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Pd-catalyzed arylation/ring-closing metathesis approach to azabicycles

Unai Martínez-Estíbalez, Nuria Sotomayor and Esther Lete*

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea, Apdo. 644, 48080 Bilbao, Spain

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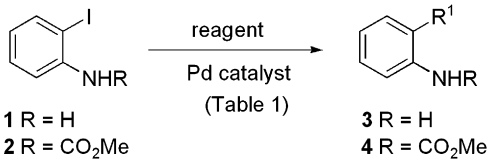
Dedicated to Professor Miguel Yus on occasion of his 60th birthday

Abstract—Palladium-catalyzed arylation followed by Grignard addition to imines and ring-closing metathesis, using Grubbs' catalysts, provides a route to six-, seven-, and eight-membered azabicycles.

Olefin ring-closing metathesis (RCM) has become a powerful tool in organic synthesis over the past decade, especially when well-characterized Mo or Ru catalysts are employed. RCM is now routinely applied to construct cyclic olefins of virtually all ring sizes containing ether, ester, amide, amine, and other functionalities.[1] Additionally, an assortment of Mo- and W-based catalysts is now available to promote asymmetric RCM, allowing access to non-racemic carbocycles and heterocycles.[2] Therefore, it has become clear that strategies based on RCM can play a crucial role in natural product synthesis.[3] Research in our group during the past years has involved the development of methods of synthesis of nitrogen heterocycles.[4] Within this context, we herein describe the combination of Pd-catalyzed arylation and Grignard reagent addition to imines with ring-closing metathesis as a strategy for the construction of six-, seven-, and eight-membered azabicycles.[5]

This strategy[6] requires first the preparation of *o*-alkenyl substituted anilines **3** and **4**. Table 1 summarizes the results for the Pd-catalyzed coupling reactions of 2-iodoaniline or the corresponding carbamate with allyl or vinyltrimethylsilane, or the corresponding stannane or boroxane compounds.

First, we examined the Heck reaction of 2-iodoaniline and allyltrimethylsilane. After extensive experimentation with different catalytic systems we found that the reaction resulted in rearrangement to propen-1-yl derivative **3b**. Thus, the use of $Pd(dba)_3/PPh_3/n\text{-}Bu_4NOAc$ in DMF at 50 °C for 24 h led to *o*-[(*E*)-2-propen-1-yl]aniline **3b** (56% yield). All attempts to avoid isomerization using lower temperatures, shorter reaction times or other catalytic systems (for instance, $Pd(AcO)_2/NEt_3$/LiCl in DMF) failed.



Scheme 1. Pd-catalyzed arylation. Preparation of anilines **3**–**4**.

Therefore, we decided to apply Stille coupling on the corresponding carbamate as described in Table 1 (entry 5). Treatment of carbamate **2** and allyltributylstannane with $Pd(dba)_2$ and PPh_3 in toluene under reflux provided the 2-allylaniline derivative **4a** in 66% yield. Although in this case, no isomerization of the alkene was observed under these Pd-catalyzed arylation reaction conditions, after hydrolysis (KOH, EtOH, reflux) of the carbamate, 2-(propen-1-yl)aniline **3b** was isolated in 76% yield. However, when $Pd(PPh_3)_4$ was used as catalyst in DMF at 100 °C, 2-allylaniline **3a** could be isolated, after washing the reaction mixture with NaF solution, in a 47% overall yield (43% from *o*-iodoaniline) (entry 6).[7]

Keywords: Pd-catalyzed arylation; Ring-closing metathesis; Imine addition; Heterocycles.
* Corresponding author. Tel.: +34 94602576; fax: +34 946012748; e-mail: esther.lete@ehu.es

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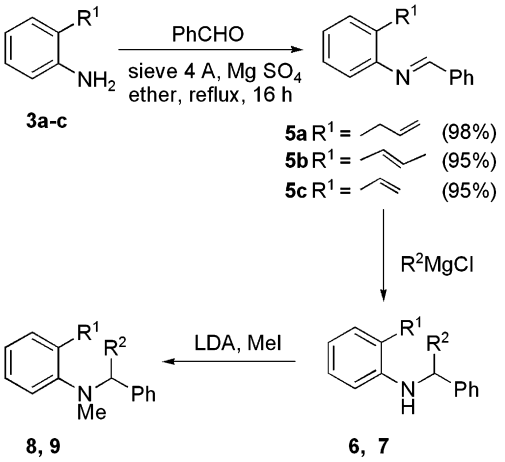
Table 1. Pd-catalyzed arylation

Entry	Substrate	Reagents and conditions	R^1	Product	Yield (%)
1	**1**	AllylTMS/Pd(dba)$_2$, PPh$_3$, *n*-Bu$_4$NOAc, sieve 4 A, DMF, 50 °C, 24 h		**3b**	56
2	**1**	AllylSnBu$_3$/Pd(dba)$_2$, PPh$_3$, toluene, reflux, 24 h		**3a**[a]	32
3	**1**	VinylSnBu$_3$/Pd(dba)$_2$, PPh$_3$, toluene, reflux, 20 h		**3c**	80
4	**1**	Trivinylcyclotriboroxane/Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DME–H$_2$O, reflux, 20 h		**3c**	55
5	**2**	AllylSnBu$_3$/Pd(dba)$_2$, PPh$_3$, toluene, reflux, 24 h		**4a**	66
6	**2**	AllylSnBu$_3$/Pd(PPh$_3$)$_4$, DMF, 100 °C, 18 h		**3a**	47[b]
7	**2**	VinylSnBu$_3$/Pd(dba)$_2$, PPh$_3$, toluene, reflux, 20 h		**4c**	60
8	**2**	VinylSnBu$_3$/Pd(PPh$_3$)$_4$, DMF, 100 °C, 18 h		**3c**	64[b]
9	**2**	Trivinylcyclotriboroxane/Pd(PPh$_3$)$_4$, K$_2$CO$_3$, DME–H$_2$O, reflux, 20 h		**4c**	77

Preparation of anilines **3**–**4**.
[a] Compound **3b** was also isolated (26%).
[b] The carbamate was hydrolyzed during work-up by washing the crude, which was washed with NaF.

In view of the moderated yields obtained, we decided to compare the procedure with the aza-Claisen rearrangement, which has been used by other authors to prepare 2-allylaniline **3a**. In our hands, treatment of *N*-allylaniline (prepared by alkylation of the aniline with allyl iodide) with $BF_3{\cdot}EtO_2$, according to the procedure described in the literature,[8] afforded the 2-allylaniline in 45% overall yield. Therefore, the Stille coupling (Table 1, entry 6) is comparable with the aza-Claisen rearrangement for the synthesis of *o*-allylaniline **3a**,[9] while the Heck reaction is the best method for the preparation of *o*-(2-propenyl)aniline **3b**.

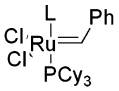
Finally, 2-vinylaniline synthesis could be accomplished both by a Stille and Suzuki coupling, either starting from *o*-iodoaniline **1** or the corresponding carbamate **2**, since the isomerization is not a problem.[10] However, as could be seen in Table 1 (entry 3), the best alternative was the Stille coupling between *o*-iodoaniline and vinyltributylstannane with Pd(dba)$_2$ as catalyst in the presence of PPh$_3$. The substituted secondary anilines **6** and **7** were synthesized by addition of Grignard reagents to *N*-benzylideneanilines **5a**–**c**, which were obtained in nearly quantitative yields by condensation of anilines **3a**–**c** with benzaldehyde. The reactions with allylmagnesium chloride were carried out by adding the Grignard reagent to a solution of the imine in THF at −78 °C and then allowing the reaction mixture to warm to −42 °C for 3 h. However, addition of vinylmagnesium chloride required higher temperatures and longer reaction times (ether, reflux, 20 h). In addition to the secondary amines, we prepared *N*-methyl substituted amines **8** and **9** via N-alkylation with MeI using LDA as base (Schemes 1 and 2, Table 2).



Scheme 2. Synthesis of secondary and tertiary anilines.

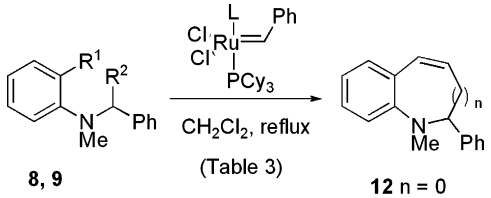
Table 2. Grignard reagents addition to imines **5a**–**c** N-alkylation

Entry	Amine	R^1	R^2	Product	Yield (%)
1	**5a**			**8a**	71
2	**5b**			**8b**	61
3	**5a**			**9a**	79
4	**5a**			**9b**	53
5	**5c**			**9c**	72



10 L = PCy_3, **11** L = Mes-N N-Mes

Figure 1. First- and second-generation Grubbs' catalysts.



8, 9

12 n = 0
13 n = 1
14 n = 2

Scheme 3. Ring-closing metathesis of substituted anilines **8**–**9**.

Table 3. Ring-closing metathesis of substituted anilines **8**–**9**

Entry	Amine	Catalyst	Time (h)	Product	Yield (%)
1	**9b**	**10** (8%)[a]	40	**12**	75
2	**9b**	**11** (8%)[a]	40	**12**	40[b]
3	**9c**	**10** (8%)[c]	64	**12**	8
4	**9c**	**11** (8%)[d]	20	**12**	14[e]
5	**8b**	**10** (8%)[d]	48	**13**	75
6	**9a**	**10** (20%)[d]	40	—	—
7	**9a**	**11** (20%)[a]	46	—	—
8	**8a**	**10** (8%)[a]	40	**14**	68
9	**8a**	**11** (8%)[a]	40	**14**	61

[a] Three portions of the catalyst were added at 0, 16, and 27 h.
[b] Conversion: 75%.
[c] Four portions of the catalyst were added at 0, 12, 24, and 36 h.
[d] Two portions of the catalyst were added at 0 and 8 h.
[e] Conversion: 50%.

With these precursors in hand, we undertook the ring-closing metathesis experiments (Table 3, Scheme 3). As it could be expected,[11] when we examined RCM of secondary amines **6** and **7** and screened first and second-generation Grubbs' catalysts **10** and **11** unreacted starting material was always recovered (see Fig. 1).

However, we were pleased to find that the six-membered ring precursor **9b** (Table 3, entries 1, 2) underwent ring closure after heating under CH_2Cl_2 reflux for 12 h, using 8 mol % first-generation Grubbs' catalyst (the reaction was monitored by TLC and ^1H NMR). 2-Phenyldihydroquinoline **12** was isolated in good yields (75% and 40%, respectively).[12] However, with amine **9c** as substrate, the yield dropped to the 8% when the same catalyst was used; the reaction was sluggish and no starting material could be recovered. The yield only could be increased to 14% (50% conversion) using second-generation Grubbs' catalyst. To obtain the seven-membered cyclic amine, the use of Grubbs catalyst **10** for the RCM of amine **8b** operating at 40 °C for 68 h (entry 5) gave an optimal result and benzazepine **13** was isolated in 75% yield. In contrast, with the same catalyst, and also with the second-generation Grubbs' catalyst, **9a** did not cyclize. Finally, amine **8a** was subjected to first- and second-generation Grubbs' catalysts under reflux of dichloromethane, and benzazocine **14**[13] was obtained in 68% and 61% yields, respectively.[14] Besides, although the formation of nitrogen heterocycles, mainly eight-membered rings, often requires the use of more expensive second-generation Grubbs' or Molybdenum catalysts, in our case the first-generation Grubbs' catalyst has turned out to be the best (Table 3, Scheme 3).

In conclusion, we have demonstrated that the palladium-catalyzed arylation may be combined with nucleophilic addition to imines, and ring-closing metathesis to provide a general approach to 2-phenyl substituted quinoline, benzazocine, and benzazepine derivatives, that could compete with previously reported strategies.[15] It should be noted that RCM has proven to be an efficient method for the direct construction, not only of six- and seven-membered azabicycles, but also of the more challenging heterocyclic eight-membered rings from the appropriate acyclic precursors.

Acknowledgments

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