

# Transition Metal-Catalysed Intramolecular Carbenoid C–H Insertion for Pyrrolidine Formation by Decomposition of $\alpha$ -Diazoesters

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Received: ((will be filled in by the editorial staff))



Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>.

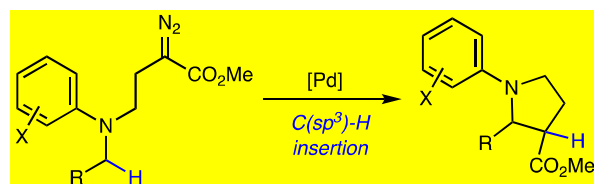
**Abstract.** The use of Pd-, Rh(II)- and Ru(II)-based catalysts has been explored in the transition metal-catalysed intramolecular carbenoid C–H insertion of  $\alpha$ -diazoesters leading to pyrrolidines. Although the outcome of the reaction was highly substrate-dependent, in general, it was possible to control the chemoselectivity of the process towards pyrrolidines by adequate catalyst selection. The Pd(0)-catalysts were as efficient as [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> in promoting the C(sp<sup>3</sup>)-H insertion of *ortho*-substituted anilines. In contrast, for anilines bearing *meta*- and *para*-substituents, the Rh(II)-catalyst provided the best chemoselectivities and reaction yields. On the other hand, [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> was the most efficient catalyst for the insertion reaction of the *N*-benzyl-*N*-phenyl and *N,N*-dibenzyl  $\alpha$ -diazoesters, while the C(sp<sup>3</sup>)-H insertion of the *N*-benzylsulfonamide substrate was only promoted by [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>. According to density functional theory (DFT) calculations, the mechanism involved in the Pd(0)- and Ru(II)-catalysed C(sp<sup>3</sup>)-H insertions differs considerably from that typically proposed for the Rh(II)-catalysed transformation. Whereas the Pd(0)-catalysed reaction involves a Pd-mediated 1,5-H migration from the C(sp<sup>3</sup>)-H bond to the carbenoid carbon atom leading to the formal oxidation of the transition metal, a Ru(II)-promoted Mannich type reaction involving a zwitterionic intermediate seems to be operative in the Ru(II)-catalysed transformation.

**Keywords:** carbenoid insertion; diazo compounds; pyrrolidines; palladium-catalysis; density functional theory calculations

## Introduction

The transition metal-catalysed intramolecular carbenoid C–H insertion by decomposition of  $\alpha$ -diazocarbonyl compounds constitutes a powerful methodology for C–C bond formation.<sup>[1]</sup> For a given

substrate, several C–H insertion pathways may be available, the chemoselectivity and regioselectivity being dependent on the nature of both the substrate and the catalyst.<sup>[2]</sup> Many transition metal complexes have proven to be effective catalysts to generate reactive metal-carbenoids starting from  $\alpha$ -diazocarbonyl compounds.<sup>[3]</sup> Among them, rhodium(II),<sup>[4]</sup> copper(I),<sup>[5]</sup> and more recently ruthenium(II) catalysts<sup>[6]</sup> have been particularly useful for the development of highly selective carbenoid C–H insertion methodologies via a variety of reaction modes. Surprisingly, palladium, one of the most commonly employed metals in homogeneous catalysis, has been scarcely applied to this type of processes.<sup>[7]</sup> In this context, we recently reported that palladium catalysts are able to promote the intramolecular carbenoid C–H insertion of  $\alpha$ -diazoesters to produce pyrrolidines through C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond formation (Scheme 1).<sup>[8,9]</sup>



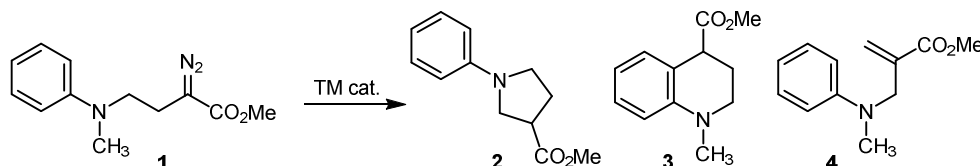
**Scheme 1.** Palladium-catalysed C(sp<sup>3</sup>)-H insertion.

Most of the extensive research on the transition metal-catalysed carbenoid C–H insertion has focused on studying different diazo compounds or a range of ligands, but without varying the nature of transition metal.<sup>[10]</sup> The aim of the current work is to compare the influence of the transition metal moiety on the reactivities and selectivities of the carbenoid C–H insertion of amino-tethered  $\alpha$ -diazoesters to

ultimately achieve selective catalyst-controlled insertion reactions. Thus, herein we present a full account of our experimental and computational studies on the transition metal-catalysed intramolecular insertion of  $\alpha$ -diazesters using Pd(0), Rh(II) as well as Ru(II) catalysts, in the search for a suitable methodology for the synthesis of pyrrolidines.

## Results and Discussion

**Table 1.** Transition metal-catalysed cyclization of  $\alpha$ -diazester **1**.



Entry	[TM cat.] (mol%) ligand (mol%)	Base <sup>[a]</sup>	Solvent	Temperature	Time	Product ratio	Yield (%) <sup>[b],[c]</sup>
1	Pd(OAc) <sub>2</sub> (10)	Cs <sub>2</sub> CO <sub>3</sub> (2)	CHCl <sub>3</sub>	reflux	48 h	<b>2/3</b> (2:1) <sup>[d]</sup>	<b>2/3</b> (2:1, 45%)
2	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	Cs <sub>2</sub> CO <sub>3</sub> (2)	DCE	80 °C	24 h	<b>2/3</b> (2.2:1) <sup>[d]</sup>	
3	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	Cs <sub>2</sub> CO <sub>3</sub> (2)	DCE	80 °C	24 h	<b>2/3</b> (2.6:1) <sup>[e]</sup>	<b>2/3</b> (2.6:1, 57%)
4	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) dppp (5)	Cs <sub>2</sub> CO <sub>3</sub> (2)	DCE	80 °C	22 h	<b>2/3</b> (2.7:1) <sup>[e]</sup>	<b>2/3</b> (2.7:1, 51%)
5	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) dppf (5)	Cs <sub>2</sub> CO <sub>3</sub> (2)	DCE	80 °C	24 h	<b>2/3</b> (2.8:1) <sup>[e]</sup>	<b>2/3</b> (2.8:1, 55%)
6	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	----	DCE	80 °C	24 h	<b>2/3</b> (2.1:1) <sup>[d]</sup>	<b>2/3</b> (2.1:1, 55%)
7	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	----	CHCl <sub>3</sub>	reflux	24 h	<b>2/3</b> (1:1) <sup>[d]</sup>	<b>2/3</b> (1:1, 60%)
8	[Pd(allyl)Cl] <sub>2</sub> (5)	----	CHCl <sub>3</sub>	reflux	24 h	<b>2/3/4</b> (1.5:1:1.2) <sup>[d]</sup>	
9	Pd(OAc) <sub>2</sub> (100)	Cs <sub>2</sub> CO <sub>3</sub> (2)	CHCl <sub>3</sub>	r.t.	100 h	<b>2/3</b> (3.5:1) <sup>[d]</sup>	<b>2/3</b> (3.5:1, 51%)
10	Pd <sub>2</sub> (dba) <sub>3</sub> (35) dppf (70)	Cs <sub>2</sub> CO <sub>3</sub> (2)	DCE	r.t.	120 h	<b>2/3</b> (5:1) <sup>[d]</sup>	<b>2/3</b> (5:1, 63%)
11	Pd(TFA) <sub>2</sub> (20)	----	CHCl <sub>3</sub>	r.t.	24 h	<b>2/3/4</b> (2.5:1:2.5) <sup>[d]</sup>	
12	[Rh(OAc) <sub>2</sub> ] <sub>2</sub> (4)	----	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	24 h	<b>2/3</b> (2.4:1) <sup>[d]</sup>	<b>2/3</b> (2.4:1, 75%)
13	[Rh(TFA) <sub>2</sub> ] <sub>2</sub> (4)	----	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	6 h	<b>2/3/4</b> (3:1:5) <sup>[d]</sup>	<b>2</b> (25%), <b>4</b> (41%)
14	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (3)	----	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	5 h	<b>2/3</b> (9:1) <sup>[d]</sup>	<b>2/3</b> (9:1, 94%)
15	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	----	CH <sub>2</sub> Cl <sub>2</sub>	-10 °C	5 h	<b>2/3</b> (9:1) <sup>[d]</sup>	<b>2/3</b> (9:1, 95%)
16	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	----	CH <sub>2</sub> Cl <sub>2</sub>	-78 °C	5 h	<b>2/3</b> (9:1) <sup>[d]</sup>	<b>2/3</b> (9:1, 89%)
17	[Ru( <i>p</i> -cymene)Cl] <sub>2</sub> (3)	----	toluene	40 °C	24 h	<b>2</b> <sup>[f]</sup>	<b>2</b> (49%)

<sup>[a]</sup> Equivalents in parentheses. <sup>[b]</sup> Yields refer to products isolated by chromatography. <sup>[c]</sup> For product mixtures the yield refers to the combined yield. <sup>[d]</sup> Product ratio measured by <sup>1</sup>H NMR. <sup>[e]</sup> Product ratio measured by GC. <sup>[f]</sup> Traces of **3** were also observed in the crude reaction mixture. Pd<sub>2</sub>(dba)<sub>3</sub>: Tris(dibenzylideneacetone)dipalladium(0). dppp: 1,3-Bis(diphenylphosphino)propane. dppf: 1,1'-Bis(diphenylphosphino)ferrocene. Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene. [(IMes)Pd(NQ)]<sub>2</sub> = 1,3-Bis(2,4,6-trimethylphenyl)imidazol-2-ylidene (1,4-naphthoquinone)palladium(0) dimer.

With these data in hand, we decided to look more closely at the palladium-catalysed carbenoid insertion of  $\alpha$ -diazester **1**. Although these reactions were performed in the presence of Cs<sub>2</sub>CO<sub>3</sub>, our previous DFT computational studies<sup>[8]</sup> suggested that when using a Pd(0) catalyst, this base is not necessary for the C–H insertion reaction to take place. This was experimentally confirmed by treatment of **1** with a catalytic amount of Pd<sub>2</sub>(dba)<sub>3</sub> in the absence of Cs<sub>2</sub>CO<sub>3</sub>, which afforded a similar result to that obtained in the presence of the base (compare entries

2 and 6, Table 1). Other palladium catalysts lacking phosphine ligands were also explored in order to increase the selectivity of the insertion reaction. Unfortunately, when using [(IMes)Pd(NQ)]<sub>2</sub> as the catalyst a 1:1 mixture of **2** and **3** was obtained (entry 7, Table 1), while [Pd(allyl)Cl]<sub>2</sub> led to a mixture of **2**, **3**, and alkene **4**<sup>[11]</sup> (entry 8, Table 1). We found that the reaction can also proceed at room temperature, although longer reaction time and higher catalyst loading are required (entries 9-10, Table 1). Thus, treatment of **1** with an equimolar

amount of Pd(OAc)<sub>2</sub> in CHCl<sub>3</sub> at room temperature gave a 3.5:1 mixture of pyrrolidine **2** and tetrahydroquinoline **3** (entry 9, Table 1), while using Pd<sub>2</sub>(dba)<sub>3</sub> (35 mol%) and dppf (70 mol%) in DCE provided a 5:1 mixture of **2** and **3** (entry 10, Table 1). Interestingly, the chemoselectivity of both reactions was quite different from that obtained when using the same catalytic systems at higher temperatures (compare entries 1 and 4 with entries 9 and 10, respectively). On the other hand, treatment of **1** with a catalytic amount of Pd(TFA)<sub>2</sub> at room temperature afforded a mixture of **2**, **3**, and alkene **4** (entry 11, Table 1).

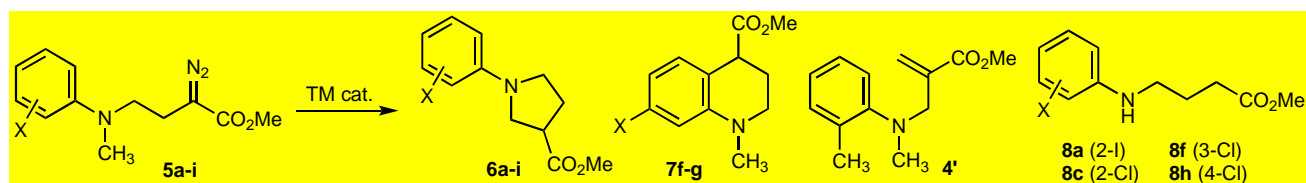
Some commercially available dirhodium(II) carboxylate catalysts as well as [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> were also explored to promote the carbenoid insertion of  $\alpha$ -diazooester **1**. The use of Rh<sub>2</sub>(OAc)<sub>4</sub> afforded a mixture of pyrrolidine **2** and tetrahydroquinoline **3** (2.4:1 ratio), which were isolated in 75% combined yield (entry 12, Table 1). Changing the catalyst from Rh<sub>2</sub>(OAc)<sub>4</sub> to Rh<sub>2</sub>(TFA)<sub>4</sub> resulted in the formation of alkene **4** as the major product (entry 13, Table 1), while [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> gave a 9:1 mixture of **2** and **3** in a combined 94% reaction yield (entry 14, Table 1).

A similar chemoselectivity was observed when the reaction was performed at lower temperatures (entries 15-16, Table 1). The best selectivity in the C–H insertion of  $\alpha$ -diazooester **1** was obtained when using [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> as the catalyst, although the yield dropped to 49% (entry 17, Table 1).

The results in Table 1 therefore indicate that the carbenoid C–H insertion of  $\alpha$ -diazooester **1** can be promoted by either Pd(0) or Pd(II), as well as by Rh(II) and Ru(II)-based catalysts, the C(sp<sup>3</sup>)–H rather than C<sub>Ar</sub>(sp<sup>2</sup>)–H insertion being favoured in all cases.

In order to seek more information about the catalyst-controlled selectivity in the above carbenoid C–H insertion of  $\alpha$ -diazooesters to form pyrrolidines, we then explored the reaction starting from a variety of substrates. Firstly, we investigated the effect of introducing substituents at the aniline ring on the process. Table 2 gathers the reactions of substrates bearing different substituents at the aryl ring in the presence of [(IMes)Pd(NQ)]<sub>2</sub>, [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> or [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> as the catalyst. For the sake of comparison, the results previously obtained with Pd<sub>2</sub>(dba)<sub>3</sub> are also included.<sup>[18]</sup>

**Table 2.** Transition metal-catalysed reactions of  $\alpha$ -diazooesters **5a-i**.



Entry	<b>5</b> (X)	[TM cat.] (mol%)/ligand (mol%)	Solvent	Temperature	Product Yield [%] <sup>[a]</sup>
1	<b>5a</b> (2-I)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	CHCl <sub>3</sub>	reflux	<b>6a</b> (89)
2	<b>5a</b> (2-I)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>6a</b> (85)
3	<b>5a</b> (2-I)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6a</b> (70)
4	<b>5a</b> (2-I)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6a</b> (66) <sup>[f]</sup>
5	<b>5b</b> (2-Br)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	CHCl <sub>3</sub>	reflux	<b>6b</b> (66)
6	<b>5b</b> (2-Br)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>6b</b> (70)
7	<b>5b</b> (2-Br)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6b</b> (82)
8	<b>5b</b> (2-Br)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6b</b> (61)
9	<b>5c</b> (2-Cl)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)/dppf (5) <sup>[b]</sup>	DCE	80 °C	<b>6c</b> (69)
10	<b>5c</b> (2-Cl)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>6c</b> (85)
11	<b>5c</b> (2-Cl)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6c</b> (88)
12	<b>5c</b> (2-Cl)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6c</b> (57) <sup>[g]</sup>
13	<b>5d</b> (2-F)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	DCE	80 °C	<b>6d</b> (62)
14	<b>5d</b> (2-F)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>6d</b> (71)
15	<b>5d</b> (2-F)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6d</b> (87)
16	<b>5d</b> (2-F)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6d</b> (56)
17	<b>5e</b> (2-Me)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	DCE	80 °C	<b>6e</b> (58)
18	<b>5e</b> (2-Me)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>6e</b> (68), <b>4'</b> (10)
19	<b>5e</b> (2-Me)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6e</b> (56), <b>4'</b> (27)
20	<b>5e</b> (2-Me)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6e</b> (46)
21	<b>5f</b> (3-Cl)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	DCE	80 °C	<b>6f/7f</b> (2.7:1, 45)
22	<b>5f</b> (3-Cl)	[(IMes)Pd(NQ)] <sub>2</sub> (4) <sup>[c]</sup>	CHCl <sub>3</sub>	reflux	<b>CM</b> <sup>[h]</sup>
23	<b>5f</b> (3-Cl)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6f</b> (92)
24	<b>5f</b> (3-Cl)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6f</b> (33) <sup>[i]</sup>
25	<b>5g</b> (3-MeO)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	DCE	80 °C	<b>6g/7g</b> (1.5:1, 47)
26	<b>5g</b> (3-MeO)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6g</b> (81)
27	<b>5g</b> (3-MeO)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6g</b> (55)

28	<b>5h</b> (4-Cl)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)/dppf (5) <sup>[b]</sup>	DCE	80 °C	<b>6h</b> (35) <sup>[j]</sup>
29	<b>5h</b> (4-Cl)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (3) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6h</b> (78)
30	<b>5h</b> (4-Cl)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6h</b> (34) <sup>[k]</sup>
31	<b>5i</b> (4-MeO)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5) <sup>[b]</sup>	CHCl <sub>3</sub>	reflux	<b>6i</b> (38) <sup>[l]</sup>
32	<b>5i</b> (4-MeO)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (3) <sup>[d]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>6i</b> (74)
33	<b>5i</b> (4-MeO)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3) <sup>[e]</sup>	toluene	40 °C	<b>6i</b> (85)

<sup>[a]</sup> Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. <sup>[b]</sup> Reaction conditions: Catalyst/ligand (see table) and Cs<sub>2</sub>CO<sub>3</sub> (2 equiv.) in CHCl<sub>3</sub> or DCE at the indicated temperature for 24 h. <sup>[c]</sup> Reaction conditions: Catalyst (see table) in CHCl<sub>3</sub> at reflux for 24 h. <sup>[d]</sup> Reaction conditions: [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> (see table) in CH<sub>2</sub>Cl<sub>2</sub> at r.t. for 5 h. <sup>[e]</sup> Reaction conditions: [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (see table) in toluene at 40 °C (bath temperature) for 24 h. <sup>[f]</sup> **8a** (≈10%) was also obtained. <sup>[g]</sup> **8c** (≈5%) was also obtained. <sup>[h]</sup> Complex mixture in which trace amounts of **6f** and **7f** were observed. <sup>[i]</sup> Small amounts of **8f** were also observed in the reaction mixture. <sup>[j]</sup> <sup>1</sup>H NMR analysis of the reaction mixture showed a ≈4:1 C(sp<sup>3</sup>)-H/C<sub>Ar</sub>(sp<sup>2</sup>)-H activation ratio. <sup>[k]</sup> **8h** (15%) was also obtained. <sup>[l]</sup> <sup>1</sup>H NMR analysis of the reaction mixture showed a ≈5:1 C(sp<sup>3</sup>)-H/C<sub>Ar</sub>(sp<sup>2</sup>)-H activation ratio.

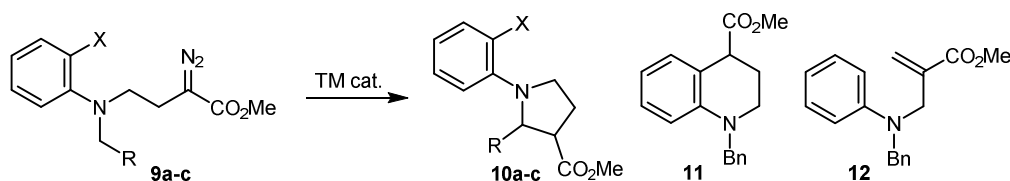
As can be seen in Table 2, the effect of the substituent on the course of the process varied according to its position on the aniline ring as well as the nature of the transition-metal catalyst employed. Thus, the *ortho*-substituted anilines chemoselectively underwent C(sp<sup>3</sup>)-H insertion to give the corresponding pyrrolidines regardless of the transition-metal catalyst or the nature of the substituent (entries 1-20, Table 2). For these substrates, the Pd(0)-catalysts were at least as efficient as [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, while [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> invariably provided the worst yields. When using either the [(IMes)Pd(NQ)]<sub>2</sub> or the Rh(II)-catalyst to promote the reaction of the highly crowded *ortho*-methyl substituted aniline **5e**, significant amounts of the rearranged alkene **4'** were also isolated (entries 18-19, Table 2). It is worth noting that no product resulting from the potentially competitive palladium-catalysed reaction of the aryl halide with the  $\alpha$ -diazoester moiety<sup>[12]</sup> was observed in any of the palladium-catalysed reactions of **5a** and **5b** (entries 1, 2, 5 and 6, Table 2). This could allow further synthetic transformation by transition metal-catalysed coupling reactions from these substrates.

On the other hand, competition between C(sp<sup>3</sup>)-H and C<sub>Ar</sub>(sp<sup>2</sup>)-H insertion was evident in the reactions involving *meta*- and *para*-substituted anilines when using Pd<sub>2</sub>(dba)<sub>3</sub> as the catalyst, despite the C(sp<sup>3</sup>)-H insertion still being the preferred reaction pathway (entries 21, 25, 28 and 31, Table 2). The use of [(IMes)Pd(NQ)]<sub>2</sub> as the catalyst to promote the reaction of **5f** resulted in a complex mixture, in which only trace amounts of the insertion products were observed (entry 22). Similar results were observed

when this catalyst was used with **5g-i**. In contrast, in the presence of either the Rh(II) or Ru(II)-based catalysts, these anilines led to the corresponding pyrrolidines with complete chemoselectivity but with different yields. Thus, whereas all the pyrrolidines were obtained in good yields when using [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, in the presence of the Ru(II)-catalyst the yields for the substrates having a Cl-substituent were far worse than for those bearing a MeO group. Interestingly, in some of the reactions using [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (entries 4, 12, 24 and 30, Table 2) minor amounts of the secondary aniline (i.e. **8a,c,f,h**), resulting from the demethylation and protonation of the starting diazoester, were also observed (*vide infra*).

The palladium-catalysed C-H insertion reaction was not limited to *N*-methylanilines but also proved suitable for secondary C(sp<sup>3</sup>)-H bonds. Table 3 gathers the results obtained in the reactions with the anilines bearing diverse *N*-methylene moieties when using the palladium catalysts as well as [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> and [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>. Thus, *N*-benzyl-2-iodoaniline **9a** chemoselectively afforded pyrrolidine **10a** (5.5:1 *cis/trans* ratio) in 66% yield when the reaction was performed in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> (entry 1, Table 3). Changing the catalyst to [(IMes)Pd(NQ)]<sub>2</sub> gave a similar reaction (entry 2, Table 3). [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> (entry 3, Table 3) and [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (entry 4, Table 3) also promoted the C(sp<sup>3</sup>)-H insertion to give ≈3.3:1 mixtures of the *cis/trans* isomers, the Rh(II)-catalyst affording the higher yield.

**Table 3.** Transition metal-catalysed reactions of  $\alpha$ -diazoesters **9a-c**.



Entry	<b>9</b>	[TM cat.] (mol%)/ligand (mol%) <sup>[a]</sup>	Solvent	Temperature	Product Yield [%] <sup>[b]</sup>
1	<b>9a</b> (X:I, R:C <sub>6</sub> H <sub>5</sub> )	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>10a</b> (66, <i>cis/trans</i> 5.5:1)



2	<b>9a</b> (X:I, R:C <sub>6</sub> H <sub>5</sub> )	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>10a</b> (70, <i>cis/trans</i> 5.5:1)
3	<b>9a</b> (X:I, R:C <sub>6</sub> H <sub>5</sub> )	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>10a</b> (75, <i>cis/trans</i> 3.3:1)
4	<b>9a</b> (X:I, R:C <sub>6</sub> H <sub>5</sub> )	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3)	toluene	40 °C	<b>10a</b> (60, <i>cis/trans</i> 3.4:1)
5	<b>9b</b> (X:I, R:CH=CH <sub>2</sub> )	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>10b</b> (58, <i>cis/trans</i> 1.7:1)
6	<b>9b</b> (X:I, R:CH=CH <sub>2</sub> )	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>10b</b> (68, <i>cis/trans</i> 1.8:1)
7	<b>9b</b> (X:I, R:CH=CH <sub>2</sub> )	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>10b</b> (80, <i>cis/trans</i> 1.6:1)
8	<b>9b</b> (X:I, R:CH=CH <sub>2</sub> )	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3)	toluene	40 °C	<b>10b</b> (43, <i>cis/trans</i> 1:1.2)
9	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	CHCl <sub>3</sub>	reflux	<i>cis</i> - <b>10c</b> (28), <sup>[c]</sup> <b>11</b> (17)
10	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)/dppf (5)	DCE	80 °C	<i>cis</i> - <b>10c</b> (19), <sup>[c]</sup> <b>11</b> (19)
11	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	Pd(PPh <sub>3</sub> ) <sub>4</sub> (5)	DCE	80 °C	<i>cis</i> - <b>10c</b> (10), <sup>[c]</sup> <b>11</b> (25)
12	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	CHCl <sub>3</sub>	reflux	<i>cis</i> - <b>10c</b> / <b>11</b> (1:1.9, 75)
13	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	[Pd(allyl)Cl] <sub>2</sub> (5)	CHCl <sub>3</sub>	reflux	<i>cis</i> - <b>10c</b> / <b>11</b> / <b>12</b> (1:1.4:1.1) <sup>[d]</sup>
14	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<i>cis</i> - <b>10c</b> / <b>11</b> (1:1.6, 73) <sup>[e]</sup>
15	<b>9c</b> (X:H, R:C <sub>6</sub> H <sub>5</sub> )	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3)	toluene	40 °C	<i>cis</i> - <b>10c</b> (47), <i>trans</i> - <b>10c</b> (44)

<sup>[a]</sup> See Table 2 for reaction conditions. <sup>[b]</sup> Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. <sup>[c]</sup> **Trans-10c** (<5%) was also observed in the crude reaction mixture. <sup>[d]</sup> Product ratio measured by <sup>1</sup>H NMR, yield not quantified. <sup>[e]</sup> **12** (<10%) was also observed in the crude reaction mixture.

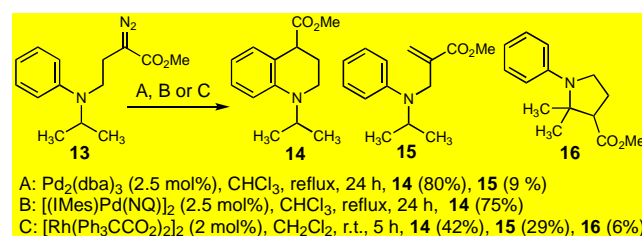
Treatment of *N*-allyl-2-iodoaniline **9b** with catalytic amounts of either Pd<sub>2</sub>(dba)<sub>3</sub> (entry 5, Table 3) or [(IMes)Pd(NQ)]<sub>2</sub> (entry 6, Table 3) in CHCl<sub>3</sub> at reflux afforded pyrrolidine **10b** (≈1.7:1 *cis/trans* ratio) in acceptable yields. The use of [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> increased the yield up to 80% (entry 7, Table 3). When the reaction was promoted by [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> a slight change in the *cis/trans* selectivity and a decrease in the cyclization yield was observed (entry 8, Table 3).

It should be pointed out that, similar to the reactions involving 2-iodoaniline **5a** and 2-bromoaniline **5b**, no product resulting from the competitive palladium-catalysed reaction of the aryl iodide with the α-diazoester moiety was observed in any of the considered palladium-catalysed reactions of 2-iodoanilines **9a-b** (entries 1, 2, 5 and 6, Table 3). On the other hand, and more importantly, no competition between the possible allylic insertion and cyclopropanation<sup>[13]</sup> was apparent in either of the transition metal-catalysed reactions of *N*-allylaniline **9b** (entries 5-8, Table 3).

The reaction of *N*-benzylaniline **9c**, which has no substituent at the *ortho* position, was also explored. Similar to the reactions involving *N*-methylaniline **1**, the C(sp<sup>3</sup>)-H and C<sub>Ar</sub>(sp<sup>2</sup>)-H insertions competed when using the Pd- or the Rh(II)-based catalysts (entries 9-14, Table 3). Thus, for example, treatment of **9c** with catalytic amounts of either [(IMes)Pd(NQ)]<sub>2</sub> (entry 12, Table 3) or [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> (entry 14, Table 3) resulted in the formation of mixtures of pyrrolidine *cis*-**10c** and tetrahydroquinoline **11** with similar C-H activation selectivities and in a yield up to 75%. In contrast, in the presence of [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>, the insertion proceeded selectively at the C(sp<sup>3</sup>)-H bond (entry 15, Table 3). While *cis*-**10c** was selectively produced with the Pd- or Rh(II)-based catalysts, no stereoselectivity was observed in the C(sp<sup>3</sup>)-H insertion when using the Ru(II) catalyst.

Interestingly, the C<sub>Ar</sub>(sp<sup>2</sup>)-H insertion was favoured in the transition metal-catalysed reactions of

*N*-isopropylaniline **13** (Scheme 2). The use of Pd<sub>2</sub>(dba)<sub>3</sub> as the catalyst led to the chemoselective formation of tetrahydroquinoline **14**, which was isolated in 80% yield together with alkene **15** (9%). Changing the catalyst to [(IMes)Pd(NQ)]<sub>2</sub> resulted in the exclusive formation of **14** (75%). In contrast, the use of [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> afforded a mixture of tetrahydroquinoline **14** (42%), alkene **15** (29%), and pyrrolidine **16** (6%). Unfortunately, no reaction was observed when **13** was treated with [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>, the starting material being recovered unchanged.



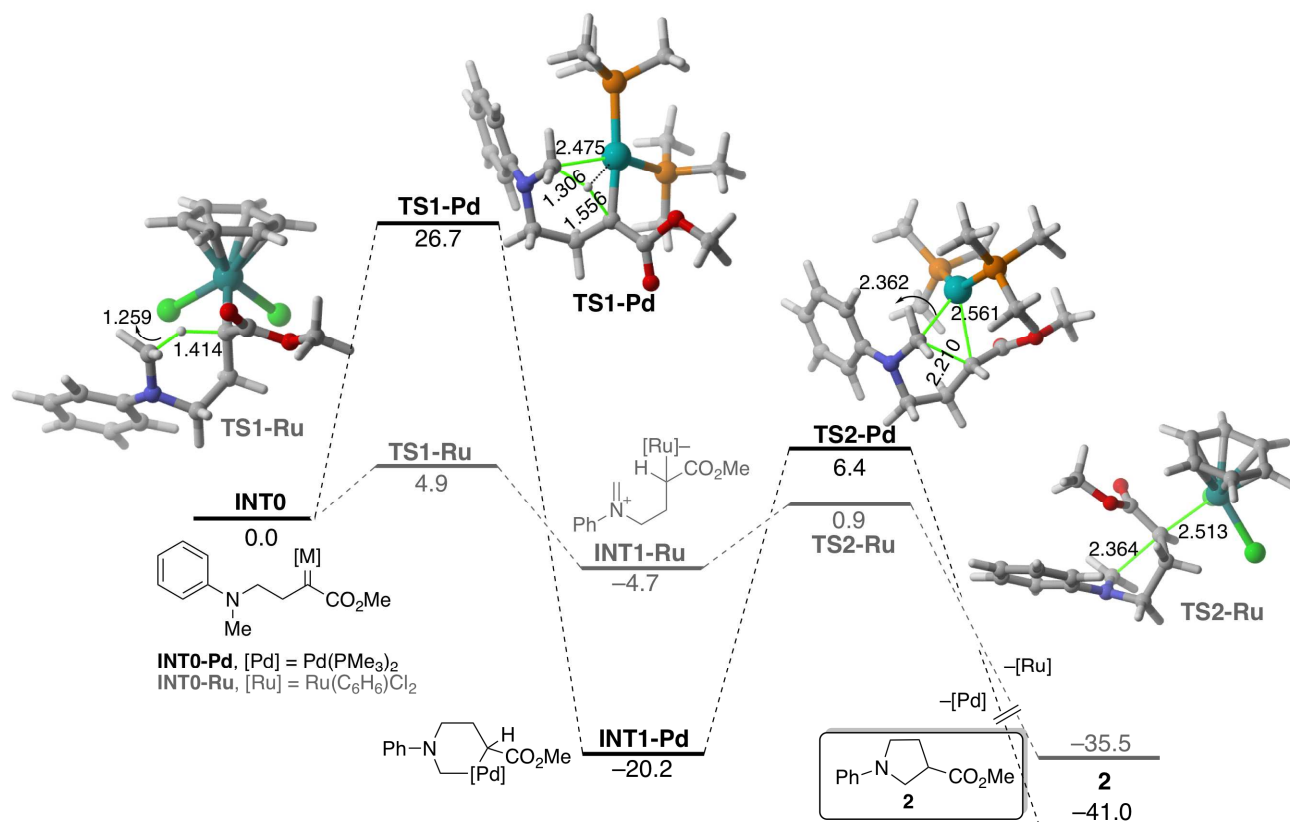
**Scheme 2.** TM-catalysed reactions of α-diazoester **13**.

Some comments on the above transition metal-catalysed C-H insertion reactions of aniline-type substrates are warranted. As in similar Rh(II)-mediated transformations,<sup>[14]</sup> the site selectivity of the metal-carbenoid insertions is probably governed by a combination of electronic, steric as well as conformational factors. Thus, in freely rotating systems, like those considered in this work, the 1,5 C(sp<sup>3</sup>)-H insertion is overwhelmingly predominant due to the entropically favourable six-membered transition states (see below). However, the sterically encumbered *N*-isopropyl aniline overturns this preference in favour of the formation of the six-membered ring by insertion into the C<sub>Ar</sub>(sp<sup>2</sup>)-H bond.

Our previous DFT calculations suggested that the Pd(0)-dppf catalysed C(sp<sup>3</sup>)-H insertion of aniline **1** proceeds via a genuine stepwise reaction mechanism

involving (i) the formation of an initial pallada(0)carbene complex, (ii) a Pd-mediated 1,5-hydrogen migration, which results in the formal oxidation of the transition metal, and (iii) the final reductive elimination leading to the observed pyrrolidine **2** with concomitant release of the active Pd(0)-dppe catalyst.<sup>[8]</sup> At this point, we first checked the generality of this unprecedented Pd(0)-mediated mechanism using the model Pd(PMe<sub>3</sub>)<sub>2</sub> (see Figure 1) and Pd(NHC) (NHC = 1,3-bis(phenyl)-imidazol-2-ylidene) catalysts (see Figure S1 in the Supporting Information). From the data in Figures 1 and S1, it

becomes clear that the C(sp<sup>3</sup>)-H insertion reaction proceeds through an identical mechanism to that reported previously for the Pd(0)-dppe catalytic system.<sup>[8]</sup> In the particular case of the Pd(NHC) catalyst, our calculations indicate that the initial 1,5-H migration is thermodynamically favoured ( $\Delta\Delta G_R = -5.0$  kcal/mol) and the subsequent reductive elimination becomes kinetically easier ( $\Delta\Delta G^\ddagger = 5.7$  kcal/mol) than the process involving PMe<sub>3</sub> as the ligand in the coordination sphere of palladium (see Figure S1).



**Figure 1.** Computed reaction profiles for the formation of pyrrolidine **2**. Relative free energies ( $\Delta G_{298}$ , at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively. All data were computed at the PCM(CHCl<sub>3</sub>)-M06L/def2-TZVPP//PCM(CHCl<sub>3</sub>)-B3LYP-D3/def2-SVP level.

Similar to the Pd(0)-catalysed process, the analogous carbenoid C-H insertion involving the Ru(II)-catalyst (Ru(C<sub>6</sub>H<sub>6</sub>)Cl<sub>2</sub> in the calculations) also proceeds stepwise (Figure 1). However, from a mechanistic point of view, the Ru(II)-mediated transformation is completely different. According to our calculations, the initial ruthena(II)carbene INT0-Ru evolves to the zwitterionic complex INT1-Ru through the transition state TS1-Ru with a rather low activation barrier of 4.9 kcal/mol in an exergonic transformation ( $\Delta G_R = -4.7$  kcal/mol). Although this step can also be viewed as a 1,5-H migration, thus resembling the Pd(0)-mediated process, it is not directly assisted by the transition metal, and therefore, no oxidation of the ruthenium centre occurs. As a result, the zwitterionic intermediate INT1-Ru, which

is stabilized by conjugation from the lone-pair of the aniline nitrogen atom, is produced. This finding sheds light on the crucial role of the heteroatom directly attached to the involved Csp<sup>3</sup> atom in the Ru(II)-promoted process, as will be discussed below. Finally, INT1-Ru is easily transformed into the observed pyrrolidine **2** via TS2-Ru (activation barrier of only 5.6 kcal/mol) in a strongly exergonic transformation ( $\Delta G_R = -30.8$  kcal/mol) that releases the active catalytic species. As depicted in Figure 1, the latter saddle point is associated with the simultaneous C-Ru bond rupture and C-C bond formation.<sup>[15]</sup> Therefore, this transformation can be considered as an intramolecular Ru(II)-promoted Mannich type reaction. The intermediacy of a zwitterionic intermediate in the Ru(II)-catalysed reactions is

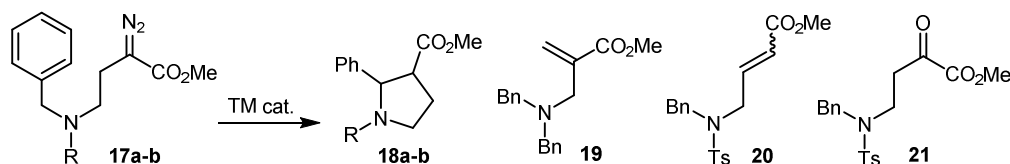
experimentally supported by the formation of minor amounts of the secondary anilines **8a,c,f,h** in the insertion reactions of  $\alpha$ -diazoesters **5a,c,f,h**. These anilines would be formed by the competitive hydrolysis of the iminium moiety and simultaneous protonolysis of the Ru(II)-enolate function of the zwitterionic species.

Interestingly, both Pd(0)- and Ru(II)-mediated mechanisms are fundamentally different from that proposed for related Rh(II)-catalysed (and also Cu-

catalysed) C–H insertions, which are assumed to proceed in a concerted but asynchronous manner that directly releases the insertion product and the metal catalyst in a single reaction step.<sup>[16]</sup>

Once the influence of the catalyst on the process was experimentally and computationally revealed, the carbenoid C(sp<sup>3</sup>)-H insertion reactions of some non-aniline substrates were investigated (Table 4).

**Table 4.** Transition metal-catalysed reactions of  $\alpha$ -diazoesters **17a-b**.



Entry	<b>17</b>	[TM cat.] (mol%)/ligand (mol%) <sup>a</sup>	Solvent	Temperature	Product Yield [%] <sup>b</sup>
1	<b>17a</b> (R:Bn)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>18a</b> (35, <i>cis/trans</i> 1:1) <b>19</b> (22)
2	<b>17a</b> (R:Bn)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)/dppf (5)	DCE	80 °C	<b>18a</b> (35, <i>cis/trans</i> 1:1) <b>19</b> (20)
3	<b>17a</b> (R:Bn)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>18a</b> (60, <i>cis/trans</i> 2:1) <sup>c</sup>
4	<b>17a</b> (R:Bn)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<b>18a</b> (40, <i>cis/trans</i> 1.1:1) <b>19</b> (54)
5	<b>17a</b> (R:Bn)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3)	toluene	40 °C	<b>18a</b> (90, <i>cis/trans</i> 2.8:1)
6	<b>17b</b> (R:Ts)	Pd <sub>2</sub> (dba) <sub>3</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>20</b> (80, <i>Z/E</i> 1:1)
7	<b>17b</b> (R:Ts)	[(IMes)Pd(NQ)] <sub>2</sub> (2.5)	CHCl <sub>3</sub>	reflux	<b>20</b> (61, <i>Z/E</i> 1:1.8)
8	<b>17b</b> (R:Ts)	[Rh(Ph <sub>3</sub> CCO <sub>2</sub> ) <sub>2</sub> ] <sub>2</sub> (2)	CH <sub>2</sub> Cl <sub>2</sub>	r.t.	<i>cis</i> - <b>18b</b> (66)
9	<b>17b</b> (R:Ts)	[Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> (3)	toluene	40 °C	<b>21</b> (38)

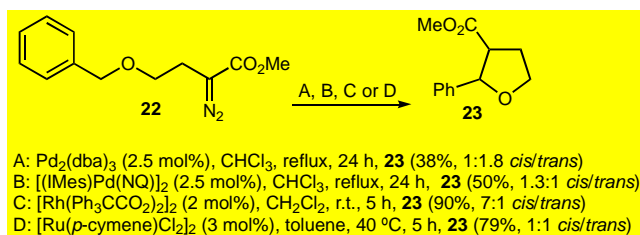
<sup>[a]</sup> See Table 2 for reaction conditions. <sup>[b]</sup> Yields refer to products isolated by chromatography and for entries in which a product mixture was obtained, the yield refers to the combined yield. <sup>[c]</sup> Trace amounts of **19** were also observed in the crude reaction mixture.

When the decomposition of *N,N*-dibenzyl- $\alpha$ -diazoester **17a** was promoted by Pd<sub>2</sub>(dba)<sub>3</sub> either with (entry 1, Table 4) or without the phosphine ligand (entry 2, Table 4), pyrrolidine **18a** (1:1 *cis/trans* ratio), resulting from the C(sp<sup>3</sup>)-H insertion, was isolated in 35% yield, together with the rearranged alkene **19**. Changing the catalyst to [(IMes)Pd(NQ)]<sub>2</sub> increased the yield of **18a** up to 60%, the *cis* isomer being predominant (entry 3, Table 4). In the presence of [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, alkene **19** was the main product (entry 4, Table 4), while [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> led to pyrrolidine **18a** (2.8:1 *cis/trans* ratio) in high yield (entry 5, Table 4).

On the other hand, *N*-benzylsulfonamide **17b** showed a notably different behaviour depending on the transition-metal catalyst employed. Thus, the use of Pd(0)-catalysts (entries 6-7, Table 4) resulted in the exclusive formation of alkene **20**, due to the 1,2-H migration of the metal-carbenoid intermediate,<sup>[2e,17]</sup> while in the presence of the Ru(II)-catalyst a complex reaction mixture was obtained, from which only ketone **21** was isolated (entry 9, Table 4). The lack of the C–H insertion product in the latter case may be ascribed to the delocalization of the nitrogen lone-pair into the sulfonyl group, which would hamper the

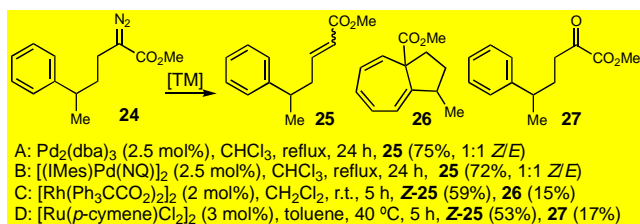
stabilization required in the corresponding zwitterionic intermediate (*vide supra*). In contrast, treatment of **17b** with the Rh(II)-catalyst afforded pyrrolidine *cis*-**18b** as the only reaction product, which was isolated in 66% yield (entry 8, Table 4). This is also consistent with the distinct mechanism proposed for the Rh(II)-catalysed C–H insertions.<sup>[16]</sup>

The reaction of  $\alpha$ -diazoester **22**, which bears a benzyloxy group instead of the *N*-substituted moiety, was then explored (Scheme 3). The Pd<sub>2</sub>(dba)<sub>3</sub>-catalyzed decomposition of **22** afforded tetrahydrofuran **23** (1:1.8 *cis/trans* ratio) in 38% yield.<sup>[18]</sup> The use of [(IMes)Pd(NQ)]<sub>2</sub> as the catalyst slightly changed the stereoselectivity of the annulation to give a 1.3:1 mixture of *cis*-**23** and *trans*-**23** in a 50% combined yield. Better results were obtained when using either [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> or [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>. However, while the Ru(II)-catalyst led to a 1:1 mixture of *cis*-**23** and *trans*-**23** (79% combined yield), the use of the Rh(II)-catalyst<sup>[19]</sup> resulted in the stereoselective formation of *cis*-**23** (7:1 *cis/trans* ratio, 90% combined yield).



**Scheme 3.** TM-catalyzed reactions of  $\alpha$ -diazoester **22**.

In order to further confirm the need for a heteroatom directly attached to the C(sp<sup>3</sup>)-H moiety involved in the carbenoid C-H insertion, we studied the reaction of  $\alpha$ -diazoester **24** (Scheme 4). Not surprisingly, no C-H insertion product was isolated in any of the transition-metal catalysed reactions with this substrate. Instead, a 1:1 mixture of **Z-25** and **E-25** was obtained when using either Pd<sub>2</sub>(dba)<sub>3</sub> (75% combined yield) or [(IMes)Pd(NQ)]<sub>2</sub> (72% yield). Similarly, in the presence of [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, **Z-25** (59%) was isolated together with a minor product (15%) identified as cycloheptatriene **26**, which arises from an intramolecular Buchner reaction.<sup>[20]</sup> The [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>-catalyzed decomposition of **24** led to the stereoselective formation of **Z-25** (53%) together with ketone **27** (17%).



**Scheme 4.** TM-catalyzed reactions of  $\alpha$ -diazoester **24**.

The transformations summarized in Schemes 3 and 4 clearly show that in the intramolecular reaction of  $\alpha$ -diazoesters, regardless of the transition metal catalytic system [Pd(0), Rh(II) or Ru(II)], the presence of a heteroatom (N or O) in the tether is essential for the successful carbenoid C(sp<sup>3</sup>)-H insertion. Regarding the nitrogen moiety, both the Pd(0)- and Ru(II)-catalysts need the presence of an amine nitrogen, while the Rh(II)-catalyst also tolerates a sulfonamide function. For the Ru(II)-promoted insertion reactions, these results are in good agreement with those expected from the computed reaction profile depicted in **Figure 1**.

DFT calculations were also carried out to understand the influence of the heteroatom on the palladium(0)-catalysed process. To this end, we compared the palladium(0)-catalysed reaction profiles involving aniline **1** and compound **24**, which begin with the corresponding palladacarbenes **INT0-Pd** and **INT0-Pd''**, respectively. From the data in **Figure 2**, it becomes clear that the first step of the transformation, which involves the metal-mediated

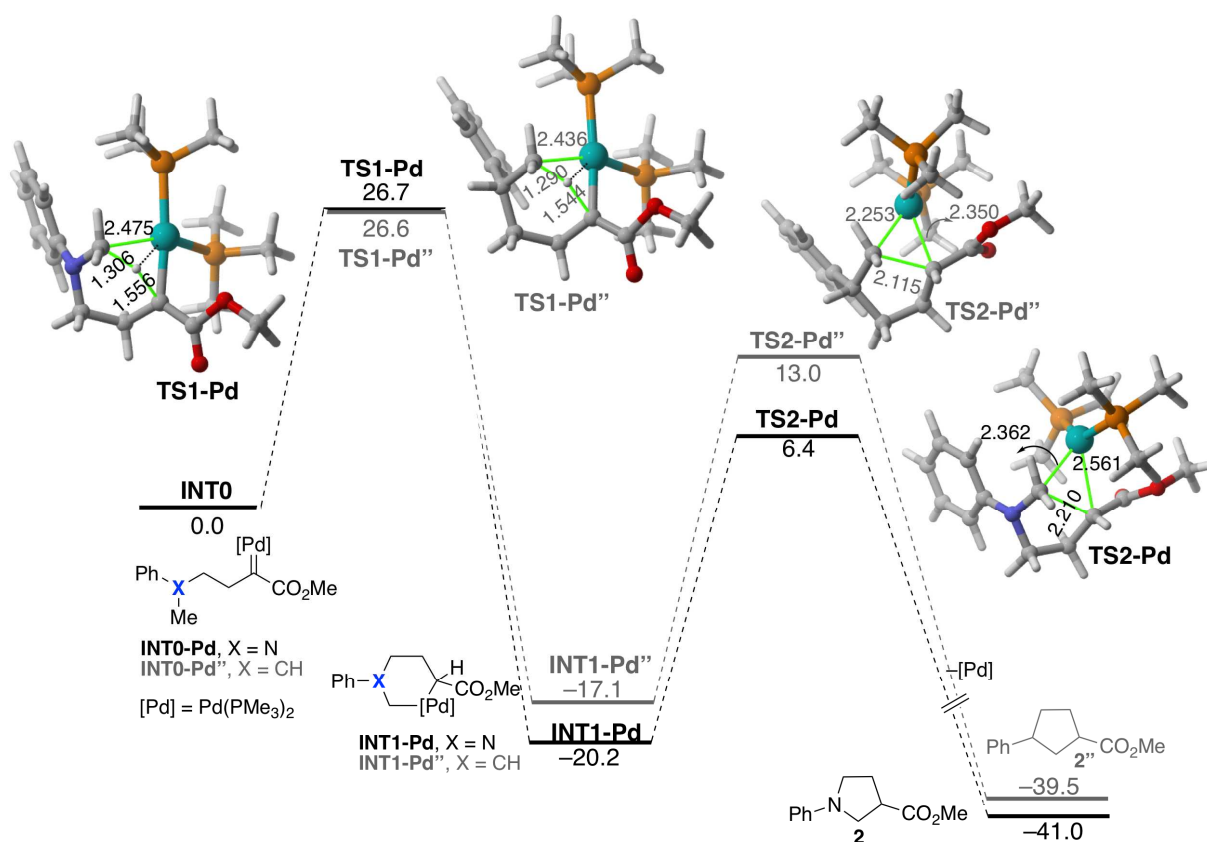
1,5-H migration, is similar for both systems, since it occurs with nearly identical activation barriers. This might be somewhat surprising if we consider the well-known higher C-H bond dissociation energy of the parent H-CH<sub>3</sub> bond (431 kJ/mol) with respect to H-CH<sub>2</sub>NH<sub>2</sub> (397 kJ/mol).<sup>[21]</sup> However, due to the delocalization of the nitrogen lone-pair into the phenyl group in **1**, the C-H bond strength in intermediates **INT0-Pd** and **INT0-Pd''** is quite similar, as indicated by the computed corresponding Wiberg Bond Indices (0.95 and 0.94, respectively). Therefore, no significant differences in the barriers of these processes should be expected. Nevertheless, this 1,5-H migration is clearly thermodynamically favoured for the reaction involving aniline **1** ( $\Delta G_R = 3.1$  kcal/mol). More importantly, the activation barrier associated with the subsequent reductive elimination process is clearly much higher for the species lacking the heteroatom ( $\Delta\Delta G^\ddagger = 6.6$  kcal/mol). Indeed, the high barrier computed for the process involving **TS2-Pd''** ( $\Delta G^\ddagger = 30.1$  kcal/mol) indicates that this final step is severely hampered, which matches the experimental findings (see above).

In summary, in the present paper we report our studies on the implementation of the transition metal-catalysed intramolecular carbenoid C(sp<sup>3</sup>)-H insertion by decomposition of  $\alpha$ -diazoesters in the synthesis of pyrrolidines. The use of Pd(0), Rh(II) as well as Ru(II) catalysts was explored for this purpose. The results obtained in the annulation reactions show that the transition metal catalyst of choice for the process was highly substrate-dependent. On the whole, although [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> proved to be the most versatile catalyst, it did not always give the highest yield and selectivity. In the reactions of *N*-alkylaniline substrates, the insertion occurred selectively on primary and secondary C(sp<sup>3</sup>)-H bonds rather than C<sub>Ar</sub>(sp<sup>2</sup>)-H bonds, regardless of the transition metal catalytic system. In general, the Rh(II)- and Ru(II)-based catalysts provided better chemoselectivity than the Pd(0)-catalysts. However, with *ortho*-substituted anilines, the Pd(0)-catalysts were at least as efficient as [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, the C(sp<sup>3</sup>)-H insertion being the only reaction observed. The generality and functional group tolerance of the insertion reaction for the synthesis of *N*-arylpyrrolidines is well illustrated by the fact that both electron-donating and electron-withdrawing groups were perfectly accommodated on the aromatic ring. The C(sp<sup>3</sup>)-H insertion was not limited to anilines but also proved to be suitable for alkylamine-type substrates. [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> was more efficient than the Pd- and Rh-based catalysts in the insertion reaction of the *N,N*-dibenzyl- $\alpha$ -diazoester, while only [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> was able to promote the insertion of the *N*-benzylsulfonamide derivative. The mechanism involved in the C-H insertion process strongly depends on the nature of the transition metal. Whereas Rh(II)-catalysts are reported to directly release the insertion product and the metal catalyst in a single reaction step,<sup>[16]</sup> either Pd(0) or Ru(II)-catalysts involve stepwise reaction mechanisms.



Despite that, the corresponding transformations are essentially different because the initially formed metallacarbene complex follows a distinct reaction pathway to produce the observed products, i.e. a metal-mediated 1,5-H migration followed by

reductive elimination is suggested for the Pd(0)-catalysed process, while a Ru(II)-promoted Mannich type reaction is proposed for the Ru(II)-mediated reaction.



**Figure 2.** Computed reaction profiles for the formation of pyrrolidine **2**. Relative free energies ( $\Delta G_{298}$ , at 298 K) and bond distances are given in kcal/mol and angstroms (Å), respectively. All data were computed at the PCM(CHCl<sub>3</sub>)-M06L/def2-TZVPP/PCM(CHCl<sub>3</sub>)-B3LYP-D3/def2-SVP level.

## Experimental Section

**Representative procedure for the Pd<sub>2</sub>(dba)<sub>3</sub>-catalysed cyclization reactions (Table 2, Entry 1).** A mixture of diazoester **5a** (60 mg, 0.17 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (3.8 mg, 0.004 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (110 mg, 0.34 mmol) in CHCl<sub>3</sub> (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The reaction mixture was partitioned between a saturated NaHCO<sub>3</sub> aqueous solution and Et<sub>2</sub>O. The organic extracts were dried and concentrated. The residue was purified by chromatography (SiO<sub>2</sub>, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **6a** (50 mg, 89%) as a colorless oil.

**Representative procedure for the [(IMes)Pd(NQ)]<sub>2</sub>-catalysed cyclization reactions (Table 2, Entry 2).** A mixture of diazoester **5a** (50 mg, 0.14 mmol), [(IMes)Pd(NQ)]<sub>2</sub> (4.0 mg, 0.0035 mmol) in CHCl<sub>3</sub> (10 mL) was stirred at reflux under Argon atmosphere for 24 h. The reaction mixture was concentrated and the residue was purified by chromatography (SiO<sub>2</sub>, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **6a** (39.5 mg, 85%).

**Representative procedure for the [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub>-catalysed cyclization reactions (Table 2, Entry 3).** A mixture of diazoester **5a** (50 mg, 0.14 mmol), [Rh(Ph<sub>3</sub>CCO<sub>2</sub>)<sub>2</sub>]<sub>2</sub> (4.0 mg, 0.003 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was stirred at room temperature under Argon atmosphere for 5 h. The reaction mixture was concentrated and the residue was purified by chromatography (SiO<sub>2</sub>, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **6a** (32.5 mg, 70%).

**Representative procedure for the [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub>-catalysed cyclization reactions (Table 2, Entry 4).** A mixture of diazoester **5a** (50 mg, 0.14 mmol), [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (2.6 mg, 0.004 mmol) in toluene (3 mL) was stirred at 40 °C under Argon atmosphere for 24 h. The reaction mixture was concentrated and the residue was purified by chromatography (SiO<sub>2</sub>, from hexanes to hexanes-EtOAc 97:3) to give pyrrolidine **6a** (30.5 mg, 66%) and aniline **8a** (4 mg, 9%).

### Computational Details

All the calculations reported in this paper were performed with the Gaussian 09 suite of programs.<sup>[22]</sup> Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP<sup>[25]</sup> in conjunction with the D3 dispersion correction suggested by Grimme et al.<sup>[24]</sup> using the double- $\zeta$  quality plus

polarization def2-SVP<sup>[25]</sup> basis set for all atoms. Reactants and products were characterized by frequency calculations,<sup>[26]</sup> and have positive definite Hessian matrices. Transition structures (TS's) show only one negative eigenvalue in their diagonalized force constant matrices, and their associated eigenvectors were confirmed to correspond to the motion along the reaction coordinate under consideration using the Intrinsic Reaction Coordinate (IRC) method.<sup>[27]</sup> Solvents effects were also taken into account using the Polarizable Continuum Model (PCM)<sup>[28]</sup> during the geometry optimizations. This level is denoted PCM-(CHCl<sub>3</sub>)-B3LYP-D3/def2-SVP. Single-point energy refinements were carried out at the M06L<sup>[29,30]</sup>/def2-TZVPP<sup>[25]</sup> level of theory employing the PCM model to account for solvation. This level is denoted PCM(CHCl<sub>3</sub>)-M06L/def2-TZVPP//PCM-(CHCl<sub>3</sub>)-B3LYP-D3/def2-SVP.

## Supporting Information

Detailed experimental procedures, characterization data and copies of NMR spectra for all new compounds, Figure S1, as well as Cartesian coordinates of all species described in the text are available in the Supporting Information.

## Acknowledgements

The authors gratefully acknowledge financial support for this work from the Spanish Ministerio de Economía y Competitividad, Fondos Europeos para el Desarrollo Regional (MINECO-FEDER) (projects CTQ2013-44303-P, CTQ2014-51912-RED, CTQ2015-64937-R and CTQ2016-78205-P).

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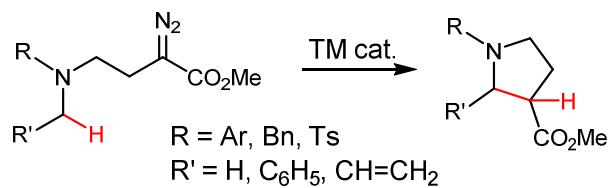
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Transition Metal-Catalysed Intramolecular  
Carbenoid C–H Insertion for Pyrrolidine Formation  
by Decomposition of  $\alpha$ -Diazoesters

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Daniel Solé,\* Arianna Amenta, Francesco Mariani,  
M.-Lluïsa Bennesar, Israel Fernández\*



- *TM cat.* : Pd(0), Ru(II) or Rh(II) catalysts
- chemoselective carbenoid Csp<sup>3</sup>-H insertion
- up to 92% yield