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Transition-metal-catalyzed α -alkylation of amines by $C(sp^3)$ -H bond activation

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Abstract

α -Substituted amines are present in a myriad of biologically active natural and synthetic products. With the objective of developing atom-economical reactions, a panel of synthetic methods allowing the direct functionalization of $C(sp^3)$ -H bonds adjacent to the nitrogen atom have been developed. The field remains dominated by the sequence α -lithiation/addition on an electrophile even if the use of reactive organolithium reagents is not compatible with all functional groups. Over the past ten years, an increasing interest has been devoted to metal-catalyzed C-H-activation, some studies being specially dedicated to $C(sp^3)$ -H bond activation. Notably, this approach has been envisioned to perform direct α -functionalization of amines. The aim of this article is to give an overview of synthetic methods for transition metal-catalyzed α -alkylation of amines by $C(sp^3)$ -H bond activation.

Keywords: amines; α -alkylation; $C(sp^3)$ -H activation; transition metals; directing group

Introduction

Both α -substituted cyclic and acyclic amines are ubiquitous moieties in natural and/or biologically active compounds. Particularly, α -alkyl cyclic amines are present in a wide array of natural alkaloids such as coniine or morphine. Inspired by Nature, medicinal chemists selected *N*-heterocycles as attractive scaffolds and, in this context, piperidine and pyrrolidine rings appears in the top 100 most frequently used rings in drugs listed in the FDA Orange book.¹ For example, methylphenidate is commercialized as concerta® by Janssen for hyperactivity troubles. In addition, α -alkyl acyclic amines are also present in a range of drugs such as strattera® (Lilly), which is used for the treatment of mental disorders (Figure 1).

Figure 1

Not surprisingly, a myriad of synthetic methods have been developed to access these motifs. Among them, one strategy based on the direct functionalization of C(sp³)-H bonds adjacent to the nitrogen atom is especially attractive.²³ The existing methods could be divided into five main reaction types: (1) oxidation leading to iminium intermediates, (2) α-lithiation, (3) generation of α-amino-radicals, (4) metal-catalyzed carbene insertion and (5) metal-catalyzed C-H functionalization (Scheme 1). In the latter case, a C(sp³)-H bond activation takes place, the term “C-H bond activation” meaning that a sigma C(sp³)-M bond is generated in one single step by cleavage of a C(sp³)-H bond.⁴

Scheme 1

The C-H activation step can proceed through different mechanisms such as a concerted oxidative addition, a sigma-bond metathesis or a base-assisted Concerted Metalation-Deprotonation (CMD).⁵

Concerted oxidative addition

σ-Bond metathesis

Carboxylate-assisted concerted metalation-deprotonation

Scheme 2

Importantly, the C(sp³)-H bond activation generally requires the presence of a directing group for both reactivity and selectivity issues.⁶ The directing group is in most cases a coordinating moiety such as a nitrogen-containing heteroaromatic, a carbonyl or an unsaturation. More

ephemerally, a C–halogen bond can act as a directing group. In this case, an oxidative addition of the metal catalyst into the C–halogen bond brings the metal close to the C(sp³)–H bond.

Herein, we present a review devoted to the α -alkylation of amines by transition metal-catalyzed C(sp³)–H bond activation.⁷ The methods are classified according to the nature of (a) the metal catalyst and (b) the nature of the directing group. For each method, details about the substrate scope, the limitations, the selectivity and/or the mechanism will be presented.^{8,9,10}

1- Ruthenium-catalyzed α -alkylation of amines

With a pyridinyl directing group

Direct ruthenium-catalyzed alkylation at the C(sp³)–H bond alpha to the nitrogen of acyclic amines was first described by Jun *et al.* in 1998 and was limited to benzylamines.¹¹ When *N*-benzyl,*N*-(3-methyl-2-pyridyl)amine **1.1** (1 equiv) was treated with an excess of hex-1-ene (5 equiv) in the presence of Ru₃(CO)₁₂ (10 mol %) in toluene at 130 °C for 6 h, the corresponding linear alkylated product **1.3** was isolated in 95% yield. The C3-methyl group on the pyridine was the key element as only traces of the alkylated product was observed when the methyl group was present at the C4- or C6-position or was replaced by a hydrogen. The presence of the methyl group at C3 slows down the free rotation of the benzyl group around the amine group, thus favoring special proximity between the C(sp³)–H bond and the ruthenium catalyst which was precoordinated to the nitrogen atom of the pyridine (Scheme 3).

Scheme 3

The method was extended to other terminal olefins. While excellent yield was obtained with non-hindered olefins (**1.8**, 93%), lower yields were observed with sterically hindered alkenes (**1.9**, 72% and **1.10**, 75%). The use of styrene resulted in 70% yield in **1.11** due to a competitive polymerization (Scheme 4).

Scheme 4

Surprisingly, when acyclic internal olefins were involved in this alkylation process, only linear products were formed and no branched alkylated compounds were detected. The formation of **1.3** from **1.1** and 3-hexene would result in an isomerization of a secondary alkyl-ruthenium complex to a primary alkyl-ruthenium as already described by Baxter *et al.* in the case of palladium and platinum complexes.¹² However, when cyclopentene and cyclohexene were utilized, the corresponding products **1.15** and **1.16** were respectively isolated in 70% and 60% yields (Scheme 5).

Scheme 5

When substrates **1.17** and **1.18**, bearing respectively a *para*-methoxy and a *para*-trifluoromethyl group on the phenyl ring of the benzylamine, were concurrently engaged in the reaction, products **1.19** and **1.20** were isolated in a 2.3:1 ratio in favor of the *para*-methoxy substituted compound (Scheme 6). This result suggested that the reaction was favored in the presence of an electron-donating group compared to an electron-withdrawing group, probably during the alkene insertion step.

Scheme 6

Three years later, compound **1.22** was isolated in 82% yield from **1.1** and ethylene (10 atm) by Murai *et al.* using similar reaction conditions [$\text{Ru}_3(\text{CO})_{12}$ (8 mol %), *i*PrOH, 140 °C].¹³ In this article,

the authors described the first direct ruthenium-catalyzed alkylation of cyclic amines. When pyrrolidine **1.23** was submitted to ethylene in the presence of additional CO (1 atm) and of the ruthenium catalyst, the carbonylated product was not detected but the di-alkylated pyrrolidine **1.24** was isolated in 92% yield with a 54:46 diastereoisomeric ratio. If the presence of CO was not essential (77% yield in its absence), the authors assumed that it could help to avoid the decomposition of the catalyst. Among the solvents screened, *i*PrOH was by far the solvent of choice (Scheme 7).

Scheme 7

When other alkenes (10 equiv), such as *n*-hexene, were involved in the reaction with **1.23**, a mixture of mono- and di-alkylation products **1.27** and **1.27'** was obtained and the use of a smaller amount of alkene did not allow the selective formation of the mono-alkylated products. Alkenes with an electron-withdrawing group or alkynes showed no reactivity. The reaction was then applied to *N*-pyridyl piperidine **1.25** leading to di-alkylated piperidine **1.28'** in 73% yield (dr = 60:40). When this alkylation process was attempted with azepane **1.26**, both mono-ethylation and di-ethylation products **1.29** and **1.29'** were isolated (**1.29**, 47% and **1.29'**, 14%, dr = 52:48), revealing that the reaction is more selective toward the mono-alkylation of larger rings (Scheme 8).

Scheme 8

To explain the role of *i*PrOH, the decomposition of the ruthenium-hydride intermediate **1.A** to a carbene complex **1.B** with the formation of dihydrogen was speculated. To avoid deactivation of the catalyst, *i*PrOH could act as a hydride donor and regenerate the active ruthenium hydride species (Scheme 9). This reversible process has already been observed with iridium complexes.¹⁴

Scheme 9

In 2012, when Maes *et al.* tried to alkylate *N*-pyridyl piperidine **1.30a** using the previously described conditions by Murai *et al.*, the 2-alkylated product **1.31a** and the unexpected piperidine **1.32** were isolated in a similar low 17% yield and **1.30a** was partially recovered (48%) (Scheme 10).¹⁵

Scheme 10

After an extensive optimization, the authors showed that the addition of a carboxylic acid [*trans*-1,2-Cy(COOH)₂ (4 mol %)] and an alcohol [2,4-dimethyl-3-pentanol (5 equiv)] were essential to reach high yields in the alkylated products. Under these optimized conditions [(1-hexene (10 equiv), $\text{Ru}_3(\text{CO})_{12}$ (4 mol %), 140 °C, 24 h)], the desired mono-alkylated piperidine **1.31a** (48%) was formed along with the di-alkylated product **1.33a** (43%, *trans/cis* = 1:1) (Table 1, entry 1). Other C4-substituted piperidines were successfully mono- and di-alkylated, the reaction being compatible with

ketal, ether and ester groups. However, mixture of diastereomers were obtained (Table 1, entries 2-3).

$ \begin{array}{c} \text{R}^1 \quad \text{R}^2 \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \quad \\ \text{H} \quad \text{H} \\ \quad \\ \text{N} \quad \text{Py} \\ \text{1.30a-1.30c} \end{array} + \text{1.2} \xrightarrow[140\text{ }^\circ\text{C, 24 h}]{\text{Ru}_3(\text{CO})_{12} (4\text{ mol \%}), \text{trans-1,2-Cy}(\text{CO}_2\text{H})_2 (4\text{ mol \%}), \text{2,4-dimethyl-3-pentanol (5 equiv)}} \begin{array}{c} \text{R}^1 \quad \text{R}^2 \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \quad \\ \text{N} \quad \text{Py} \\ \text{1.31a-1.31c} \end{array} + \begin{array}{c} \text{R}^1 \quad \text{R}^2 \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \quad \\ \text{N} \quad \text{Py} \\ \text{1.33a-1.33c} \end{array} $ <p>Py = 2-pyridyl</p>			
entry	1.30	1.31 (yield, dr)	1.33 (yield, dr)
1	<p>1.30a</p>	<p>1.31a (48%)</p>	<p>1.33a (48%, 1:1)^[a]</p>
2	<p>1.30b</p>	<p>1.31b (39%, 1:1)^[a]</p>	<p>1.33b (47%, 4:1:1)</p>
3	<p>1.30c</p>	<p>1.31c (32%, 1:3)^[a]</p>	<p>1.33c (53%, 4:1:1)</p>

[a] *trans/cis* ratio.

Table 1

The protocol was extended to 2-methylpiperidine **1.30d** (**1.35**, 78%, *trans/cis* = 5:3) and, for the alkylation of this compound, 3,4,5-trifluorobenzoic acid was chosen. After separation of the diastereomers, the *trans*-piperidine **1.35** was converted into (±)-solenopsin A, a natural alkaloid (Scheme 11).

Scheme 11

Further studies have been performed to gain a better understanding of the role of both carboxylic acid and alcohol during the alkylation process. Kinetic profiles revealed that the reaction was much faster in the presence of a carboxylic acid with no induction period. Most importantly, the acid additive was essential to reach full conversion of the starting material by preventing the catalyst deactivation (which occurs after approximately 6 h in the absence of a carboxylic acid). Interestingly, the authors have shown that, in the absence of acid catalyst, side reactions such as reduction of the alkene and alcohol oxidation to the corresponding ketone were favored against alkylation. Finally, when 2,4-dimethyl-3-pentanol was omitted or replaced by *tert*-BuOH, the mono-alkylated product was selectively formed albeit with poor yields. These observations led the authors to suggest that both *trans*-1,2-Cy(COOH)₂ and 2,4-dimethyl-3-pentanol were involved in the catalyst activation.

Thus, in the presence of a carboxylic acid additive, the catalytic cycle depicted in Scheme 12 was proposed by the authors. Intermediate Ru(0) complex **1.C** would first be formed by two successive coordinations (carbonyl group of carboxylic acid and hydroxyl group of the alcohol) favored by hydrogen bonding between the two entities. This interaction would then facilitate the oxidative addition of the ruthenium into the O-H bond of the alcohol and, after protonation of the alcohol, Ru(II) hydride complex **1.E** possessing a carboxylate ligand would be released. Subsequent alkene insertion would lead to complex **1.F** which would give, after coordination of amine **1.25** and C(sp³)-H bond activation following a CMD mechanism, the complex **1.G** and liberation of the carboxylic acid. As the last step, reductive elimination would furnish the mono-alkylated product (or the di-alkylated product after a second cycle) and regeneration of the Ru(0) complex.

Scheme 12

Another mechanism (Scheme 13) was also reported in the absence of a carboxylic acid additive. In this case, ruthenium alkoxide **1.H**, formed from **Ru(0)** complex by oxidative addition, would be the active catalyst. It could lead to the desired compound through a mechanism similar to the one described in Scheme 12, but the major pathway would involve a β -H elimination furnishing the dihydride ruthenium complex **1.I**. After alkene insertion and reductive elimination, the corresponding alkane would be released as well as the **Ru(0)** complex.

Scheme 13

Consecutive to this work, Maes *et al.* tried to expand their method to functionalized alkenes by using methyl vinyl ketone **1.36** (10 equiv) as the alkylating reagent.¹⁶ While no conversion of

piperidine **1.25** was observed under the previously optimized conditions, α,β -unsaturated ketone **1.37** was totally converted to butan-2-one (27%) as well as polymerized products. Replacing methyl vinyl ketone **1.36** by its dioxolane protected equivalent **1.38** revealed to be the solution (21% conversion of **1.25**) and, after an optimization of the reaction conditions [**1.38** (20 equiv), $\text{Ru}_3(\text{CO})_{12}$ (8 mol %), 3,4,5-trifluorobenzoic acid (7 mol %), 2,4-dimethyl-3-pentanol (40 equiv), 140 °C, 17 h], 90% conversion of **1.25** was obtained providing the desired mono-alkylated piperidine **1.39** and the di-alkylated piperidine **1.40** in 39% and 35% yields respectively. Once again, the carboxylic acid catalyst was essential to control the alkylation process by limiting the alkene reduction (Scheme 14).

Scheme 14

The scope of the method was then evaluated (Table 2). Piperidines substituted at C4 led to a mixture of mono- and di-alkylated products. Worthy of note, the reaction conditions are compatible with the presence of an ester moiety (Table 2, entry 1). For the C3-substituted piperidines, a regioselective mono-alkylation at the less hindered α position of the piperidine was observed and 2,5-disubstituted piperidines **1.41b** and **1.41c** were isolated in 63% and 75% yields respectively as a mixture of diastereoisomers (Table 2, entries 2-3). Both methyl and phenyl substituent at the C2 position were well tolerated since 2,6-disubstituted piperidines **1.41d** and **1.41e** were isolated in 84% and 82% respectively (Table 2, entries 4-5). Pseudo-allylic strain caused by the presence of the directing group on the nitrogen atom would push the C2-substituent of the piperidine to an axial position, and consequently, the *cis*-diastereoisomer was less stable than the *trans*-diastereoisomer. As a result, compounds **1.41d** and **1.41e** were formed as a 1:3 mixture of *cis/trans* diastereoisomers (Table 2, entries 4-5). Surprisingly, the hypothesis of a potential evolution of the *cis/trans* ratio over time through an hypothetical epimerization process was not discussed.

$ \begin{array}{c} \text{R}^1\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-N-Py} \\ \text{H} \quad \text{H} \\ \text{1.30c-1.30g} \end{array} + \begin{array}{c} \text{Me} \\ \text{1.38} \\ \text{(20 equiv)} \end{array} \xrightarrow[140\text{ }^\circ\text{C, 17 h}]{\begin{array}{c} \text{Ru}_3(\text{CO})_{12} \text{ (7 mol \%)} \\ \text{3,4,5-trifluorobenzoic acid (8 mol \%)} \\ \text{2,4-dimethyl-3-pentanol (40 equiv)} \end{array}} \begin{array}{c} \text{R}^1\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-N-Py} \\ \text{1.41a-1.41e} \end{array} + \begin{array}{c} \text{R}^1\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-N-Py} \\ \text{1.42a} \end{array} $		
Py = 2-pyridyl		
entry	1.30	1.41 (yield, <i>cis/trans</i>)
1	1.30c	1.41a (39%, 2:1)
2	1.30e	1.41b (63%, 1.7:1)
3	1.30f	1.41c (75%, 2.8:1)
4	1.30d	1.41d (84%, 1:2.8)
5	1.30g	1.41e (82%, 1:3.1)

Table 2

N-pyridyl pyrrolidines and azepanes were successfully alkylated under the reaction conditions and, once again, the greater reactivity of smaller rings *versus* larger rings (pyrrolidine > piperidine > azepane) was highlighted (Table 3).

$ \begin{array}{c} \text{Ru}_3(\text{CO})_{12} \text{ (7 mol \%)} \\ \text{3,4,5-trifluorobenzoic acid (8 mol \%)} \\ \text{2,4-dimethyl-3-pentanol (40 equiv)} \\ \hline 140^\circ\text{C, 17 h} \end{array} $			
	1.23-1.26 Py = 2-pyridyl	1.38 (20 equiv)	1.43a-1.43b 1.44a-1.44b
entry	1.23-1.25	1.43	1.46 (yield, <i>cis/trans</i>)
1	 1.23	 1.43a (46%)	 1.44a (38%, 3.8:1)
2	 1.26	 1.43b (34%)	 1.44b (15%, 2:1)

Table 3

Interestingly, a challenging substrate such as the bicyclic amine **1.45** was compatible with the reaction conditions furnishing **1.46** in 47% yield. (Scheme 15).

Scheme 15

Further transformations were then realized to underline the synthetic utility of this alkylation process. The pyridine directing group was efficiently removed by using mild reaction conditions (MeOTf then NaBH₄) and, for example, piperidine **1.47** was isolated from **1.39** in 72% overall yield. The treatment of **1.39** under catalytic acidic conditions delivered ketone **1.48** in 93% yield (Scheme 16).

Scheme 16

In order to develop milder conditions for the α-alkylation of amines, Ackermann *et al.* reported a ruthenium(II)-catalyzed C(sp³)-H alkylation of pyrrolidines. The treatment of an excess of pyrrolidine **1.23** (3 equiv) with 1-decene (1 equiv) in the presence of [RuCl₂(PPh₃)₃] (5 mol %), BINAP (6 mol %) and AgOTf (12 mol %) in *i*-BuOH at 120 °C for 18 h was found to be effective. Under these conditions, only the mono-alkylated pyrrolidine **1.49** was formed in 73% isolated yield (Scheme 17).¹⁷

Scheme 17

The influence of substituents of the pyridine ring on the alkylation process was then examined. While the presence of a methyl group at the C6-position was detrimental to the reaction (**1.51a**, 1%), both electron-donating (Me, OMe) and electron-withdrawing (F, CF₃) groups at the C5-, C4- or C3-position delivered the expected mono-alkylated pyrrolidines **1.51b-1.51f** (64-94%). Interestingly, treatment of pyrrolidine **1.50g**, bearing an isoquinoline as the directing group, also gave the expected product **1.51g**, albeit in a lower 67% yield (Scheme 18).

Scheme 18

The alkylation of 3-methyl-2-(pyrrolidin-1-yl)pyridine **1.50b** using a broad variety of terminal alkenes was then explored, compounds **1.53a-1.53h** being isolated with good to excellent yields (40-90%). Notably, valuable functional groups such as silane, ketone, methoxy or tosylate were well tolerated. This alkylation process proved to be highly chemoselective since alkenes incorporating a methoxy group, a tosylate or a halide delivered the expected products **1.53b-1.53d** in 60-86% yield and no undesired nucleophilic substitution on the carbon bearing a OMe, OTs group or a Cl, Br atom was observed providing that the aprotic dichloroethane was used as the solvent. The reaction also tolerated the presence of a ketone (**1.53f**) and styrene derivatives led to the expected pyrrolidines **1.53g-1.53h** with 65% and 73% yield respectively (Scheme 19).

Scheme 19

A limitation was encountered with 2-methylpyrrolidine **1.54** since the alkylated product **1.55** was formed in a low 7% yield (Scheme 20).

Scheme 20

Some investigations were performed to gain a better insight into the mechanism of the alkylation. The reaction was not inhibited in the presence of a radical scavenger [TEMPO (3 equiv)], indicated that no radical pathway was involved. Moreover, deuterium incorporation studies suggested that the C(sp³)-H bond cleavage was not the rate determining step.

The removal of the pyridyl directing group was achieved by platinum-catalyzed hydrogenation followed by hydride reduction (**1.56**, 61%) (Scheme 21).

Scheme 21

In summary, an intensive work has been achieved in the field of *N*-pyridyl directed α -alkylation of cyclic amines. The catalytic system based on a [Ru(II)] complex developed by Ackermann et al.

proved particularly attractive since it allows the selective monoalkylation of pyrrolidines with high yields.

Without any directing group

Pyrrolidine **1.57** was found to direct C(sp³)-H bond activation α to the nitrogen. Indeed, in 2004, Yi *et al.* described a coupling reaction between pyrrolidine **1.57** (1 equiv) and ethylene (6 equiv) catalyzed by RuHCl(CO)(PCy₃)₂ (5 mol %) in THF at 80 °C for 24 h.¹⁸ Under these conditions, cyclic imine **1.61a** was isolated in a moderate 61% yield (Table 4, entry 1). In addition, the scope of the reaction was quite limited. Hindered alkene such as 3,3-dimethyl-1-butene gave a mixture of cyclic imine **1.61b** and mono-alkylated pyrrolidine **1.62b** (29% GC yield, **1.61b**/**1.62b** = 55:45) (Table 4, entry 2). If 2-methyl-pyrrolidine **1.58** and eight-membered cyclic amine **1.59** gave the desired cyclic imines **1.61c** (84% GC yield) and **1.61d** (76% GC yield) (Table 4, entries 3-4), a mixture of both **1.61e** and **1.62e** was obtained when azepane **1.60** was engaged in the reaction (51%, **1.61e**/**1.62e** = 60:40) (Table 4, entry 5). No rationalization of the difference of reactivity between seven- and eight-membered rings was proposed. Surprisingly, no conversion was observed with piperidine.

entry	1.57-1.60	alkene	1.61 (+ 1.62)	1.61/1.62	yield
1		H ₂ C=CH ₂		100:0	86% ^[a] , 61% ^[b]
2			+	55:45	29% ^[a]
3		H ₂ C=CH ₂			84% ^[a]
4		H ₂ C=CH ₂			76% ^[a]
5		H ₂ C=CH ₂	+	60:40	87% ^[a] , 51% ^[b]

[a] GC yield. [b] Isolated yield.

Table 4

With these results in hand, efforts have then been made to gain a better understanding of the nature of ruthenium active species and a possible catalytic cycle, described in Scheme 22, was proposed by the authors. Coordination of the nitrogen to the ruthenium center would first form

complex **1.K**. A subsequent C(sp³)-H bond cleavage followed by alkene insertion would generate intermediate **1.M**. The formation of ethane during the reaction led the authors to suppose that complex **1.M** would then undergo dehydrogenation followed by C(sp²)-H imine bond activation to produce ruthenium hydride **1.O**. After alkene insertion and reductive elimination, cyclic imine **1.Q** would be released. In particular cases, e.g. hindered alkenes or large rings, dehydrogenation from the dialkylruthenium **1.M** can be slow down thus favoring direct reductive elimination to form mono-alkylated product **1.R**.

Scheme 22

2- Iridium-catalyzed α -alkylation of amines

With a pyridinyl directing group

In 2011, Shibata *et al.* reported the first iridium-catalyzed enantioselective C(sp³)-H alkylation of acyclic amines with alkenes using a pyridine as a directing group.^{19,20,21} When 2-(ethylamino)pyridine **2.1** (1 equiv) and styrene (8 equiv) were stirred in DME at 75 °C for 48 h in the presence of cationic iridium complex [Ir(cod)₂]⁺BF₄⁻ (10 mol %) and (*S*)-TolBINAP (10 mol %), the enantio-enriched amine **2.2** was isolated in 76% yield and with good enantioselectivity (ee = 88%) (Scheme 23). While quinoline was as effective as pyridine to direct the alkylation, other nitrogen-containing heterocycles (pyrimidine, pyrazine, substituted pyridines) gave lower yields and/or enantiomeric excess (data not shown). It is worth mentioning that these conditions involving an iridium catalyst are milder than those using a ruthenium catalyst.

Scheme 23

Two sets of reaction conditions (methods A and B) differing from the amount of alkene, time and temperature were then used to alkylate 2-(ethylamino)pyridine **2.1** with a variety of alkenes. The electronic and steric properties of styrene derivatives do not seem to have a significant influence on the yield nor on the enantiomeric excess of the alkylated amine **2.1** (Table 5).

Alkene 2.3	Ar	2.4 (yield %)	<i>ee</i> (%)
2.3a	4-MeO-C ₆ H ₄	2.4a (76)	87
2.3b	4-F-C ₆ H ₄	2.4b (60)	87
2.3c	3-Br-C ₆ H ₄	2.4c (83)	90
2.3d	2-Br-C ₆ H ₄	2.4d (76)	86

Table 5

Functionalized alkenes such as acrylate derivatives or vinylsilanes also reacted with amine **2.1** to give the expected products **2.6a-2.6d**. Interestingly, allyltriphenylsilane as well as 1-phenyl-but-1,3-diene were suitable coupling partners (Scheme 24).²²

Scheme 24

The influence of the length of the alkyl chain of the amine partner was also investigated. Even if higher time and/or higher temperature were required, alkylation of compounds **2.7a-2.7c** proceeded smoothly in the presence of styrene (**2.8a-2.8c**, 58-69%, 73-86% *ee*) (Table 6, entries 1-3). However, no conversion of hindered amines, such as **2.7d**, was observed under the same conditions (Table 6, entry 4).

entry	T (°C)	R	2.7	2.8 (yield %)	ee (%)
1	85	CH ₂ CH ₃	2.7a	2.8a (69)	83
2	85	(CH ₂) ₂ CH ₃	2.7b	2.8b (58)	86
3	95	(CH ₂) ₄ CH ₃	2.7c	2.8c (60)	73
4	135	CH(CH ₃) ₂	2.7d	2.8d (0)	-

Table 6

Removal of the pyridyl group of **2.4a** (87% ee) was then successfully conducted with good yield (81%) and without a loss of enantiomeric excess (87% ee) (Scheme 25). At this stage, the absolute configuration of **2.9** could be determined and appeared to be (*S*).

Scheme 25

According to the authors, the steric differentiation occurred during the cleavage of the C–H bond. The presence of an enantiopure ligand on the metal center induces the enantioselectivity delivering a (*pro-S*) or (*pro-R*) iridium hydride. After alkene insertion and then reductive elimination, an optically enriched (*S*)- or (*R*)-amine can be obtained.

Very recently, Nishimura *et al.* extended the iridium-catalyzed C(sp³)–H alkylation to 3-carbonyl-2-(alkylamino)pyridines **2.10a–2.10d**.²³ The main advantage of this method is based on the significant decrease in the quantity of alkene (2 equiv instead of 8 equiv in the case of 2-aminopyridine) and the absence of external ligand. The conformational rigidity of substrates of type **2.10**, due to hydrogen bonding between the oxygen of the carbonyl group and the NH group, could favor the right conformation leading to a more rapid C(sp³)–H bond activation.

The reaction proved quite general. A myriad of 3-carbonyl-2-(alkylamino)pyridines bearing different amido groups were alkylated in the presence of styrene (2 equiv) under the developed conditions {[IrCl(cod)]₂ (10 mol %), NaBAR^F₄ (Ar^F = 3,5-(CF₃)₂C₆H₃) (10 mol %), dichloroethane, 80 °C, 20 h}. Notably, the presence of a primary amide or an ester at the C3 position of the pyridine was also compatible (**2.11a–2.11d**, 88–92%) (Scheme 26).

Styrene derivatives, simple terminal alkenes as well as allylic alcohols also proved to be good partners in the alkylation process. Notably, the use of an enyne delivered the alkylated product **2.12d** in 76% yield. Limitations were reached with *iso*-butylvinyl ether and *t*-butyl acrylate since a mixture of linear and branched products were formed (**2.12e-f** and **2.13e-f**) (Scheme 27). Moreover, cyclopentene and 1,1-diphenylethylene were found to be inactive.

Removal of the pyridinyl directing group was achieved by formation of a carbamate followed by *N*-methylation of the pyridine and subsequent cleavage of the pyridium intermediate.²⁴ Thus, carbamate **2.14** was obtained in three steps from **2.11a** with an overall yield of 61% (Scheme 28).

Scheme 28

A classical catalytic cycle (coordination, oxidative addition, alkene insertion and reductive elimination) was then postulated by the authors. Deuterium-labeling experiments have indicated that both C(sp³)-H bond cleavage and alkene insertion were reversible steps.

With a benzoxazole directing group

The methods developed by Shibata and Nishimura suffer from one drawback since tertiary amines could not be alkylated. To circumvent this limitation, Opatz *et al.* developed new conditions to perform racemic iridium-catalyzed C(sp³)-H alkylation of tertiary amines with alkenes using a BenzOxAzol-2-yl (BOA) moiety as a directing group.²⁵ Acyclic amine **2.15** (1 equiv) was treated with ethyl acrylate (8 equiv) in the presence of [Ir(cod)₂]BARF (BARF = tetrakis(3,5-trifluoromethylphenyl)borate) (7 mol %) in DME at 85 °C, the mono-alkylated product **2.16** was isolated in 64% yield. Using hex-1-ene as the coupling partner also delivered the expected product **2.18** albeit in a moderate 53% yield. Worthy of note, no conversion was observed with the dimethyl analog **2.19** (Scheme 29).

Scheme 29

The method was extended to cyclic secondary amines such as piperidine **2.21**, which was transformed to the mono-alkylated piperidines **2.22a-2.22d** with moderate yields (39-57%) (Table 7). However, *N*-benzoxazol-pyrrolidine was found to be too reactive and a mixture of mono-, di- and tri-alkylated products was obtained (not shown). The enhanced reactivity of pyrrolidines compared to piperidines in C(sp³)-H activation seems to be general and may be due to geometrical factors favoring the C-H insertion of the metal in the five-membered rings.

[Ir]	T (°C)		2.22	yield %
[Ir(cod) ₂]BF ₄	140 °C, μW		 2.22a	57
[Ir(cod) ₂]BARF	140 °C, μW		 2.22b	48
[Ir(cod) ₂]BARF	140 °C, μW		 2.22c	42
[Ir(cod) ₂]BARF	85 °C		 2.22d	39

Table 7

Even if moderate yields were mostly obtained due to the incomplete conversion of piperidine **2.21** and/or formation of the di-alkylated product, the key advantage of this method relies on the use of a benzoxazol-2-yl (BOA) moiety. Contrary to the 2-pyridyl group, the BOA directing group is easily introduced²⁶ and is efficiently removed in a single step.²⁷ However, as shown in Scheme 30, harsh conditions were employed.

Scheme 30

With *t*-butoxythiocarbonyl directing group

Inspired by the work of Hodgson,²⁸ Yu *et al.* turned their attention to *tert*-butoxy thiocarbonyl directing group, which can be easily introduced and removed.²⁹ However, this group proved to be unstable under iridium-catalyzed alkylation conditions. With the more acid-stable menthoxy-thiocarbonyl directing group present in pyrrolidine **2.25**, the alkylation proceeded smoothly (80% yield) but with poor diastereoselectivity (dr = 1.5:1). Moreover, the piperidine analog was not compatible under these conditions. Finally, a good compromise was achieved with the simpler 3-pentoxythiocarbonyl derivative. When pyrrolidine **2.29** (1 equiv) and ethyl acrylate (8 equiv) were treated in the presence of [Ir(cod)₂]OTf (10 mol %) in degassed chlorobenzene at 85 °C for 6 h, a mixture of the mono- and the di-alkylated pyrrolidines **2.30a** and **2.31a** was isolated in 68% yield (**2.30a**/**2.31a** = 1:1.8).

Scheme 31

When styrenes and other simple alkenes were used, a mixture of mono- and di-alkylated pyrrolidines was obtained. In contrast, allyl arenes, allyl nitriles or allyl sulfones delivered exclusively the di-alkylated products. Functional groups present on the alkene partner, such as a nitrile, a ketone, a sulfone or a phthalimide were also compatible with the reaction conditions (Table 8).

alkene	2.30/2.31	yield
	2.30b/2.31b (1.2:1)	42%
	2.30c/2.31c (1.5:1)	62%
	2.30d/2.31d (0:1)	62%
	2.30e/2.31e (0:1)	40%
	2.30f/2.31f (0:1)	55%
	2.30g/2.31g (0:1)	73%
	2.30h/2.31h (0:1)	70%

Table 8

The influence of substituents on the pyrrolidine cycle was then investigated. Both C2- and C3-substituted pyrrolidines **2.32a** and **2.32b** delivered the corresponding products **2.33a** and **2.33b** with moderate to good yields. Functionalized substrates such as the spirocyclic pyrrolidine **2.32c** or the L-proline ethyl ester **2.32d** were then successfully engaged in the alkylation process (**2.33c**, 40% and **2.33d**, 48%, *trans/cis* = 6:1). Piperidine **2.32e** was also alkylated in the presence of additional $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ (10 mol %), albeit with a lower yield (**2.33e**, 30%) (Scheme 32). Worthy of note, acyclic secondary amines were not alkylated under these conditions.

Scheme 32

The synthetic utility of this alkylation protocol was enhanced due to the easy removal of the 3-pentoxothiobenzamides directing group by treatment with TFA at 65 °C. A subsequent one-pot protection by a Fmoc group finally produced pyrrolidine **2.34** in 68% (Scheme 33).

Scheme 33

With a β,γ -unsaturated amide directing group

An iridium-catalyzed intramolecular oxidative coupling of alkenes and amides initiated by a preliminary C(sp³)-H bond activation alpha to the nitrogen atom was reported in 2004 by Sames and coworkers.³⁰ In this particular case, a double bond was regenerated at the end of the process. The reaction was catalyzed using [Ir(coe)₂Cl]₂ (coe = cyclooctene) (10 mol %) with the carbene ligand IPr [*N,N'*-bis-(2,6-diisopropylphenyl)-imidazolyl carbene] (2 equiv) in the presence of norbornene (4 equiv). Under these conditions, substrate **2.35** was converted to both the 5-*exo* and the 6-*endo* cyclization products **2.36** and **2.37** with 66% and 17% NMR yield respectively. Despite the addition of an excess of hydrogen acceptor (norbornene), the reduction product **2.38** was also formed in 10% NMR yield (Scheme 34)

Scheme 34

This method was then successfully extended to pyrrolidines **2.39a** and **2.39b**, respectively substituted by a silyl ether and an ester group (Scheme 35).

Scheme 35

When the pre-formed iridium complex **2.41** was heated at $150\text{ }^\circ\text{C}$ for 1 h, the expected products **2.36** and **2.37** were obtained in satisfying yields (Scheme 36). This experimental observation suggests that complex **2.41** would play an active role in the formation of the bicyclic products.

Scheme 36

As a result, the authors have proposed a catalytic cycle described in Scheme 37. Active iridium complex **2.41** would first be generated from $[\text{Ir}(\text{coe})_2\text{Cl}]_2$. Oxidative addition followed by the alkene insertion *via* a carbometalation (favored over hydrometalation and β -hydride elimination) would then form the iridium hydride **2.43**. A β -H elimination was favored over a reductive elimination since dihydride iridium complex **2.44** was formed while saturated product **2.46** was not observed. Hydrogenation of the sacrificial norbornene would regenerate the active iridium **2.41**, delivering **2.45**. Subsequent isomerization of the double bond would finally furnish product **2.36**.

Scheme 37

With a styrenyl directing group

In 2017, an iridium-catalyzed asymmetric cycloisomerization of styrenyl anilines involving a $\text{C}(\text{sp}^3)\text{-H}$ activation was reported.³¹ After a ligand screening, (*S*)-DTBM-SEGPHOS was selected in association with $[\text{IrCl}(\text{C}_2\text{H}_4)_2]_2$ and the reaction was carried out in toluene (Scheme 38). The reaction delivered a wide array of indolines possessing a quaternary center at the C3 position with high degree of enantiocontrol. From a mechanistic point of view, an oxidative addition of iridium into the C-H bond of a *N*-methyl substituent followed by an intramolecular carbometalation on the pendant double bond and a reductive elimination was proposed.

With an urea directing group

Nishimura and co-workers reported an iridium-catalyzed alkylation of *N*-methyl ureas with terminal olefins operating through a C(sp³)-H activation process.³² The catalytic system was composed of the hydroxo-iridium complex [Ir(OH)(cod)₂] and of the biphosphine ligand 1,2-bis(diisopropylphosphino)benzene (dippbz). A variety of alkene could be involved in the reaction delivering the alkylated ureas with excellent yields. The reaction required the presence of a N-H on the urea allowing the formation of a transient amido-iridium complex **2.51** prior to the C-H activation step was proposed (Scheme 39).

3- Rhodium-catalyzed α-alkylation of amines³³

With conjugated dienes as directing groups

In 2010, a rhodium-catalyzed intramolecular alkylation of amines of type **3.1** at the allylic C(sp³)-H bond adjacent to the nitrogen atom was reported to form a diversity of pyrrolidines.^{34,35} The alkylation of substrate **3.1a** was catalyzed by [RhCl(PPh₃)₃] (10 mol %) and AgSbF₆ (10 mol %) in dichloroethane (65 °C) and the corresponding substituted pyrrolidine **3.2a** was isolated in 90% yield as a single diastereomer (Table 9, entry 1). A methyl substituent at the internal position of the alkene was tolerated (**3.2b**, 81%) (Table 9, entry 2). Substrate **3.1c**, bearing a phenyl group at the conjugated diene moiety, smoothly reacted to deliver the 2,3-disubstituted pyrrolidine **3.2c** in good yield (64%) and good diastereoselectivity (dr = 7:1) (Table 9, entry 3). Polysubstituted pyrrolidines **3.2d** and **3.2e** were also synthesized (Table 9, entries 4-5).

		3.1a-3.1e		3.2a-3.2e	
entry	3.1	3.2			yield, dr
1	3.1a		3.2a		90%, > 20:1
2	3.1b		3.2b		81%, > 20:1
3	3.1c		3.2c		64%, 7:1
4	3.1d		3.2d		59%, 15:1
5	3.1e		3.2e		76%, 8:1

Table 9

A DFT study of the mechanism revealed that the chemoselective allylic C(sp³)-H bond activation of substrate **3.1a** would be directed by the conjugated diene *via* the preliminary formation of rhodium(I) complex **3.A**. After allylic C-H activation, insertion of the inner ene part of the diene by hydorrhodation would produce the bis-allylic rhodium complex **3.C**. Subsequent reductive

elimination would allow the cyclization, forming a product-rhodium complex. After a ligand exchange with the starting material, the *cis*-divinyl cyclized product **3.2a** would be delivered with high diastereoselectivity (Scheme 40).

One year later, an asymmetric version of this transformation was developed.³⁶ An extensive screening of chiral ligands revealed that diphosphines were detrimental to the reaction whereas the use of easily accessible phosphoramidites gave encouraging results in regard with both yield and enantioselectivity. The best result was finally achieved using $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ (5 mol %) with chiral ligand **L1*** (25 mol %) in the presence of AgOTf (12 mol %) in DME. Under these conditions, substrate **3.1a** was converted to pyrrolidine **3.2a** in 90% yield with 90% enantiomeric excess (dr > 19:1). Worthy of note, a variety of enantio-enriched 2,3-divinylpyrrolidines was also efficiently synthesized (data not shown).³⁷

With a pyridyl directing group

More recently, Schnürch and co-workers developed a rhodium-catalyzed alkylation of benzylic amines using either alkyl bromides or alkenes. The mechanism of the reaction using olefins was particularly investigated and the authors show that a C(sp²)-H activation of an *in situ* formed imine was taking place instead of a direct C(sp³)-H activation at the benzylic position (Scheme 42).

Scheme 42

Conclusion

Since the pioneering work reported by Jun *et al.* in 1998, an extensive work has been realized to develop metal-catalyzed α -alkylation of amine through C(sp³)-H bond activation. Ruthenium and iridium catalysts clearly dominate the field, allowing the α -alkylation of both cyclic and acyclic amines with alkenes as partners. In general, these reactions required a directing group on the nitrogen atom and the pyridyl group is the most frequently used. The scope of the developed methods is broad both in term of amine and alkene diversity. However, several challenges still need to be addressed. First, the alkylation reactions generally necessitate high temperatures, which could not be always compatible with functionalized molecules and the development of milder conditions is still desirable. Pyrrolidines are particularly reactive under the various reported alkylation conditions and mixture of mono- and dialkylated products are often observed. On the contrary, larger *N*-heterocycles such as piperidines and azepanes revealed often reluctant in the alkylation reactions. Examples of α -alkylation of amines in the absence of any directing group are scarce and, to increase the atom economy of the process, the use of traceless directing group could be interesting. Finally, only few asymmetric α -alkylation of amines through C-H activation have been reported so far and the development of a robust and general enantioselective reaction would have a high synthetic value.³⁸

- ¹ a) Taylor RD, MacCoss M, Lawson ADG. *J. Med. Chem.* 2014;57:5845-5859. b) McGrath NA, Brichacek M, Njardarson JT. *J. Chem. Educ.* 2010;87:1348-1349.
- ² (a) Mitchell EA, Peschiulli A, Lefevre N, Meerpoel L, Maes BUW. *Chem. Eur. J.* 2012;18:10092-10142; (b) Campos KR. *Chem. Soc. Rev.* 2007;36:1069-1084.
- ³ For some recent general reviews on C(sp³)-H activation, see: a) Chu JCK, Rovis T. *Angew. Chem. Int. Ed.* 2018; 57:62-101. b) Karimov RR, Hartwig JF. *Angew. Chem. Int. Ed.* 2018;57:4234-4241. c) Xu Y, Dong G. *Chem. Sci.* 2018;9:1424-1432. d) Saint-Denis TG, Zhu RY, Chen G, Wu QF, Yu JQ. *Science* 2018;359:in press.
- ⁴ Labinger JA, Bercaw JE. *Nature* 2002;417:507-514.
- ⁵ For general reviews concerning C-H activation mechanisms, see: a) Balcells D, Clot E, Eisenstein O. *Chem. Rev.* 2010;110:749-823. b) Ackermann L. *Chem. Rev.* 2011;111:1315-1345. c) Davies DL, Macgregor SA, McMullin CL. *Chem. Rev.* 2017;117:8649-8709.
- ⁶ For a general review on directing groups in catalysis, see Rousseau G, Breit B. *Angew. Chem. Int. Ed.* 2011;50: 2450-2494.
- ⁷ For a general review devoted to the functionalization by metal-catalyzed C(sp³)-H bond activation, see (a) Jazzar R, Hitce J, Renaudat A, Sofack-Kreutzer J, Baudoin O. *Chem. Eur. J.* 2010;16:2654-2672; For a general review devoted to the metal-catalyzed arylation of non activated C(sp³)-H bonds, see (b) Baudoin O. *Chem. Soc. Rev.* 2011;40:4902-4911.
- ⁸ For a general review on metal-catalyzed C-H alkylation using alkenes, see Dong Z, Ren Z, Thompson SJ, Xu Y, Dong G. *Chem. Rev.* 2017;117:9333-9403.
- ⁹ Alkylation at the C(sp³)-H bond adjacent to nitrogen atom of amides whose the carbonyl does not assist the C(sp³)-H bond cleavage will not be reviewed. For an example, see Pedroni J, Boghi, M, Saget T, Cramer N. *Angew. Chem. Int. Ed.* 2014;53:9064-9067.
- ¹⁰ Early-transition-metal-catalyzed hydroaminoalkylation reactions have been the purpose of several proper and recent reviews and will not be discussed here, see ref. 8 and: (a) Ryken SA, Schafer LL. *Acc. Chem. Res.* 2015; 48:2576-2586; (b) Chong E, Garcia P, Schafer LL. *Synthesis* 2014;46:2884-2896; (c) Eisenberger P, Schafer LL. *Pure Appl. Chem.* 2010;82:1503-1515; (d) Roesky PW. *Angew. Chem. Int. Ed.* 2009;48:4892-4894.
- ¹¹ Jun CH. *Chem. Commun.* 1998;1405-1406.
- ¹² Reger DL, Garza DG, Baxter JC. *Organometallics* 1990;9:873-874.
- ¹³ Chatani N, Asaumi T, Yorimitsu S, Ikeda T, Kakiuchi F, Murai S. *J. Am. Chem. Soc.* 2001;123:10935- 10941
- ¹⁴ Lee DH, Chen J, Faller JW, Crabtree RH. *Chem. Commun.* 2001;213-214.
- ¹⁵ Bergman SD, Storr TE, Prokopová H, Aelvoet K, Diels G, Meerpoel L, Maes BUW. *Chem. Eur. J.* 2012 ;18:10393-10398.
- ¹⁶ Kulago AA, Van Steijvoort BF, Mitchell EA, Meerpoel L, Maes BUW. *Adv. Synth. Catal.* 2014;356:1610-1618.
- ¹⁷ Schinkel M, Wang L, Bielefeld K, Ackermann L. *Org. Lett.* 2014;16:1876-1879.
- ¹⁸ Yi CS, Yun SY. *Organometallics* 2004;23:5392-5395.
- ¹⁹ Pan S, Endo K, Shibata T. *Org. Lett.* 2011;13:4692-4695.
- ²⁰ C(sp³)-H bond cleavage of 2-(ethylamino)pyridine by using an iridium complex was already reported in the literature. In this case, stoichiometric iridium-carbene complexes were obtained but no further functionalization was explored, see ref. 14 and (a) Clot E, Chen J, Lee DH, Sung SY, Appelhans LN, Faller JW, Crabtree RH. *J. Am. Chem. Soc.* 2004;126:8795-8804; (b) Li X, Appelhans LN, Faller JW, Crabtree RH. *Organometallics* 2004;23:3378-3387.
- ²¹ This method was then applied to the enantioselective alkylation at the C(sp³)-H bond alpha to nitrogen of lactams, see Tahara Y, Michino M, Ito M, Kanyiva KS, Shibata T. *Chem. Commun.* 2015;51:16660-16663.
- ²² Pan S, Matsuo Y, Endo K, Shibata T. *Tetrahedron* 2012;68:9009-9015.
- ²³ Nagai M, Nagamoto M, Nishimura T, Yorimitsu H. *Chem. Lett.* 2017;46:1176-1178.
- ²⁴ Jana CK, Grimme S, Studer A. *Chem. Eur. J.* 2009;15:9078-9084.
- ²⁵ Lahm G, Opatz T. *Org. Lett.* 2014;16:4201-4203.
- ²⁶ Formation by nucleophilic substitution between an amine and 2-chlorobenzoxazole in the presence of Hünig's base, see (a) Gim HJ, Cheon YJ, Ryu JH, Jeon R. *Bioorg. Med. Chem. Lett.* 2011;21:3057-3061. Formation by metal-free oxidative coupling of an amine with benzoxazole in the presence of Bu₄NI and *tert*-butylhydroperoxide, see (b) Froehr T, Sindlinger CP, Kloeckner U, Finkbeiner P, Nachtsheim BJ. *Org. Lett.* 2011;13:3754-3757; (c) Kloeckner U, Weckenmann NM, Nachtsheim BJ. *Synlett* 2012;97-100.
- ²⁷ Treatment of (benzoxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline with KOH in ethylene glycol at 140 °C or with LiAlH₄ in refluxing THF delivered the expected 1,2,3,4-tetrahydroisoquinoline in 67% and 82% yield

respectively. However, in the presence of mono-alkylated substrates, moderate yield was obtained or harsher conditions were used. Moreover, no example was reported in the presence of secondary amines.

²⁸ (a) Hodgson DM, Kloesges J. *Angew. Chem. Int. Ed.* 2010;49:2900-2903; (b) Hodgson DM, Mortimer CL, McKenna JM. *Org. Lett.* 2015;17:330-333.

²⁹ Tran AT, Yu JQ. *Angew. Chem. Int. Ed.* 2017;56:10530-10534.

³⁰ DeBoef B, Pastine SJ, Sames D. *J. Am. Chem. Soc.* 2004;126:6556-6557.

³¹ Torigoe T, Ohmura T, Suginome M. *Angew. Chem. Int. Ed.* 2017;56:14272-14276.

³² Yamauchi D, Nishimura T, Yorimitsu H. *Angew. Chem. Int. Ed.* 2017;56:7200-7204.

³³ Rhodium-catalyzed alkylation of benzylic amines with alkenes or alkyl bromides was reported in 2015 by Schnürch and coworkers. However, mechanistic and kinetic studies revealed that the alkylation occurred *via* C(sp²)-H bond activation thanks to the formation of an imine intermediate. As none rhodium intermediate of type C(sp³)-[Rh]-H is formed during the all process, this work will not be detailed in this review, see (a) Pollice R, Dastbaravardeh N, Marquise N, Mihovilovic MD, Schnürch M. *ACS Catal.* 2015;5:587-595; (b) Pollice R, Schnürch M. *J. Org. Chem.* 2015;80:8268-8274; For a similar observation, see Jo EA, Lee JH, Jun CH. *Chem. Commun.* 2008;5779-5781.

³⁴ Li Q, Yu ZX. *J. Am. Chem. Soc.* 2010;132:4542-4543.

³⁵ For a DFT study of the mechanism, see Li Q, Yu ZX. *Organometallics* 2012;31:5185-5195.

³⁶ Li Q, Yu ZX. *Angew. Chem. Int. Ed.* 2011;50:2144-2147.

³⁷ One of these products was used as a chiral ligand in rhodium-catalyzed enantioselective conjugated additions, see Li Q, Dong Z, Yu ZX. *Org. Lett.* 2011;13:1122-1125.

³⁸ A palladium-catalyzed enantioselective C-H α -functionalization of amines including one example of alkylation has been recently reported, see: Jain P, Verma P, Xia G, Yu JQ. *Nat. Chem.* 2017;9:140-144.