most often as substrate, other cyclic amines were reported as well. The beauty of this work is that in every case,

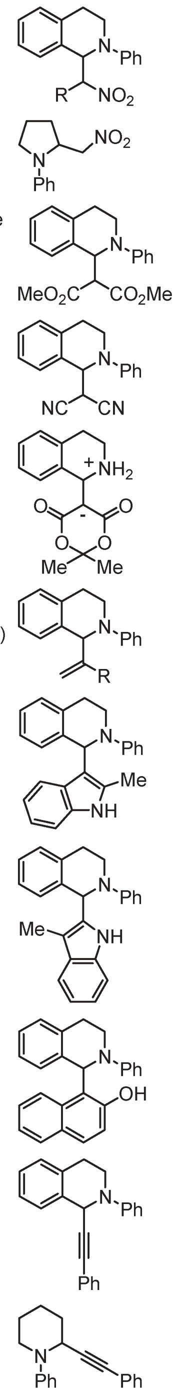


Scheme 15

Table 19 Cu-catalyzed cross-dehydrogenative couplings



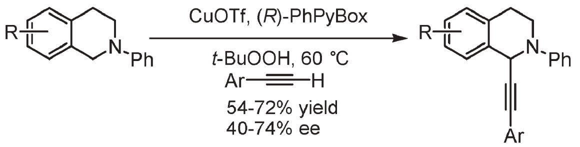
Substrate	R	Product	% Yield
284	$MeNO_2$, $EtNO_2$		R = H, **288**, 84[a]; R = Me, **289**, 69[a]
285	$MeNO_2$		**290**, 53[a]; 4% bis
284	MeO_2C–CH_2–CO_2Me		**291**, 74[a]
284	NC–CH_2–CN		**292**, 46[a]
286			**293**, 73[a]
284	DABCO (10 mol%)		R = Ac, **294**, 53[b]; R = CN, **295**, 61[b]
284			**296**, 80[b]
284			**297**, 95[b]
284			**298**, 63[b]
284	H–≡–Ph		**299**, 73[c]
287	H–≡–Ph		**300**, 12[c]



[a] Reactions were performed at 25 °C. [b] Reactions were performed at 50 °C. [c] Reactions were performed at 100 °C.

neither coupling component required prior functionalization. The authors note that the temperatures at which the reactions were run correlated well with the ease of activation of the reactive pronucleophile (*i.e.* $MeNO_2$, 25 °C; MBH/Friedel-Crafts, 50 °C, alkynes, 100 °C). This data suggests that the rate of formation of the iminium species was faster than the rate of activation of the nucleophile.

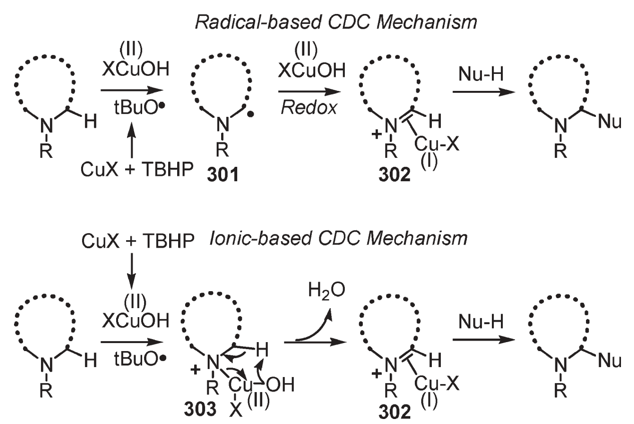
Of paramount importance to this review was Li's disclosure of the first enantioselective coupling of terminal alkynes with sp^3 C–H bonds adjacent to nitrogen in tetrahydroisoquinolines, which is catalyzed by pyridinyl bisoxazoline (PyBox)/copper(I) complexes (eqn. (10)).[54] This novel and important method provided access to several biologically important chiral tetrahydroisoquinoline alkaloids.



(10)

Based on literature precedent regarding oxidations of amines to iminium species, copper-catalyzed oxidative couplings with nucleophiles, referred to by Li as cross-dehydrogenative couplings (CDC), could proceed *via* either a radical-based mechanism or an ionic-based mechanism (Scheme 16). The radical mechanism would proceed *via tert*-butoxyl-mediated H-abstraction to generate carbon-centered radical **301**, followed by oxidation, presumably by copper, to iminium complex **302**. In the ionic mechanism, Lewis-acidic XCuOH species, generated *via* oxidation of CuX with TBHP, would coordinate to the amine to form complex **303**, which undergoes H-abstraction, generating the same iminium complex **302**, while also reducing Cu(II) to Cu(I). In both mechanisms, addition of nucleophiles to **302** would generate the CDC product, and release Cu(I) to complete the catalytic cycle.

The authors argued that the radical-based mechanism was not responsible for their reported CDC reactions on the basis that addition of two equivalents of 2,6-di-*tert*-butyl-4-methyl phenol (BHT), a well-known radical scavenger, to the CDC reaction of **284** with nitromethane did not impact the yield of the CDC product **288**. While this result may suggest an ionic mechanism, the authors could not rule out the possibility of *tert*-butylperoxy substituted intermediates. The authors commented that in order to fully understand the exact mechanism by which this powerful transformation proceeds, further studies were required.



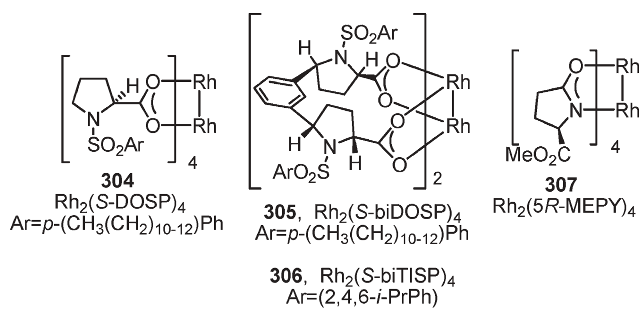
Scheme 16

6. Metal-catalyzed carbene insertions

By far the most exceptional example of metal-catalyzed sp^3 C–H bond activation adjacent to nitrogen in heterocycles was the intermolecular, asymmetric C–H insertion of aryldiazoacetates into cyclic *N*-Boc-protected amines, which was catalyzed by dirhodium tetraprolinate complexes **304–307** (Scheme 17). This powerful method was originally reported by Davies and co-workers for the highly regio-, diastereo-, and enantioselective C–H insertion of a range of aryldiazoacetates into *N*-Boc-pyrrolidine (**26**) catalyzed by chiral dirhodium complex **304** (Table 20).[55] Application of this method to cyclic amines of various ring sizes revealed the 5, 7, and 8-membered substrates worked very well, delivering C–H insertion products with a high degree of regio-, diastereo-, and enantioselectivity. In contrast, *N*-Boc-azetidines gave a complex mixture of products, and *N*-Boc-piperidine gave the expected C–H insertion products with good enantioselectivity but lower yield and diastereoselectivity.

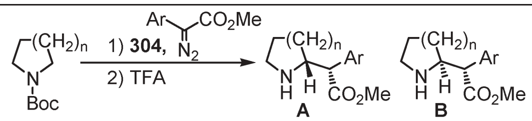
Competition studies between *N*-Boc-pyrrolidine and *N*-Boc-piperidine showed that C–H insertion was 20 times slower in the latter, and the authors proposed that although the axial C–H adjacent to nitrogen was in an electronically-favorable alignment, the chair conformation of the substrate produced a steric environment which was not favorable for the catalyst. This was in accord with the successful coupling of piperidine systems containing sp^2-hybridized centers, which were unable to adopt a well-defined chair conformation (Table 20).

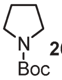
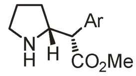
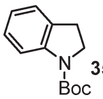
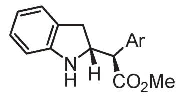
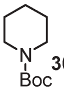
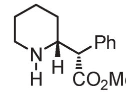
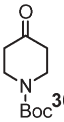
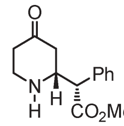
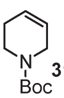
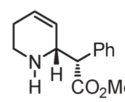
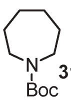
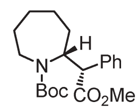
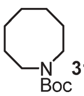
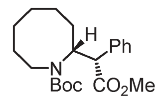
Nevertheless, the enantioselective C–H insertion of methyl phenyldiazoacetate with *N*-Boc-piperidine is an important reaction because it provides a direct route to *threo*-methylphenidate (Ritalin, **318**). Variation of the prolinate ligands in the catalyst revealed **305** as an improved catalyst for this important synthetic transformation, providing **318** in 73% yield (71 : 29 mixture of diastereomers) and 86% ee (eqn. (11)). The same reaction was also reported by Winkler and co-workers using Doyle's $Rh_2(5R\text{-MEPY})_4$ catalyst **307**, which afforded **318** with improved diastereoselectivity (97 : 3) but lower enantioselectivity (69% ee).[56] More recently, Davies' C–H insertion process was employed to produce a library of methylphenidate analogs for binding affinity studies at dopamine and serotonin transport sites.[57]



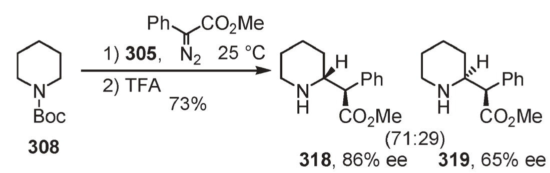
Scheme 17

Table 20 Rh-catalyzed C–H insertion of Boc-protected cyclic amines with methyl aryldiazoacetates



Substrate	Ar	Major Product	% Yield, (A : B, %ee A)
 **26**	Ph		**313**, 72 (96 : 4, 94)[a]
	p-ClPh		**314**, 70, (97 : 3, 94)[a]
	p-MePh		**315**, 67, (97 : 3, 93)[a]
	2-Nap		**316**, 49, (96 : 4, 93)[a]
 **35**	*p*-BrPh		**317**, 38, (>97 : 3, 90)[c]
 **308**	Ph		**318**, 44, (64 : 36, 89)[a]
 **309**	Ph		**319**, 46, (66 : 34, 88)[b]
 **310**	Ph		**320**, 63, (78 : 22, 80)[b]
 **311**	Ph		**321**, 72, (>95 : 5, 92)[b]
 **312**	Ph		**322**, 74, (>95 : 5, 90)[b]

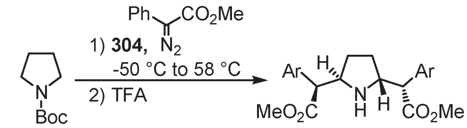
[a] Reaction was performed at −50 °C. [b] Reaction was performed at 25 °C. [c] Reaction was performed at 50 °C.



(11)

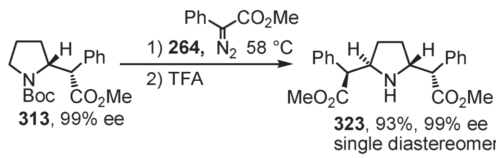
During the optimization of the enantioselective C–H insertion of methyl phenyldiazoacetate into *N*-Boc-pyrrolidine, Davies and co-workers discovered that monosubstituted product **313** could be resubjected to the very same reaction conditions to deliver C_2-symmetric, 2,5-disubstituted-*N*-Boc-pyrrolidine **323** in excellent yield and near complete diastereoselectivity (eqn. (12)). In contrast, subjection of **313** to the same conditions, but using *ent*-**304** as catalyst resulted in a complex mixture of diastereomers and/or regioisomers, highlighting the intrinsic mismatched pairing of catalyst and substrate. Through further development, a one-pot process for the synthesis of **313** from *N*-Boc-pyrrolidine was developed, which was generally applicable to a range of aryldiazoacetates, providing C_2-symmetric, 2,5-disubstituted-*N*-Boc-pyrrolidines **323–327** in good yield and very high enantioselectivity (Table 21).[58] It is interesting to note that the enantioselectivity observed in the ''iterative'' C–H activation

Table 21 One-pot, Rh-catalyzed formation of C_2-symmetric amines



Ar	% Yield, (%ee)
Ph	**323**, 78 (98)
p-ClPh	**324**, 50, (96)
p-MePh	**325**, 51, (96)
2-Nap	**326**, 62, (88)
p-MeOPh	**327**, 40, (97)

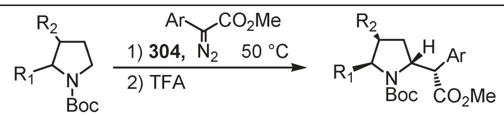
process was greater than the single C–H activation results shown in Table 20, emphasizing the double diastereoselective process that was occurring.

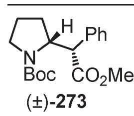
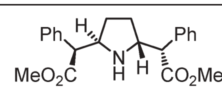
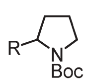
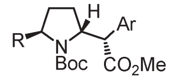
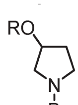
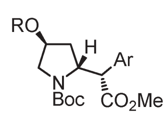


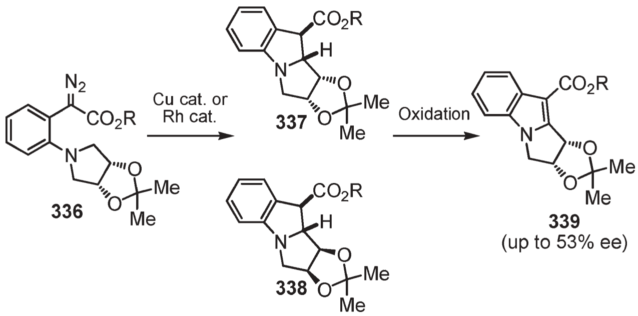
(12)

The inherent diastereofacial bias of catalyst **304** in 2-substituted *N*-Boc-pyrrolidine substrates was further exploited through the development of a kinetic resolution of racemic, 2- and 3-substituted pyrrolidines, to provide C–H insertion products in good yield (50% maximum) with a high level of both diastereo- and enantioselectivity (Table 22).[55,59] The clean synthesis of **325** is particularly noteworthy due to the presence of a total of 5 potential sites for C–H insertion (4 adjacent to nitrogen, 1 adjacent to oxygen. The TBDPS-protecting group plays a critical role in achieving selective functionalization at only one of these sites, presumably due to creation of a steric environment which is inaccessible by the catalyst. Indeed, similar substrates which contained smaller

Table 22 Rh-catalyzed kinetic resolution *via* C–H insertion in substituted *N*-Boc-pyrrolidines



Substrate	Ar	Major Product	% Yield, (% ee, dr)
 (±)-**273**	Ph		**323**, 45, (91, 97 : 3)
 R = CO$_2$Me (±)-**328**	*p*-BrPh		**332**, 66, (79, 94 : 6)
R = CH$_2$OAc (±)-**329**	*p*-BrPh		**333**, 62, (94, 89 : 11)
R = CH$_2$OTBDPS (±)-**330**	*p*-BrPh		**334**, 85, (98, 97 : 3)
 R = TBDPS (±)-**331**	*p*-BrPh		**335**, 64, (>99, 97 : 3)



Scheme 18

protecting groups, such as TMS, Ac, or Me, were not applicable to kinetic resolutions.

Sulikowski has also reported intramolecular variants of the C–H insertion approach on substrate **336** as a method to access 1,2-disubstituted mitosene **339**, which could prove useful in the synthesis of mitomycin and related natural products (Scheme 18).[60] In these examples, both Rh and Cu catalysts were employed to affect the C–H insertion; however the catalysts developed by Davies were not part of this study. Although the selectivities were modest, the overall efficiency of the reaction was high, affording the C–H insertion products **337** and **338** in >90 yield in most cases. All four possible isomers were separated, oxidized to mitocene **339** with DDQ, and assayed for ee. Surprisingly, all four isomers afforded different levels of enantioselectivity, ranging from 4% to 53% ee). It is possible that re-examination of this transformation with the current state of the art catalysts would provide improved selectivities.

7. Concluding remarks

Due to the importance of functionalized, nitrogen-containing heterocycles as both pharmaceutical agents and auxiliaries in asymmetric synthesis, direct functionalization of sp^3 C–H bonds adjacent to nitrogen continues to be a field of enormous potential. Although this conceptually represents the most direct method to access these privileged structures, very few are truly practical, scalable methods, and most have mainly remained academic. Only recently have research groups begun to report catalytic methods that affect this transformation, and of those reported, few achieve this in an enantioselective manner. Asymmetric, metal-catalyzed direct functionalization of nitrogen-containing heterocycles are the state of the art in C–C cross coupling reactions, and considerable development should be invested towards this goal. Direct functionalization of sp^3 C–H bonds in piperidine also remains one of the more challenging areas of research, which is of particular importance due to the prevalence of the 2-substituted piperidine core in both natural products and pharmaceuticals. The development of practical, general methods for the direct functionalization of nitrogen-containing heterocycles would have a tremendous impact on the way synthetic chemists approach the construction of complex targets; however more mechanistic insight is required in order to develop an appropriate process to effectively accomplish this challenging task. We hope that the concepts and results presented in this review serve as an effective point of entry into developing new methodologies that meet these criteria.

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