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Grubbs catalysts in intramolecular carbene C(sp^3)–H insertion reactions from α-diazoesters†

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Grubbs catalysts are described as a useful alternative to promote intramolecular carbene C–H insertion from α-diazoesters. Moreover, no competition arises from the possible metathesis reactions on substrates bearing alkene and alkyne moieties. DFT calculations were also carried out to gain insight into the reaction mechanism involved in these transformations.

The rich coordination chemistry of ruthenium and hence the diversity of ruthenium complexes have led to the development of a number of catalytic transformations that can be used for the rapid assembly of complex molecules with high atom economy.[1] In particular, the ruthenium carbenes collectively known as Grubbs catalysts have been extensively applied in metathesis reactions.[2] The outstanding performance of these reactions derives from the remarkable selectivity of Grubbs complexes for unsaturated reactants, which allows chemoselective targeting of alkenes and alkynes in intricate frameworks of organic functional groups. Moreover, a growing number of nonmetathetic catalytic transformations promoted by Grubbs carbene complexes have also been described and after optimization some of them are showing synthetic utility.[3]

In parallel, it has also been reported that the reaction of diazo compounds with different ruthenium complexes affords ruthenium-carbene species, which can participate, *inter alia*, in cyclopropanation[4] and C–H insertion reactions.[5] However, in comparison with the well-established rhodium catalysts,[6] ruthenium complexes are relative newcomers in these fields, despite being considerably more cost-effective.

As part of our ongoing research on the synthesis of nitrogen heterocycles, we have been exploring both ring-closing metathesis strategies[7] and intramolecular transition metal-catalyzed carbene C–H insertion reactions as annulation methodologies.[8] Ruthenium alkylidene complexes, which are the key intermediates in olefin metathesis, clearly resemble the ruthenium-carbene species generated from diazo compounds. We therefore wondered if typical olefin metathesis catalysts (Fig. 1) could also be used to promote carbene C(sp^3)–H insertion reactions from diazo derivatives and whether competition would arise between alkene metathesis and C–H insertion. Herein we report a joint experimental-computational study of the Grubbs catalyst-promoted C–H insertion from amino-tethered α-diazoesters to prepare pyrrolidines, providing insight into the scope and mechanism of this novel, synthetically useful nonmetathetic reaction.

We began our investigation by focusing on the reaction of *N*-benzyl-*N*-^{t}butyl-α-diazoesters **1a–e** (Table 1), comparing the efficiency of **Ru-1**, **Ru-2**, and **Ru-3** with that of [Ru(*p*-cymene)Cl$_2$]$_2$, which has been successfully used to promote similar insertion processes.[5a,8b] To our delight, treatment of **1a** with first generation Grubbs catalyst **Ru-1** in refluxing CH_2Cl_2 resulted in the stereoselective formation of the *cis*-pyrrolidine **2a** in excellent yield (entry 1). Similar reactions were observed with second generation Grubbs catalyst **Ru-2** (entry 2) and Hoveyda–Grubbs catalyst **Ru-3** (entry 3). Strikingly, all three catalysts were considerably more efficient than [Ru(*p*-cymene)Cl$_2$]$_2$ in promoting this C(sp^3)–H insertion reaction (entry 4). The same behavior was observed when starting from α-diazoesters **1b** and **1c** (entries 5–12).

In contrast, each ruthenium catalyst was differently affected by the presence of rather bulky *ortho*-substituents. Thus, **Ru-1** gave the highest yield when the substrate had an *ortho*-bromo group (entries 13–16), but was less efficient in promoting the

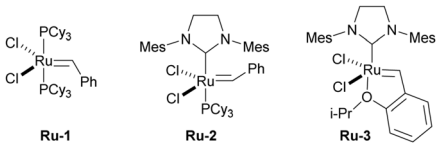

Fig. 1 Commonly used Grubbs catalysts.

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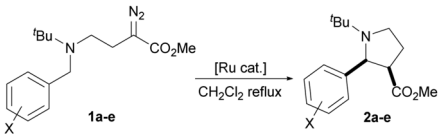
Table 1 C–H insertion reactions of α-diazoesters **1a–e**[a]



Entry	1 (X)	[Ru cat.]	dr	Products[b] (%)
1	**1a** (H)	**Ru-1**	>98 : 2	**2a** (90)
2	**1a** (H)	**Ru-2**	>98 : 2	**2a** (92)
3	**1a** (H)	**Ru-3**	>98 : 2	**2a** (82)
4	**1a** (H)	[Ru(*p*-cymene)Cl_2]$_2$[c]	>98 : 2	**2a** (69)
5	**1b** (4-Cl)	**Ru-1**	>98 : 2	**2b** (89)
6	**1b** (4-Cl)	**Ru-2**	>98 : 2	**2b** (80)
7	**1b** (4-Cl)	**Ru-3**	>98 : 2	**2b** (74)
8	**1b** (4-Cl)	[Ru(*p*-cymene)Cl_2]$_2$[d]	>98 : 2	**2b** (57)
9	**1c** (2-F)	**Ru-1**	>98 : 2	**2c** (98)
10	**1c** (2-F)	**Ru-2**	>98 : 2	**2c** (80)
11	**1c** (2-F)	**Ru-3**	>98 : 2	**2c** (85)
12	**1c** (2-F)	[Ru(*p*-cymene)Cl_2]$_2$[d]	>98 : 2	**2c** (70)
13	**1d** (2-Br)	**Ru-1**	>98 : 2	**2d** (80)
14	**1d** (2-Br)	**Ru-2**	>98 : 2	**2d** (62)
15	**1d** (2-Br)	**Ru-3**	>98 : 2	**2d** (73)
16	**1d** (2-Br)	[Ru(*p*-cymene)Cl_2]$_2$[d]		—[e]
17	**1e** (2-MeO)	**Ru-1**	>98 : 2	**2e** (60)
18	**1e** (2-MeO)	**Ru-2**	>98 : 2	**2e** (81)
19	**1e** (2-MeO)	**Ru-3**		—[f]
20	**1e** (2-MeO)	[Ru(*p*-cymene)Cl_2]$_2$[d]		—[g]

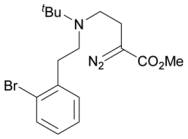
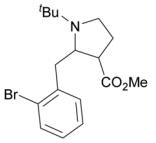
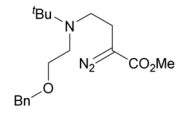
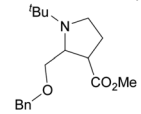
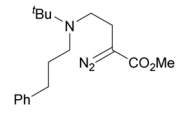
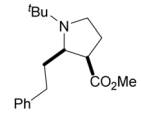
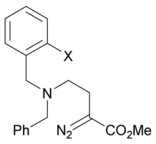
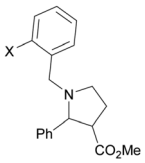
[a] Reaction conditions: catalyst (3 mol%) in CH_2Cl_2 at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] 31 h. [d] 48 h. [e] A 1 : 1 mixture of **1d** and **2d** was obtained. [f] A 1 : 1.4 mixture of **1e** and **2e** was obtained. [g] A 6 : 1 mixture of **1e** and **2e** was obtained.

insertion from α-diazoester **1e**, which bears an *ortho*-methoxy substituent (entries 17–20). On the other hand, when using **Ru-3** the reaction of **1e** (entry 19) progressed more slowly than that of **1d** (entry 15). Once again, [Ru(*p*-cymene)Cl_2]$_2$ afforded poor results.

To ascertain whether the efficiency of the C–H insertion depends on the activation inherent to the benzylic position, the reaction of α-diazoesters **3**, **5**, and **7** was explored (Table 2). The three Grubbs catalysts regioselectively promoted the insertion reaction of **3** (entries 1–3) to give pyrrolidine **4** (*cis*/*trans* mixtures). Similar results were observed when these catalysts were used with *N*-(benzyloxyethyl) α-diazoester **5** (entries 4–6). In contrast, treatment of **7** with **Ru-1** resulted in both regio- and stereoselective insertion to give *cis*-pyrrolidine **8** in 70% yield (entry 7), while in the presence of **Ru-3** a slow reaction was observed (entry 8). These results therefore indicate that the Grubbs catalysts can promote carbene C–H insertion into less activated C(sp^3)–H bonds, and that remote electronic effects may accelerate the reaction.

Interestingly, the Grubbs catalysts were able to discriminate between the two secondary benzylic C(sp^3)–H bonds of α-diazoesters **9a** and **9b**, probably due to a combination of steric and electronic effects. Thus, the reaction of **9a** regioselectively afforded pyrrolidine **10a** (*cis*/*trans* mixtures) in good yields (entries 9–11). In contrast, the reactions of **9b** provided **10b** as the major product along with minor amounts of the pyrrolidine arising from the insertion into a C–H bond at the 2-fluorobenzyl position (entries 12–14).

Table 2 C–H insertion reactions of α-diazoesters **3**, **5**, **7** and **9a–b**[a]

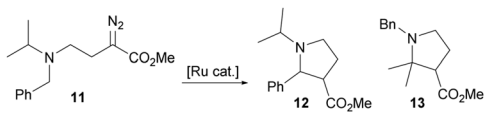
Entry	Diazoester	[Ru cat.]	Product yield[b] (%)
			
1	**3**	**Ru-1**	**4** (98, *cis*/*trans* 1.5 : 1)
2	**3**	**Ru-2**	**4** (92, *cis*/*trans* 1 : 1)
3	**3**	**Ru-3**	**4** (87, *cis*/*trans* 1 : 1)
			
4	**5**	**Ru-1**	**6** (91, *cis*/*trans* 1 : 1.4)
5	**5**	**Ru-2**	**6** (80, *cis*/*trans* 1 : 1.7)
6	**5**	**Ru-3**	**6** (82, *cis*/*trans* 1 : 1.3)
			
7	**7**	**Ru-1**	**8** (70)
8	**7**	**Ru-3**	—[c]
			
9	**9a**, X = I	**Ru-1**	**10a** (87, *cis*/*trans* 6 : 1)
10	**9a**, X = I	**Ru-2**	**10a** (79, *cis*/*trans* 12 : 1)
11	**9a**, X = I	**Ru-3**	**10a** (95, *cis*/*trans* 3 : 1)
12	**9b**, X = F	**Ru-1**	**10b** (86, *cis*/*trans* 4.4 : 1)[d]
13	**9b**, X = F	**Ru-2**	**10b** (73, *cis*/*trans* 7 : 1)[e]
14	**9b**, X = F	**Ru-3**	**10b** (60, *cis*/*trans* 2.3 : 1)[f]

[a] Reaction conditions: catalyst (3 mol%) in CH_2Cl_2 at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] A 5 : 1 mixture of **7** and **8** was obtained. [d] A 8 : 1 mixture of **10b** and the regioisomeric pyrrolidine **10b′** was obtained. [e] A 2.8 : 1 mixture of **10b** and **10b′** was obtained. [f] A 2.5 : 1 mixture of **10b** and **10b′** was obtained.

Seeking more information about the Grubbs catalyst-mediated carbene C–H insertion, we then explored the reaction of α-diazoester **11** (Table 3).

The use of the three catalysts to promote the decomposition of **11** led to mixtures of pyrrolidines **12**, arising from the insertion into the benzylic C–H bond, and **13**, which results from the insertion into the

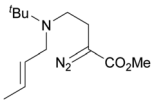
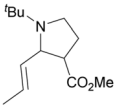
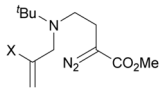
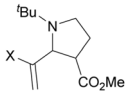
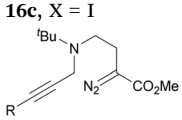
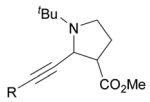
Table 3 C–H insertion reactions of α-diazoester **11**[a]



Entry	[Ru cat.]	Products yield[b] (%)
1	**Ru-1**	**12** (61, *cis*/*trans* 5.8 : 1), **13** (32)
2	**Ru-2**	**12** (56, *cis*/*trans* 7.8 : 1), **13** (41)
3	**Ru-3**	**12** (36, *cis*/*trans* 3.6 : 1), **13** (58)

[a] Reaction conditions: catalyst (3 mol%) in CH_2Cl_2 at reflux for 24 h. [b] Yields refer to products isolated by chromatography.

Table 4 C–H insertion reactions of α-diazoesters **14**, **16a–c** and **18a–c**[a]

Entry	Diazoester	[Ru cat.]	Product yield[b] (%)
			
1	**14**	**Ru-1**	**15** (70, *cis*/*trans* 6 : 1)
2	**14**	**Ru-3**	**15** (52, *cis*/*trans* 5 : 1)
			
3	**16a**, X = Me	**Ru-1**	**17a** (93, *cis*/*trans* 4 : 1)
4	**16a**, X = Me	**Ru-2**	**17a** (98, *cis*/*trans* 2 : 1)
5	**16a**, X = Me	**Ru-3**	**17a** (89, *cis*/*trans* 5.6 : 1)
6	**16b**, X = Br	**Ru-1**	**17b** (98, *cis*/*trans* 10 : 1)
7	**16b**, X = Br	**Ru-2**	**17b** (40, *cis*/*trans* 11 : 1)[c]
8	**16b**, X = Br	**Ru-3**	**17b** (70, *cis*/*trans* 10 : 1)[d]
9	**16c**, X = I	**Ru-1**	**17c** (52, *cis*/*trans* 7 : 1)
10	**16c**, X = I	**Ru-2**	—[e]
11	**16c**, X = I	**Ru-3**	—[e]
			
12	**18a**, R = H	**Ru-1**	**19a** (70, *cis*/*trans* 6 : 1)
13	**18a**, R = H	**Ru-2**	**18a**
14	**18a**, R = H	**Ru-3**	**19a** (88, *cis*/*trans* 7 : 1)
15	**18b**, R = Me	**Ru-1**	**19b** (89, *cis*/*trans* 3 : 1)
16	**18b**, R = Me	**Ru-2**	—[f]
17	**18b**, R = Me	**Ru-3**	**19b** (75, *cis*/*trans* 4 : 1)
18	**18c**, R = TMS	**Ru-1**	**19c** (87, *cis*/*trans* 4 : 1)
19	**18c**, R = TMS	**Ru-2**	**19c** (62, *cis*/*trans* 4.5 : 1)
20	**18c**, R = TMS	**Ru-3**	**19c** (80, *cis*/*trans* 7 : 1)

[a] Reaction conditions: catalyst (3 mol%) in CH_2Cl_2 at reflux for 24 h. [b] Yields refer to products isolated by chromatography. [c] The cyclopropanation product (50%) was also obtained (see the ESI). [d] The cyclopropanation product (20%) was also obtained. [e] Complex mixture. [f] A 1.3 : 1 mixture of **18b** and **19b** was obtained.

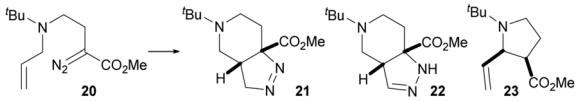
tertiary C(sp^3)–H bond (entries 1–3). While **Ru-1** and **Ru-2** gave **12** as the major product, **Ru-3** led predominantly to **13**.

The C–H insertion catalyzed by Grubbs complexes was also suitable for allylic and propargylic C(sp^3)–H bonds (Table 4).

Thus, α-diazoester **14** chemoselectively afforded pyrrolidine **15** (*cis*/*trans* mixture) in yields of 70% in the presence of **Ru-1** (entry 1) and 52% with **Ru-3** (entry 2). Notably, no product resulting from the possible ring-closing metathesis was observed in either reaction.[9]

Gem-disubstituted alkenes **16a–c** also underwent C–H insertion to give pyrrolidines under the action of Grubbs catalysts. Starting from α-diazoester **16a**, the three catalysts chemoselectively promoted C–H insertion to give **17a** in good yields (entries 3–5). In contrast, while the insertion reaction from bromo alkene **16b** was selectively promoted by **Ru-1** (entry 6), the use of either **Ru-2** or **Ru-3** led to the formation of significant amounts of the corresponding cyclopropanation product (entries 7 and 8).[10] On the other hand, for iodo alkene **16c**, only **Ru-1** was able to promote the C–H insertion (entry 9).

The Grubbs catalysts were also used to promote insertion into propargylic C(sp^3)–H bonds of α-diazoesters bearing either terminal or internal alkynes (entries 12–20), **Ru-1** and **Ru-3** being far more active than **Ru-2**.



Scheme 1 Reactions of α-diazoester **20**.

Finally, *N*-allyl-α-diazoester **20** was prepared (Scheme 1). This diazo derivative proved to be thermally unstable and in CH_2Cl_2 solution at room temperature evolved to pyrazolo[4,3-*c*]-pyridine **21** through an intramolecular dipolar cycloaddition reaction.[11] However, treatment of **20** with **Ru-1** in CH_2Cl_2 at reflux afforded a 1 : 2 : 1 mixture of **21**, **22** (arising from a 1,3-hydrogen shift from **21**),[11] and the C–H insertion product **23**. The use of **Ru-2** and **Ru-3** led to only trace amounts of **23** along with **21** and **22**. Once again, no product from the ring-closing metathesis was detected in any of the reaction mixtures.

To shed light on the reaction mechanism and selectivity of the C–H insertion catalyzed by Grubbs complexes, Density Functional Theory (DFT) calculations at the dispersion corrected PCM(CH_2Cl_2)-B3LYP-D3/def2-TZVPP//PCM(CH_2Cl_2)-B3LYP-D3/def2-SVP level were carried out.[12] To this end, the process involving **1a** and the **Ru-1** catalyst was explored (Fig. 2). The process begins with the formation of the corresponding ruthena-carbene intermediate with the concomitant release of N_2. Our calculations indicate that the formation of **INT0**, where the new carbene ligand replaces a phosphine in **Ru-1**, is strongly favoured ($\Delta\Delta G$ = 29.2 kcal mol^{-1}) over the formation of **INT0′**, where the carbene ligands are interchanged. From **INT0**, the zwitterionic intermediate **INT1-*cis*** is produced in a highly exergonic process (ΔG_R = −8.3 kcal mol^{-1}) *via* the transition state **TS1-*cis*** ($\Delta G^{\neq}$ = 11.1 kcal mol^{-1}). This step can be viewed as a 1,5-hydrogen migration that is not directly assisted by the metal, therefore resembling the mechanism involved in related Ru(II)[8b] and Pd(II)–C–H activation processes previously reported by us.[8d] Interestingly, the analogous transformation leading to the isomer **INT1-*trans*** is both kinetically ($\Delta\Delta G^{\neq}$ = 7.4 kcal mol^{-1}) and thermodynamically ($\Delta\Delta G_R$ = 4.4 kcal mol^{-1}) disfavoured over the process involving **INT1-*cis***, which is fully consistent with the complete stereoselectivity observed experimentally. Finally, the transformation ends up with the highly exergonic (ΔG_R = −26.2 kcal mol^{-1}) formation of the observed pyrrolidine **2a**. This final step proceeds *via* **TS2-*cis***, a saddle point associated with the formation of the new C–C bond and the concomitant regeneration of the active Ru(II)-catalyst, with a rather low activation barrier of 10.5 kcal mol^{-1}.

In addition, we wished to understand why the alternative metathesis reaction is not competitive in substrates that also have a reactive unsaturated C–C bond. Our calculations suggest that the formation of the key metallacyclobutane intermediate from the substrate bearing an allyl substituent is strongly disfavored ($\Delta\Delta G$ = 32.4 kcal mol^{-1}) over the formation of the zwitterionic intermediate involved in the C–H insertion reaction (see Fig. S1 in the ESI†).

Finally, it should be noted that although a wide range of functional groups are well tolerated under metathesis conditions, the use of substrates with a strong Lewis base such as an

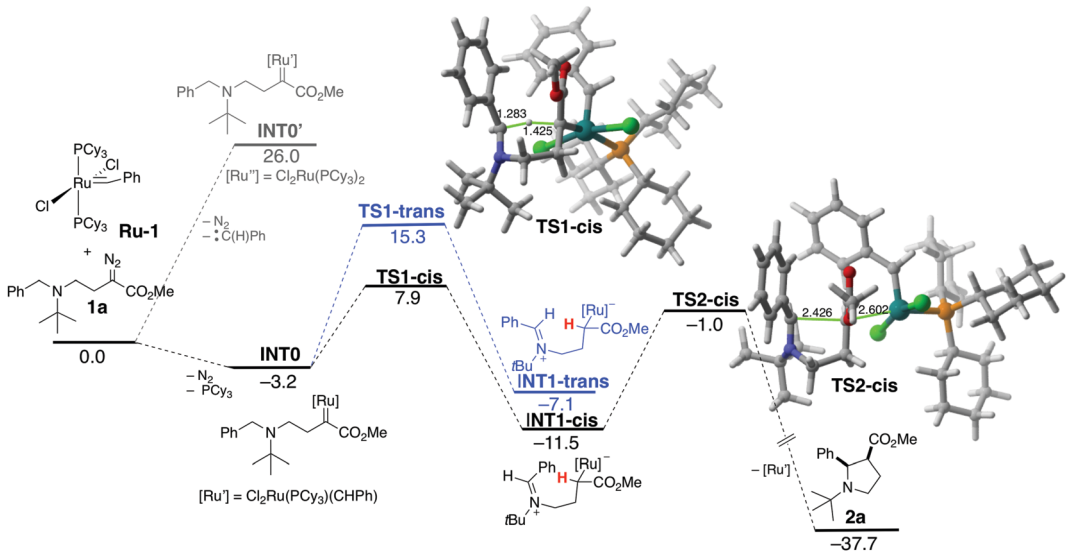


Fig. 2 Computed reaction profile for the formation of **2a** from **1a**. Relative free energies (Δ*G*, at 298 K) and bond lengths are given in kcal mol^{-1} and angstroms, respectively. All data have been computed at the PCM(CH_2Cl_2)-B3LYP-D3/def2-TZVPP//PCM(CH_2Cl_2)-B3LYP-D3/def2-SVP level.

amine usually deactivates the catalyst.[13] In contrast, not only does the amine moiety not hinder the carbene C–H insertion catalyzed by Grubbs complexes, but it seems crucial for the success of the reaction, which nicely agrees with the computed reaction profile depicted in Fig. 2.[14]

In summary, we have described the first examples of Grubbs complexes used to catalyze carbene C–H insertion from diazo derivatives. On the whole, the first generation Grubbs catalyst was the most versatile, although it did not always give the highest yield. Our studies clearly demonstrate not only that Grubbs complexes constitute a useful alternative to promote intramolecular carbene C–H insertion, but also that no competition from the possible metathesis reactions arises when starting from substrates with alkene or alkyne moieties.

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Conflicts of interest

There are no conflicts to declare.

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