Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 2548

www.rsc.org/obc

PAPER

An atom efficient route to *N*-aryl and *N*-alkyl pyrrolines by transition metal catalysis†

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Received 5th July 2010, Accepted 13th January 2011
DOI: 10.1039/c0ob00383b

The synthesis of *N*-aryl, *N*-tosyl, and *N*-alkyl pyrrolines from allyl alcohols and amines has been developed. The reaction sequence includes a palladium-catalyzed allylation step in which non-manipulated allyl alcohol is used to generate the diallylated amine in good to excellent yield. An excess of allyl alcohol was necessary for efficient diallylation of the amine, where the excess alcohol could be recycled three times. For aryl and tosyl amines, $Pd[P(OPh)_3]_4$ was used and for benzyl and alkyl amines a catalytic system comprising $Pd(OAc)_2$, P^nBu_3, and BEt_3 was used. Both the electronic properties and the steric influence of the amine affected the efficiency of the allylation. The isolated diallylated amines were transformed into their corresponding pyrrolines by ring-closing metathesis catalyzed by $(H_2IMes)(PCy_3)Cl_2RuCHPh$ in good to excellent yield. A one-pot reaction was developed in which aniline was transformed into the corresponding pyrroline without isolating the diallylated intermediate. This one-pot reaction was successfully scaled-up to 1 mL of aniline in which the *N*-phenyl pyrroline was isolated in 95% yield. The versatility of the reaction in which 3-methyl-1-phenyl pyrroline was prepared in two-steps was demonstrated.

Introduction

N-aryl pyrrolidines are core structures in a wide range of biologically active compounds (Fig. 1). These compounds have shown promising biological activity toward a plethora of diseases through: (*i*) inhibition of the lethal protease activity in anthrax toxin,[1] (*ii*) inhibition of the Syk kinase related to thrombosis and non Hodgkin's lymphoma,[2] (*iii*) alteration of the antagonistic activity of neuropeptide Y receptor related to food intake, learning activity, Alzheimers and Parkinson's diseases,[3] (*iv*) cytotoxic agent activity against human microvascular endothelial cells related to diabetes and tumor growth.[4]

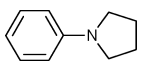

Fig. 1 Core structure of biologically active compounds.[1–4]

The great potential in these compounds requires new divergent atom efficient synthetic routes.[5] Traditionally, these compounds are synthesized by aromatic nucleophilic substitution of aryl halides by a cyclic amine.[6] Besides giving stoichiometric amounts of waste this synthetic route limits the presence of halides on the aromatic counterpart. Another synthetic route is to react an arylamine with 1,4-dihalobutane. However, this procedure also generates stoichiometric amounts of waste. Recently, a palladium-catalyzed diallylation of tosylamides, followed by ring-closing metathesis (RCM) was reported.[7] Allyl carbonates, generated from allyl alcohol, were used as the allylating agent. Even though the overall yield is 81%, this procedure only gives 40.5% atom economy. An advantage with generating the pyrroline is that the double bond can be functionalized in a subsequent step. We wanted to expand the scope to include arylamines, benzylamines, and alkylamines. Furthermore, it is desirable to substitute the allyl carbonate that generates stoichiometric amounts of waste with the less expensive and renewable allyl alcohol.[8] This would give a procedure with only ethene and water as side-products.

Whereas the palladium-catalyzed Tsuji–Trost monoallylation of amines using allyl halides, acetates, carbonates, *etc* is a well studied reaction,[9] the diallylation of amines using allyl alcohol is not.[10,11] In most cases, an acid is added to the reaction mixture in order to promote the transformation.[11a,d,f] As the reaction is reversible, a drying-agent has been used to drive the reaction to completion.[12] We describe an unprecedented synthetic route to pyrrolines in which allyl alcohols are used. A broad substrate scope is presented, where different anilines, benzylamine, tosyl amide, and alkyl amine have been used. The reaction proceeds by a palladium-catalyzed diallylation of the amine, followed by a ruthenium-catalyzed RCM to generate the corresponding pyrrolines with only ethene and water as side-products.

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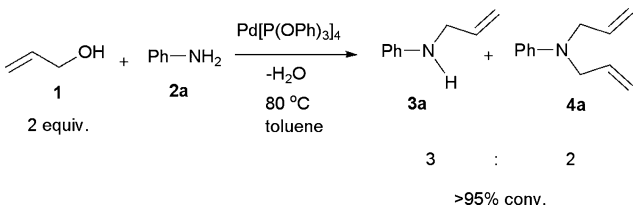
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c0ob00383b

Results and discussion

Palladium-catalyzed allylation of amines

A. Ligand effect on Pd for the allylation of aniline (2a). Initially, two different palladium-catalysts were studied in the allylation of **2a**. Allyl alcohol (**1**) (2 equiv.) was added to a toluene solution of **2a** (1 equiv.) and $Pd(PPh_3)_4$ or $Pd[P(OPh)_3]_4$[11e] (2 mol%), and the reaction was performed at 80 °C. The $Pd(PPh_3)_4$ catalyst gave poor results (30% conv., 4 h) whereas the $Pd[P(OPh)_3]_4$ catalyst gave above 95% conversion of **2a** to afford a 3 : 2 ratio of monoallylated (**3a**) : diallylated (**4a**) amine after 1 h (Scheme 1). It is hypothesized that the difficulty with using allylic alcohols result from the oxidative addition step, *i.e.* the carbon–oxygen bond cleavage, to generate the π-allyl palladium intermediate. However, a more electron donating PPh_3 ligand would promote this step better than the more electron deficient $P(OPh)_3$ ligand. Clearly, the oxidative addition step is not the limiting step in this reaction. The ease of oxidative addition is also supported by Yamamoto's report where **1** was oxidatively added to $Pd(PCy_3)_2$ to generate Pd(diallylether)(PCy_3) at 30 °C.[13] Another interpretation of the difficulty with using allyl alcohols as substrates is that the generated ether or diallylated amine chelate to the metal that poisons the catalyst. Yamamoto reported a temperature of 150 °C for thermolysis of Pd(diallylether)(PCy_3). However, to generate such an intermediate requires that one ligand dissociates. When using electron-deficient phosphites that are more π-acidic, due to strong back-donation, the dissociation of ligands may be prevented. An alternative mechanism proceeding through a metal hydride has also been proposed.[11b,c]



Scheme 1 Allylation of **2a**.

B. Effect of 1. With 2 equivalents of **1**, full conversion of **2a** to a mixture of **3a** and **4a** in a 3 : 2 ratio was observed after 60 min (Fig. 2). After 4 h, this ratio was increased to 3 : 1 in favor of **4a**. This is in conflict to the report by Ikariya, where 84% yield of diallylated product and no **3a** was reported. When 4 equivalents of **1** was used, full conversion of **2a** to a mixture of **3a** and **4a** in a 1 : 4 ratio was observed after 60 min. When 8 equivalents of **1** was used, >95% conversion to **4a** was observed within 1 h, and no **3a** was detected in the ^{1}H NMR spectrum. One explanation for the requirement of an excess amount of **1** is that the reaction is reversible and the excess alcohol employed is used to shift the equilibrium towards product.[12] To test this hypothesis, the reaction using 2 equivalents of **1** was performed in the presence of molecular sieves. However, this led to no formation of **4a** and instead diallyl ether was observed as the only product in the ^{1}H NMR spectrum.[11c]

C. Recycling the excess of 1. The excess amount of **1** used in the reaction is negative for the atom economy and therefore recycling of the alcohol was investigated. Allylation of **2a** was performed using 8 equivalents of **1** and the reaction was run for 1 h after which the conversion was analyzed by ^{1}H NMR where >95% conversion to the desired **4a** and no **3a** was observed. The reaction mixture was cooled down and the solvent mixture (toluene, **1**, and formed water) was vacuum transferred to another Schlenk-tube containing $Pd[P(OPh)_3]_4$. Model substrate **2a** and two additional equivalents of **1** were added to the condensed reaction mixture. This solution was degassed by 3-pump-thaw cycles and the reaction was run for 1 h. We recycled the solvent mixture three times without observing any deviation in reactivity between the runs, demonstrating the ability to perform an atom economic process (Fig. 3). Note, that every run yields 2 equivalents of water. In the fifth run, 10 equivalents of water in the reaction mixture did not influence the reactivity negatively demonstrating the robustness of the reaction system.[12]

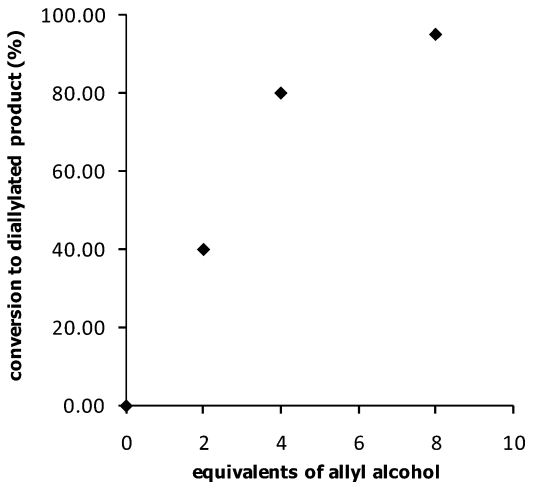


Fig. 2 Dependence of **1** for the formation of **4a**.

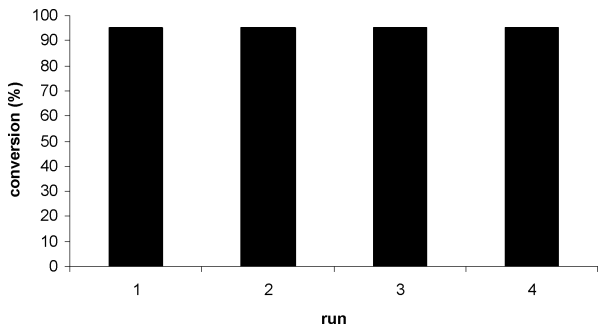
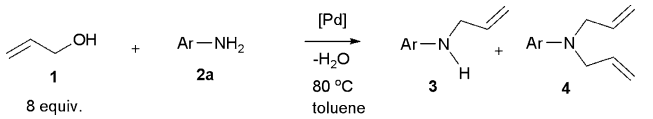


Fig. 3 Recycling of the solvent system.

D. Electronic and steric influence of the amine. Next, the correlation between the electronic and steric properties of the anilines and the rate for the formation of diallylated amine was investigated. From the report of Ikariya and coworkers only one example with **2a** was presented.[11e] As the oxidative addition was probably not the rate-limiting step, it was hypothesized that the nucleophilic attack or the proton transfer by the amine was the rate-determining step. Further insight into the nucleophilic attack was gained by varying the electronic and steric properties of the aniline by varying the substitution in the *para*- and *ortho*-positions.

Model substrate **2a** was rapidly transformed into **4a** in above 95% conversion within 30 min (Table 1, entry 1). The ratio of **4a** : **3a**

Table 1 Effect of substituent in the allylation



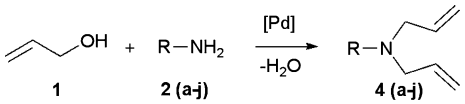
entry	substrate	Substituent	conv. 30 min (%)	ratio (**4** : **3**) (di : mono)
1	**2a**	H	95	1.9 : 1
2	**2b**	*p*-F	85	0.6 : 1
3	**2c**	*p*-MeO	49	0.16 : 1
4	**2d**	*p*-Me	95	0.9 : 1
5	**2e**	*o*-Me	93	0.3 : 1

The reactions were run using 7 mmol of **1**, 0.875 mmol of **2a**, and 2 mol% of $Pd[P(OPh)_3]_4$ in 1.25 mL of toluene at 80 °C. Reactions were monitored by ^1H NMR spectroscopy using mesitylene as internal standard.

was 1.9 : 1. The *p*-fluoro substituted aniline (**2b**) was transformed more slowly (85% conversion within 30 min). The ratio of di : mono (**4b** : **3b**) allylation was 0.6 : 1. The *p*-Me substituted aniline (**2d**) was transformed in above 95% conversion within 30 min in analogy to aniline. However, the ratio of di : mono (**4d** : **3d**) allylation was 0.9 : 1. The *o*-Me substituted aniline (**2e**) was also transformed in above 93% conversion within 30 min. However, the ratio of di : mono (**4e** : **3e**) allylation was 0.3 : 1. The *p*-methoxy substituted aniline (**2c**) was transformed in 49% conversion within 30 min in a 0.16 : 1 ratio di : mono (**4c**:**3c**). Clearly, the nucleophile has a profound effect in efficiency of the diallylation of anilines by $Pd[P(OPh)_3]_4$, where both electron donating and withdrawing substituents lower the conversion to the diallylated product. It is noteworthy that the first allylation step may not be influenced by the electronic properties of the aniline to the same extent as the second allylation step. The electronic influence of the amine may affect both the nucleophilicity of the amine and also the ability for the amine to work as a proton mediator in the removal of water. We are currently investigating the mechanism. The steric influence of the substitution pattern of the aniline also has a profound effect of the second allylation step, in which **2d** proceeds to above 50% conversion whereas **2e** proceeds to 23% conversion within 30 min. In this case, the nucleophilicity is most likely influenced by the steric properties of the amine.

E. Scope of the amines. After this initial study in which the rate of the allylation of the anilines was studied the scope of the amines was investigated with regard to the isolated diallylated amine. Most diallylated amines were isolated by column chromatography in good to excellent yields (Table 2). Model substrate **2a** was diallylated in 1 h, using 2 mol% of $Pd[P(OPh)_3]_4$ and **4a** was isolated in 95% yield after column chromatography (Table 2, entry 1). The *p*-F substituted **2b** was diallylated in 8 h using 2 mol% of catalyst and **4b** was isolated in 98% yield (Table 2, entry 2). The longer reaction time compared to **2a** is in accordance to the lower reaction rate (Table 1, entries 1 and 2). In the case of the *p*-MeO aniline, 5 mol% of $Pd[P(OPh)_3]_4$ was used and the diallylated product was generated in full conversion after 4 h (Table 2, entry 3). Attempts to isolate the product by column chromatography led to decomposition. Diallylation of *p*-Me substitued **2d** was performed using 2 mol% of catalyst for 4 h to generate **4d** in 95% yield (Table 2, entry 4). The *o*-Me substituted **2e** was allylated in 57% yield after 8 h using 2 mol%

Table 2 Palladium-catalyzed allylation of amines



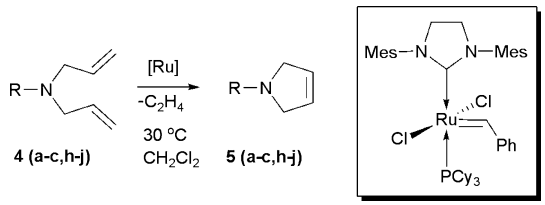
entry	substrate	*R*	[Pd] (mol%)	time (h)	product	yield[a] (%)
1	**2a**	Ph	2	1	**4a**	95
2	**2b**	*p*-F-Ph	2	8	**4b**	98
3	**2c**	*p*-MeO-Ph	5	4	**4c**	>95[b]
4	**2d**	*p*-Me-Ph	2	4	**4d**	95
5	**2e**	*o*-Me-Ph	2	8	**4e**	57
6	**2f**	Mes	10	10	**4f**	52
7	**2g**	$(Ph)_2CH$	2	22	**4g**	88
8	**2h**	Ts	10	6	**4h**	40[b]
9	**2i**	Bn	5	15	**4i**	97[c]
10	**2j**	Cy	5	19	**4j**	92[c]

[a] The reactions were run using 7 mmol of **1**, 0.875 mmol of **2a**, and 2 mol% of $Pd[P(OPh)_3]_4$ in 1.25 mL of toluene at 80 °C. Yields refer to isolated yields. [b] Conversion by ^1H NMR. [c] The reactions were run using 7 mmol of **1**, 0.875 mmol of **2a**, and 5 mol% of $Pd(OAc)_2$, 20 mol% P^nBu_3, and 22 mol% of BEt_3 in 2 mL of THF at 66 °C.

of catalyst (Table 2, entry 5). Clearly, the steric influence of the *ortho* substituent has a dramatic effect of the efficiency of the allylation. The diallylation of mesitylamine (**2f**) proceeds in 52% yield after 10 h using 10 mol% of catalyst (Table 2, entry 6). The low efficiency in terms of yield, reaction time, and catalyst loading may be explained by both steric and electronic effects. The major side product was the monoallylated mesitylamine (**3f**). The diallylation of aminodiphenylmethane (**2g**) was performed using 2 mol% of catalyst. The reaction was run for 22 h and the diallylated product (**4g**) was isolated in 88% yield (Table 2, entry 7). The diallylation of electron deficient *p*-toluenesulfonamide (**2h**) proceed in 40% yield after 6 h using 10 mol% of $Pd[P(OPh)_3]_4$ (Table 2, entry 8). The major side product was the monoallylated amide. The lower efficiency may be explained by the lower nucleophilicity of the sulfonamide. The diallylation of benzylamine (**2i**) did not proceed using $Pd[P(OPh)_3]_4$ as catalyst. One explanation is that **2i** or product (**4i**) coordinates palladium and inhibits catalysis. Instead the palladium phosphite catalyst was exchanged for a catalytic system comprising $Pd(OAc)_2$, P^nBu_3, and BEt_3.[14] With this palladium source, both benzylamines and alkylamines were efficiently transformed. Benzylamine was diallylated in 97% yield using 5 mol% of palladium-catalyst in 15 h (Table 2, entry 9). The allylation was performed on cyclohexylamine (**2j**) to generate the diallylated product (**4j**) in 92% yield after 19 h (Table 2, entry 10).

F. Ring-closing metathesis of diallylated aryl, tosyl and alkyl amines. RCM was performed on the diallylated amines with $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (Table 3) used to prepare the pyrrolines.[15] The reactions were monitored by ^1H NMR by integrating known signals of the starting material and the product using mesitylene as internal standard. Substrate **4a** was transformed into *N*-phenyl pyrroline (**5a**) in above 95% conversion within 1 h at 30 °C using 2 mol% of catalyst (Table 3, entry 1). The pyrroline **5a** was isolated by column chromatography in 75% yield. The diallylated *p*-F aniline **4b** was transformed by RCM to afford the corresponding pyrroline (**5b**) in above 95% conversion over night using 2 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (Table

Table 3 Ruthenium-catalyzed ring-closing metathesis to generate the pyrrolines

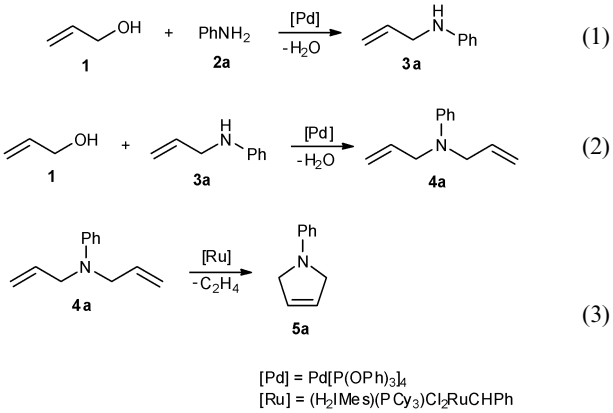


entry	substrate	*R*	[Ru] (mol%)	time (h)	product	conv[a] (%)[b]
1	**4a**	Ph	2	1	**5a**	>95
2	**4b**	*p*-F-Ph	2	12	**5b**	>95
3	**4c**	*p*-MeO-Ph	5	12	**5c**	85
4	**4h**	Ts	2	1	**5h**	>95
5	**4i**	Bn	10	1.5	**5i**	70[c]
6	**4j**	Cy	10	1	**5j**	70[c]

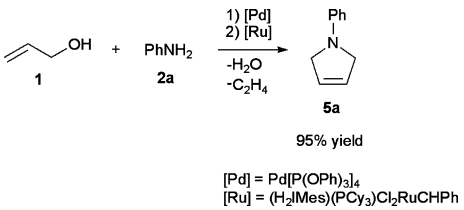
[a] Reactions were run using 5×10^{-5} mol of diallylated amine and 2–10 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ in DCM at 30 °C. [b] The yield was determined by ^1H NMR using mesitylene as internal standard. [c] Reactions were run using microwave irradiation at 50 °C.

3, entry 2). The scope of this approach, when compared to other methodologies involving nucleophilic aromatic substitutions, is nicely demonstrated by the addition of a fluorine atom on the arylamine.[6] In the case of the diallylated *p*-methoxy aniline **4c**, a crude mixture from the diallylation was used and RCM generated a mixture of desired pyrroline **5c** and the aromatized pyrrole (**5c′**) in 85% conversion after 12 h using 5 mol% of catalyst (Table 2, entry 3). The RCM of the diallylated *p*-toluenesulfonamide (**4h**) generated the corresponding pyrroline (**5h**) in above 95% conversion (Table 3, entry 4). The more basic benzylamine derivative **4i** required protonation by HCl prior to RCM.[16] The reaction was run for 90 min at 50 °C using microwave irradiation to generate the pyrroline (**5i**) in 70% conversion.[17] After protonation, the diallylated cyclohexylamine was ring-closed to afford a 3 : 2 mixture of pyrrole and pyrroline (**5j**) in 70% conversion after 1 h at room temperature. Prolonged reaction time favored formation of pyrrole.

G. One-pot two-step procedure to pyrrolines from 1 and 2a. Encouraged by the results of this two-step procedure, we explored a one-pot procedure to make pyrrolines. There is a need to design an efficient system for the tandem catalytic diallylation of amines followed by ring-closing metathesis. As such, the rates for the individual steps, *i.e.* palladium-catalyzed monoallylation, diallylation and also ruthenium-catalyzed RCM were studied. The allylation is reversible and therefore the initial kinetics (<30% conversion) were measured.[12] The reactions were run at 65 °C in C_6D_6 using 2 mol% of catalyst and monitored by ^1H NMR using mesitylene as internal standard. The monoallylated aniline **3a** gives a characteristic signal in the ^1H NMR spectrum at δ 3.50 ppm and the diallylated aniline **4a** gives a characteristic signal at δ 3.73 ppm. The monoallylation of **2a** proceeded with an observed rate of 1.3×10^{-8} mol s^{-1} (eqn (1)). The diallylation of **3a** proceeded with an observed rate of 4.5×10^{-8} mol s^{-1} (eqn (2)). The rate of the RCM at this temperature was too fast to measure. Within the time before we were able to lock and shim (2 min) the reaction had proceeded to full conversion giving **5a** with a characteristic signal in the ^1H NMR spectrum at δ 3.80 ppm. Therefore, the temperature was decreased to 25 °C and the observed rate at this temperature was 4.2×10^{-8} mol s^{-1} (eqn (3)).



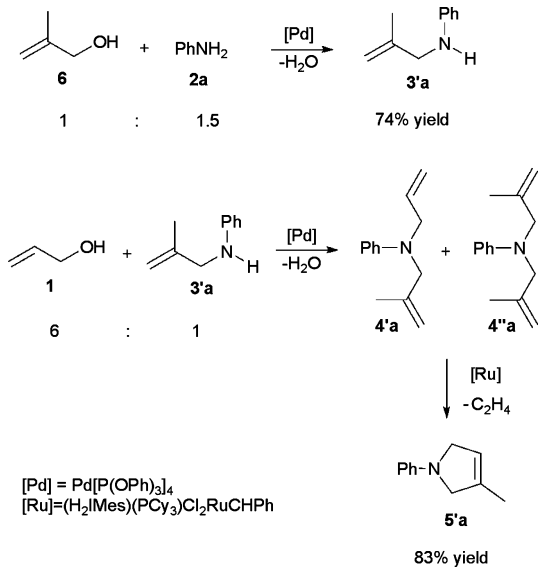
Finally, a one-pot procedure was designed. From the kinetic data, it was clear that the palladium-catalyst and ruthenium-catalyst were not compatible at the same reaction temperature. Therefore, a catalytic system was designed where the allylation of **2a** was followed by RCM. The allylation was performed using 2 mol% of $Pd[P(OPh)_3]_4$ at 65 °C for 1 h. Then the temperature was decreased to 30 °C and 5 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ was added to the reaction mixture *via* syringe. After 2 h the reaction was finished with 95% overall yield of **2a** to **5a** was observed using mesitylene as internal standard (Scheme 2). Encouraged by the results we decided to scale-up this reaction to 1 mL of **2a**. The diallylation was performed using 2 mol% of $Pd[P(OPh)_3]_4$ at 80 °C for 4 h. The reaction mixture was cooled down to 30 °C and 5 mol% of $(H_2IMes)(PCy_3)Cl_2RuCHPh$ was added to the reaction mixture and it was stirred for 3 h. Pyrroline **5a** was isolated in 95% yield by column chromatography. The remaining 5% was the corresponding pyrrole and starting material. If the generated water is excluded in the reaction, the atom economy of this transformation is 80%.



Scheme 2 One-pot catalytic system.

H. Preparation of 3-methyl-1-phenyl-pyrroline (5′a). Next the methodology was expanded to compounds that are difficult to synthesize by conventional methods. For example, the synthesis of **5′a** has only been reported using lithium trimethylsilyldiazomethane and non-commercially available *N*,*N*-disubstituted α-amino ketones.[18] Model substrate **2a** was monoallylated by 2-methyl-2-propen-1-ol (**6**) (0.75 equiv.) using 2 mol% of $Pd[P(OPh)_3]_4$ at 80 °C in 74% isolated yield. The corresponding *N*-(2-methyl-2-propenyl)aniline (**3′a**) was allylated by **1** to generate *N*-(2-methyl-2-propenyl)(allyl)aniline (**4′a**) in 80% yield. The remaining 10% was *N*-(2-methyl-2-propenyl)$_2$aniline (**4′′a**). These two compounds were not easily separated. Instead the reaction mixture was transferred to a new reaction flask with

2 mol% $(H_2IMes)(PCy_3)Cl_2RuCHPh$ where **4′a** was ring-closed at a higher rate to generate the trisubstituted pyrroline in favour of generating the tetrasubstituted pyrroline from *N*-(2-methyl-2-propenyl)$_2$aniline (**4″a**). After purification by column chromatography the desired 3-Me-1-Ph pyrroline (**5′a**) was isolated in 83% yield.



Scheme 3 Generation of **5′a**.

Conclusions

The catalytic system where the palladium-catalyzed diallylation of amines is followed by a ruthenium-catalyzed ring-closing metathesis shows high atom economy. Only water and ethene are generated as side-products. Furthermore, the procedure offers synthetic advantages over stoichiometric methodologies. The catalytic procedure expands the functional group tolerance on the aryl group of the amine. For example, a fluorine atom may be present on the aromatic ring. Compared to the allylation protocol using allyl carbonates this novel methodology widened the scope of amines to anilines, benzylamines and also alkyl amines. A one-pot procedure where aniline was converted to *N*-Ph pyrroline in 95% overall conversion was demonstrated. 3-Me-1-Ph pyrroline was conveniently synthesized using the protocol in 61% overall yield.

Experimental section

General remarks

All reactions were conducted in oven-dried glassware under an argon atmosphere using standard Schlenk techniques. Solvents were purified by passage through alumina[19] or distilled according to literature procedures. ^{1}H NMR spectra were recorded on a 300 or 400 MHz spectrometer in $CDCl_3$ at room temperature and were referenced by the residual solvent signal. Allyl alcohol was distilled from magnesium and stored under argon. Aniline was distilled under reduced pressure and stored under argon. $(H_2IMes)(PCy_3)Cl_2RuCHPh$[20] and $Pd[P(OPh)_3]_4$[11c] were prepared according to literature procedures. All other reagents were purchased from commercial suppliers and used without further purification. Characterization data for **4a**,[11e] **4b**,[21] **4c**,[11a] **4d**,[11a] **4e**,[22] **4f**,[23] **4g**[24] **4h**,[25] **4i**,[14] **4j**,[14] **5a**,[26] **5b**,[27] **5c′**,[28] **5h**,[25] **5i**,[29] **5j**,[30] **5′a**[18] was previously reported.

Preparation of *N*,*N*-diallylaniline (4a)

A flame-dried Schlenk tube was charged with $Pd(dba)_2$ (10 mg, 0.0175 mmol), dissolved in 0.4 mL of DCM, and $P(OPh)_3$ (18 μL, 0.07 mmol) was added *via* syringe. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature for 30 min. The solvent was removed *in vacuo*. Toluene (1.25 mL) and aniline (82 μL, 0.875 mmol) were added to the tube *via* syringe. The solution was degassed by three freeze-pump-thaw cycles. Degassed allyl alcohol (476 μL, 7 mmol) was added *via* syringe and the resulting mixture was stirred at 80 °C for 4 h and monitored by ^{1}H NMR and TLC. The mixture was concentrated and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford a yellowish clear oil as the pure product (0.144 g, 95% yield).

Preparation of *N*-allyl-*N*-benzylprop-2-en-1-amine (4i)

A flame-dried Schlenk tube was charged with $Pd(OAc)_2$ (9.8 mg, 0.0438 mmol), THF (2 mL), and benzylamine (94 μL, 0.875 mmol). The slurry was degassed by three freeze-pump-thaw cycles. Degassed allyl alcohol (476 μL, 7 mmol), BEt_3 (263 μL, 0.2 mmol), and P^nBu_3 (44 μL, 0.175 mmol) were added *via* syringe and stirred at 66 °C for 15 h. The reaction was monitored by ^{1}H NMR and TLC. The mixture was concentrated *in vacuo* and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford a clear oil as the pure product (0.164 g, 97% yield).

Preparation of 1-phenyl pyrroline (5a)

A flame-dried Schlenk tube was charged with $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (0.8 mg, 1 μmol), 1 mL of a DCM solution of diallylated aniline (0.05 M, 5×10^{-5} mol), was added and the reaction was performed at 30 °C. The yield was determined by ^{1}H NMR using mesitylene as internal standard.

Preparation of 1-phenyl pyrroline (5a) from aniline (2a)

Ruthenium catalyst (37 mg, 0.0438 mmol) was weighed into a round bottom flask. The unpurified crude mixture of *N*,*N*-diallylaniline prepared as described above, was added *via* syringe and stirred at room temperature for 3 h. The reaction was monitored by ^{1}H NMR.

Preparation of 1-phenyl pyrroline (5a) from 1 mL aniline (2a)

A flame-dried Schlenk tube was charged with $Pd(dba)_2$ (120.8 mg, 0.21 mmol), dissolved in 4 mL of DCM, and $P(OPh)_3$ (220 μL, 0.84 mmol) was added *via* syringe. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature for 30 min. The solvent was removed *in vacuo*. Toluene (10 mL) and aniline (957 μL, 10.5 mmol) were added to the tube *via* syringe. The solution was degassed by three freeze-pump-thaw cycles. Degassed allyl alcohol (5.713 mL, 84 mmol) was added *via* syringe and the resulting mixture was stirred at 80 °C for 4 h. Ruthenium

catalyst (446 mg, 0.525 mmol) was weighed into a round bottom flask. The unpurified crude mixture of *N*,*N*-diallylaniline prepared as described above, was added *via* syringe and stirred at room temperature for 3 h. The mixture was concentrated and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford the pure product (1.447 g, 95% yield).

Preparation of 1-benzyl pyrroline (5i)

A microwave vial (Biotage™) was charged with *N*-allyl-*N*-benzylprop-2-en-1-amine (10 mg, 0.053 mmol) in 1 mL of a dried DCM and 100 μL of 1 M HCl. The solution was stirred at room temperature for 1 h. The mixture was evaporated and azeotropically dried with toluene twice. Under an argon atmosphere, ruthenium catalyst (4.5 mg, 0.0053 mmol) dissolved in 0.5 mL DCM was added to the protonated amine. The microwave irradiation was carried out for 90 min (50 °C, 0–1 bar). The crude mixture was treated with $NaHCO_3$ and extracted with Et_2O. The residue was evaporated *in vacuo*. The reaction mixture was analyzed by ^{1}H NMR.

Preparation of 3-methyl-1-phenyl pyrroline (5′a)

A flame-dried Schlenk tube was charged with $Pd(dba)_2$ (30 mg, 0.0525 mmol), dissolved in 0.5 mL of DCM, and $P(OPh)_3$ (55 μL, 0.21 mmol) was added *via* syringe. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature for 30 min. The solvent was removed *in vacuo*. Toluene (1.5 mL) and aniline (360 μL, 3.95 mmol) were added to the tube *via* syringe. The solution was degassed by three freeze-pump-thaw cycles. 2-methyl-2-propen-1-ol (222 μL, 2.625 mmol) was added *via* syringe and the resulting mixture was stirred at 80 °C for 4 h and monitored by ^{1}H NMR. The mixture was concentrated and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford a colorless oil as the pure product (0.285 g, 74% yield). A flame-dried Schlenk tube was charged with $Pd(dba)_2$ (7.8 mg, 0.0136 mmol), dissolved in 0.4 mL of DCM, and $P(OPh)_3$ (14 μL, 0.0544 mmol) was added *via* syringe. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature for 30 min. The solvent was removed *in vacuo*. Toluene (1 mL) and *N*-(2-methyl-2-propenyl)aniline (100 mg, 0.68 mmol) were added to the tube *via* syringe. The solution was degassed by three freeze-pump-thaw cycles. Degassed allyl alcohol (278 μL, 4.08 mmol) was added *via* syringe and the resulting mixture was stirred at 80 °C for 2 h and monitored by ^{1}H NMR. The mixture was concentrated and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford a mixture of *N*-(2-methyl-2-propenyl)$_2$aniline and *N*-(2-methyl-2-propenyl)(allyl)aniline. Ruthenium catalyst (18.5 mg, 0.0218 mmol) dissolved in 2 mL DCM was added to the mixture and the reaction was run for 4 h at room temperature. The mixture was concentrated and the crude reaction mixture was purified by column chromatography on silica gel using chloroform–pentane as eluent to afford the pure product (75.7 mg, 83% yield).

Recycling experiment

Four flame-dried Schlenk tubes were charged with $Pd(dba)_2$ (10 mg, 0.0175 mmol), dissolved in 0.4 mL of DCM, and $P(OPh)_3$ (18 μL, 0.07 mmol) was added *via* syringe. The slurry was degassed by three freeze-pump-thaw cycles and stirred at room temperature for 30 min. The solvent was removed *in vacuo*. Toluene (1.25 mL) and aniline (82 μL, 0.875 mmol) were added to the first tube *via* syringe. The solution was degassed by three freeze-pump-thaw cycles. Degassed allyl alcohol (476 μL, 7 mmol) was added *via* syringe and the resulting mixture was stirred at 80 °C for 1 h and monitored by ^{1}H NMR. The second Schlenk tube was cooled to –196 °C. The remaining allyl alcohol and toluene from the first tube were vacuum transferred to the second tube. After adding aniline (82 μL, 0.875 mmol) and allyl alcohol (119 μL, 1.75 mmol) *via* syringe, the reaction was run as above.

Kinetic studies

Aniline allylation. 0.6 mL of aniline solution (0.145 M in C_6D_6) was added to an the NMR tube with $Pd[P(OPh)_3]_4$ (0.00174 mmol) under an argon atmosphere. Allyl alcohol (59 μL, 0.87 mmol) was added *via* syringe, the NMR tube was shaken, and inserted into the spectrometer preheated to 65 °C. The kinetics of the allylation were determined by ^{1}H NMR spectroscopy. The reaction was followed with ^{1}H NMR spectroscopy by integrating the ratio of *N*-allylaniline at δ 3.50 ppm. and *N*,*N*-diallylaniline at δ 3.73 ppm and the mesitylene signal at δ 2.21 ppm.

***N*-allylaniline allylation.** 0.6 mL of *N*-allylaniline (0.145 M in C_6D_6) was added to an the NMR tube with $Pd[P(OPh)_3]_4$ (0.00174 mmol) under an argon atmosphere. Allyl alcohol (59 μL, 0.87 mmol) was added, the tube was shaken, and inserted into the spectrometer preheated to 65 °C. The kinetics of the transformation from *N*-allylaniline to *N*,*N*-diallylaniline was determined by ^{1}H NMR spectroscopy by integrating ratio of *N*-allylaniline at δ 3.50 ppm. and *N*,*N*-diallylaniline at δ 3.73 ppm and the mesitylene signal at δ 2.21 ppm.

Ring-closing metathesis. 0.6 mL of *N*,*N*-diallylaniline (0.145 M in C_6D_6) was added to an the NMR tube with $(H_2IMes)(PCy_3)Cl_2RuCHPh$ (1.45 mg, 0.00174 mmol) under an argon atmosphere. The tube was shaken and inserted into the spectrometer at room temperature. The kinetics of the formation of 1-phenyl-2,5-dihydro-1*H*-pyrrole from *N*,*N*-diallylaniline was determined by using ^{1}H NMR spectroscopy by integrating the signal of *N*,*N*-diallylaniline at δ 3.73 ppm, 1-phenyl-2,5-dihydro-1*H*-pyrrole at δ 3.80 ppm and the mesitylene signal at δ 2.21 ppm.

Acknowledgements

Financial support from the Department of Biochemistry and Organic Chemistry, Uppsala University and Magnus Bergwalls Stiftelse is gratefully acknowledged. We thank Prof. L. Kuo for fruitful discussions.

Notes and references

1 M. Pellecchia, *US 2010/0016292 A1*.
2 Z. J. Jia, C. Venkataramani, W. Huang, M. Mehrotra, Y. Song, Q. Xu, S. M. Bauer, and A. Pandey, *WO 2009/136995 A2*.
3 T. Okuno, N. Kouyama, and M. Sakagami, *WO2007/125952 A1*.

4 J. L. Kane, B. H. Hirth, C. Yee, M. M. Staveski, H.-P. Biemann, and M. J. Pregel, *US 2007/0254894 A1*.
5 (*a*) R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233; (*b*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259.
6 L. Zhang, B. Qiu, X. Li, X. Wang, J. Li, Y. Zhang, J. Liu, J. Li and J. Shen, *Molecules*, 2006, **11**, 988.
7 S. Cerero, J. Cortes, M. Moreno-Manas, R. Pleixats and A. Roglans, *Tetrahedron*, 1998, **54**, 14869.
8 (*a*) E. Arceo, P. Marsden, R. G. Bergman and J. A. Ellman, *Chem. Commun.*, 2009, 3357; (*b*) O. Kamm and C. S. Marvel, *Org. Synth.*, 1941 **Coll Vol. 1**, 42, 1921, Vol. **1**, 15.
9 (*a*) J. Tsuji, *Acc. Chem. Res.*, 1969, **2**, 144; (*b*) B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; (*c*) M. Johansen and K. A. Jorgensen, *Chem. Rev.*, 1998, **98**, 1689.
10 (*a*) Y. Tamaru, *Eur. J. Org. Chem.*, 2005, 2647; (*b*) J. Muzart, *Tetrahedron*, 2005, **61**, 4179; (*c*) J. Muzart, *Eur. J. Org. Chem.*, 2007, 3077.
11 (*a*) S.-C. Yang and C.-W. Hung, *Synthesis*, 1999, 1747; (*b*) F. Ozawa, H. Okamoto, S. Kawagishi, S. Yamamoto, T. Minami and M. Yoshifuji, *J. Am. Chem. Soc.*, 2002, **124**, 10968; (*c*) F. Ozawa, T. Ishiyama, S. Yamamoto, S. Kawagishi and H. Murakami, *Organometallics*, 2004, **23**, 1698; (*d*) H. Kinoshita, H. Shinokubo and K. Oshima, *Org. Lett.*, 2004, **6**, 4085; (*e*) Y. Kayaki, T. Koda and T. Ikariya, *J. Org. Chem.*, 2004, **69**, 2595; (*f*) S.-C. Yang, Y.-C. Hsu and K.-H. Gan, *Tetrahedron*, 2006, **62**, 3949.
12 S. Lemarie-Audoire, M. Savignac, J. P. Genet and J.-M. Bernard, *Tetrahedron Lett.*, 1995, **36**, 1267.
13 T. Yamamoto, M. Akimoto, O. Saito and A. Yamamoto, *Organometallics*, 1986, **5**, 1559.
14 M. Kimura, M. Futamata, K. Shibata and Y. Tamaru, *Chem. Commun.*, 2003, 234.
15 (*a*) R. H. Grubbs, (Ed), *Handbook of Metathesis*, Wiley-VCH, Weinheim, 2003; (*b*) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746; (*c*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (*d*) R. Stürmer, B. Schäfer, V. Wolfart, H. Stahr, U. Kazmaier and G. Helmchen, *Synthesis*, 2001, 46.
16 G. C. Fu, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856.
17 (*a*) D. Balan and H. Adolfsson, *Tetrahedron Lett.*, 2004, **45**, 3089; (*b*) C. Yang, W. V. Murray and L. J. Wilson, *Tetrahedron Lett.*, 2003, **44**, 1783.
18 H. Ogawa, T. Aoyama and T. Shiori, *Heterocycles*, 1996, **42**, 75.
19 A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
20 A. P. Blum, T. Ritter and R. H. Grubbs, *Organometallics*, 2007, **26**, 2122.
21 K. H. Kang, K. I. Choi;, H. Y. Koh, Y. Kim, B. Y. Chung and Y. S. Cho, *Synth. Commun.*, 2001, **31**, 2277.
22 J. Jacob and W. D. Jones, *J. Org. Chem.*, 2003, **68**, 3563.
23 P. Barmettler and H.-J Hansen, *Helv. Chim. Acta*, 1990, **73**, 1515.
24 O. Rahman, T. Kihlberg and B. Långström, *Org. Biomol. Chem.*, 2004, **2**, 1612.
25 C. Che, W. Li, S. Lin, J. Chen, J. Zheng, J. C. Wu, Q. Zheng, G. Zhang, Z. Yang and B. Jiang, *Chem. Commun.*, 2009, 5990.
26 L. Adak, K. Chattopadhyay and B. C. Ranu, *J. Org. Chem.*, 2009, **74**, 3982.
27 L. A. Gharat, N. K. Joshi, J. M. Gajera, and P. S. Yadav, *WO/2008/010061 A2.*.
28 H. C. Ma and X. Z. Jiang, *J. Org. Chem.*, 2007, **72**, 8943.
29 A. L. Miller, II and N. B. Bowden, *Chem. Commun.*, 2007, 2051.
30 Z. Ding and J. J. Tufariello, *Synth. Commun.*, 1990, **20**, 227.

