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Tandem Enyne Metathesis-Diels−Alder Reaction for Construction of Natural Product Frameworks

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Enynes connected through aromatic rings are used as substrates for metathesis reactions. The reactivity of three ruthenium carbene complexes is compared. The resulting 1,3-dienes are suitable precursors of polycyclic structures via a Diels−Alder process. Some domino RCM-Diels−Alder reactions are performed, suggesting a possible beneficial effect of the ruthenium catalyst in the cycloaddition process. Other examples require Lewis acid cocatalyst. When applied to aromatic ynamines or enamines, a new synthesis of vinylindoles is achieved. Monitorization of several metathesis reactions with NMR shows the different behavior for ruthenium catalysts. New carbenic species are detected in some reactions with an important dependence on the solvent used.

Introduction

Multiple bond metathesis reactions are synthetically useful tools to achieve molecular complexity in an elegant way.[1] Both double-double bond and double-triple bond processes are possible, being the mos-used intramolecular reactions. The ring-closing alkene-alkyne reaction[2] formally implies the formation of a carbon−carbon bond and the migration of the alkylidene part onto the alkyne carbon, to form a diene, constituting a complete atom economical reaction (Scheme 1). This reaction has been developed later than the diene version. However, in the past 5 years there has been great interest in intramolecular enyne metathesis especially with regard to further transformations of the resulting conjugated dienes.[3] Thus, tandem transformations have led to synthetic applications in the field of polycycle construction and natural product syntheses.

The success of the metathesis reactions involving metal carbenes has arrived after the development of new stable and easy to handle catalysts. In this work we will use some of the ruthenium alkylidene complexes developed by Grubbs.[4] Three generations of complexes are depicted in Chart 1 and are thought to present, in general, increasing activities in the olefin RCM. Catalyst **1** is the cheapest one but is thermally unstable and, in general, fails to react with substituted olefins. Catalyst **2** is described to give better results when using substituted olefin fragments. Finally the latter complex **3**, is a representative of the third generation of ruthenium catalysts, in which a tethered oxygen substitutes the ligand that is dissociated. There are efficient methods for the synthesis[5] of these new catalysts, although there are

SCHEME 1

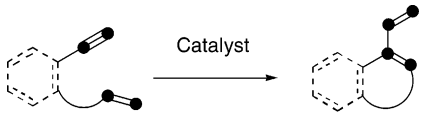
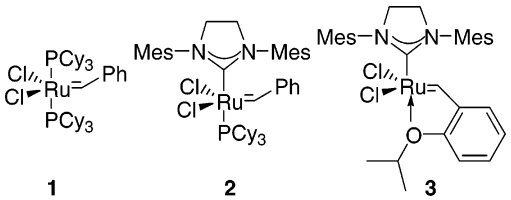


CHART 1



1 **2** **3**

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(1) For recent reviews on the olefin metathesis reaction, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (d) Philips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (g) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37.

(2) For recent reviews on enyne metathesis, see: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (b) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133.

(3) Recent references on intramolecular ruthenium-based enyne metathesis: (a) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654. (b) Duboc, R.; Henaut, C.; Savignac, M.; Genêt, J.-P. Bhatnagar, N. *Tetrahedron Lett.* **2001**, *42*, 2461. (c) Rückert, A.; Eisele, D.; Blechert, S. *Tetrahedron Lett.* **2001**, *42*, 5245. (d) Yao, Q. *Org. Lett.* **2001**, *3*, 2069. (e) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, 787. (f) Marco-Contelles, J.; Arroyo, N.; Ruiz-Caro, J. *Synlett* **2001**, 652. (g) Ackermann, L.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2001**, 397. (h) Clark, J. S. Townsend, R. J.; Blake, A. J.; Teat, S. J.; Johns, A. *Tetrahedron Lett.* **2001**, *42*, 3235. (i) Bentz, D.; Laschat, S. *Synthesis* **2000**, 1766. (j) Smulik, J. A.; Diver, S. T. *J. Org. Chem.* **2000**, *65*, 1788. (k) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (l) Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 5465. (m) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543. (n) Kotha, S.; Sreenivasachary, N. *Chem. Commun.* **2000**, 503.

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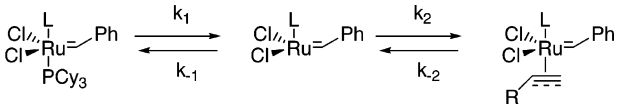
SCHEME 2



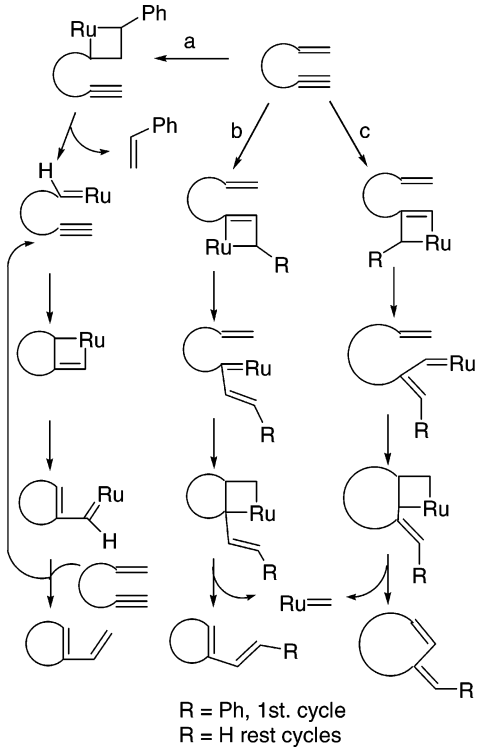
still few data about their practical results, especially in enyne metathesis.[6] There is not a clear rule that indicates the best catalyst to use in each example. Subtle variations in the substrate structure and in the type of final product may lead to different results with each type of carbene complex. In particular, the substitution pattern, the steric demand of the substrate, the ring size to be formed, and the presence of coordinating heteroatoms have important influence on the results.

With regard to the mechanism, the metathesis reaction begins with the dissociative loss of a phosphine and the formation of a 14 e^- intermediate (Scheme 2). The formation of this infrequent unsaturated complex was demonstrated with kinetic studies.[7] The increase in the activity of the second generation catalysts is not due to increase in the rate of the phosphine dissociation but to a better ratio of the coordination of the olefin constant (k_2) and that for the phosphine recovery (k_{-1}). This stage was studied for the alkene-alkene reaction but is shared by the enyne process.

In contrast to diene metathesis there are still some obscure points in the following stages of the enyne reaction. In principle, up to three reaction courses would be possible, depending on the type of coordination of the metal with the system. The metal may coordinate with the double bond (path a, Scheme 3) or with the triple bond with two possible regiochemistries (paths b and c). Hoye has monitored the reaction by NMR and shown the formation of carbenes compatible with the first reaction course (path a).[8] Additionally, this path explains better the results obtained in cascade metathesis reactions with dienynes. Nevertheless, with substituted alkynes, Mori has obtained products coming from path c, which implies the initial coordination of the metal with the triple bond.[9] Probably several reaction mechanisms are competing and operate depending on the substrate (steric and electronic effects) and the reaction conditions. In addition, the intermolecular reaction developed more recently after pioneering studies by Blechert[10] is better explained by first coordination of the metal with the triple bond. One possible explanation would be the kinetic versus thermodynamic control of the addition of metal alkylidenes to triple bonds, which might depend on the substitution of the triple bond.

As ring-closing enyne metathesis provides 1,3-dienes, the combination of this reaction with a Diels−Alder

SCHEME 3



cyclization is attractive and allows great increment of the molecular complexity. This approach can be accomplished by addition of all of the reactives from the beginning of the process or by addition of the dienophyle when the metathesis is completed. In the first case only electron-deficient dienophyles can be used in order to avoid undesired cross-metathesis reactions.[11] The latter approach has been used for the synthesis of indenes[12] and polycyclic β-lactams.[13] Some examples in which this approach is carried out in a stepwise fashion have also been reported.[14]

In a preliminary communication of this work,[15] we showed the formation of tri- and tetracyclic compounds by the tandem metathesis-Diels−Alder reaction of aromatic enynes. Herein we describe the complete results of our study in which we have compared the reactivity of the different generations of catalysts. We have monitorized some reactions by NMR to give some more data on the enyne metathesis reaction course. This methodology is also applied to the synthesis of the indole nucleus.

Results and Discussion

Enynes connected through an aromatic ring are interesting substrates that have found scarce use in this

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(6) Wakamatsu, H.; Blechert, S. *Angew. Chem, Int. Ed.* **2002**, *41*, 794. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168. (c) Van Veldhuizen, J. J.; Garber, S. B.; Kingbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.

(7) See: (a) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543. (b) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749. (c) Aagaard, O. M.; Meier, R. J.; Buda, F. *J. Am. Chem. Soc.* **1998**, *120*, 7174.

(8) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277.

(9) Kitamura, T.; Sato, Y.; Mori, M. *Chem. Commun.* **2001**, 1258.

(10) For a recent review on olefin cross metathesis see: Connon, S. J.; Blechert, S. *Angew. Chem, Int. Ed.* **2003**, *42*, 1900.

(11) See: (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Moreno-Mañas, M.; Pleixats, R.; Santamaria, A. *Synlett* **2001**, 1784 and ref 3i. For a recent example of a three-component tandem metathesis/Diels−Alder reaction, see: Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439.

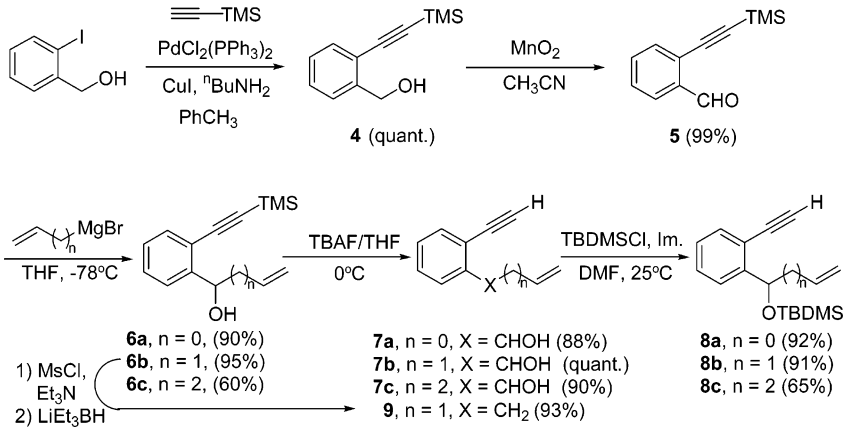
(12) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294.

(13) Schurer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877.

(14) See: (a) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561. (b) Guo, H.; Madhushaw, R. J.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, *58*, 5627. (c) Schürer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203.

(15) For a preliminary communication of part of this work, see: Rosillo, M.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2001**, *42*, 7029.

SCHEME 4



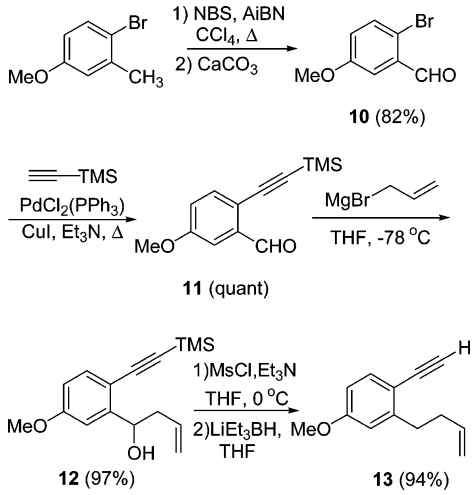
chemistry.[11b] However, these compounds can be easily prepared and would give, upon metathesis, dienes containing fused bicycles that may undergo a Diels−Alder process to give finally two or three new cycles in one step.

We first carried out the synthesis of 1,6-, 1,7- and 1,8 enynes. Starting from 2-iodobenzyl alcohol, a Sonogashira coupling with trimethylsilylacetylene gave quantitatively alcohol **4**, which was oxidized with MnO_2 to give **5** in 99% yield. This aldehyde was treated with suitable Grignard reagents to afford the corresponding enynes **6**, which were deprotected to give compounds **7**. These alcohols were protected to give the silylderivatives **8**. Additionally compound **6b** was mesylated and treated with superhydride to give **9** (Scheme 4).

To effect a new approach to Dane's diene, a well-known substrate thoroughly used for the synthesis of estradiol derivatives, we carried out the synthesis of the corresponding enyne precursor. Thus, 4-bromo-3-methylanisole was dibromated with NBS to give a dibromide intermediate, which upon basic treatment gave aldehyde **10** in 82% yield after the two steps. Sonogashira coupling afforded **11** quantitatively, which was treated with allylmagnesium bromide to give **12**. The final step was the elimination of the hydroxyl group via mesilation-superhydride reduction, yielding **13**. We have to note the excellent yield of all steps of this synthesis, the global yield from commercial 4-bromo-3-methylanisole being 68%. The order of the reactions is important. When we tried the Sonogashira coupling with the starting anisole or after treating aldehyde **10** with the Grignard reagent, the yields were much lower (Scheme 5).

2-Iodophenol and 2-iodoaniline were selected as starting materials for the synthesis of enynes containing heteroatoms. These were submitted to Sonogashira coupling conditions to give **14** and **15**. Mitsunobu reaction with allyl and homolallyl alcohols afforded enynes **17a,b**, whereas **18** was obtained via nucleophilic substitution. Amine **18** was acetylated to give compound **19**. The final deprotection of the alkyne yielded the desired enynes **20b**, **21a,b**, and **22**. The synthesis of **20a** was a slight modification of this route, as the amine was acetylated after the Sonogashira reaction and the resulting amide **16** was allylated following the Smith procedure that uses powdered KOH in anhydrous THF with tetrabutylam-

SCHEME 5



monium iodide.[16] In this reaction the TMS group is also lost, giving directly the desired enyne **20a** in 98% yield (Scheme 6).

All previously prepared substrates were reacted in the presence of ruthenium catalysts **1** and **2**. Compound **8b** was used as a model to study the best reaction conditions. Temperature, solvent, and catalyst loading were compared using first generation catalyst, and the results are summarized in Table 1. Following these results the selected reaction conditions consisted of using 7% catalyst in refluxing dichloromethane. With regard to catalyst **2**, the current thinking is that intermediates coming from this complex are able to complete more turnovers than those derived from **1** although they are formed in less extension. Thus, the amount of catalyst loading would be less important. As the reaction of compound **8b** did not complete with catalyst **2** in any of the conditions used, we used **8c**. We reacted this compound (entries 8−10) with 3%, 5%, and 7% of catalyst **2** and found similar results. We selected a 5% loading for the rest of reactions.

The above selected conditions were used with the rest of substrates (entry 6, Table 1 for catalyst **1** and entry 9 for catalyst **2**). Table 2 summarizes the results obtained in these reactions.

Alcohol **7a** gave the corresponding diene, which could only be observed in the spectrum of the crude mixture.

(16) Keusenkothen, P. F.; Smith, M. B. *Tetrahedron Lett.* **1992**, *48*, 2977.

SCHEME 6

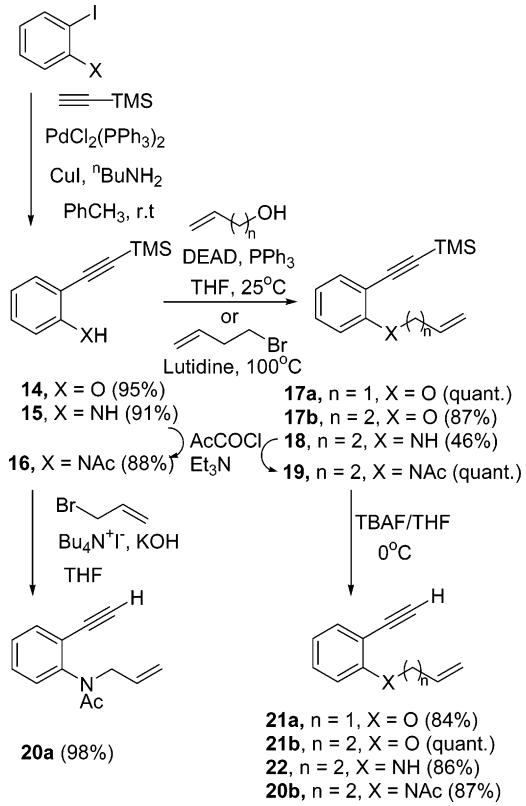
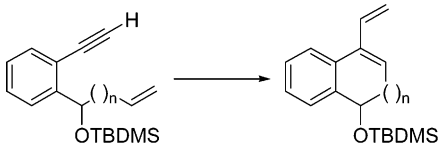


TABLE 1. Selection of Reaction Conditions



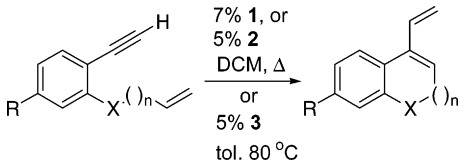
entry	substrate	solvent	temp	catalyst, loading	yield[a]
1	**8b**	benzene	rt	**1**, 5%	60%
2	**8b**	toluene	rt	**1**, 5%	58%
3	**8b**	DCM	rt	**1**, 5%	70%
4	**8b**	DCM	reflux	**1**, 5%	79%
5	**8b**	DCM	reflux	**1**, 3%	75%
6	**8b**	DCM	reflux	**1**, 7%	85%
7	**8b**	DCM	reflux	**1**, 10%	85%
8	**8c**	DCM	reflux	**2**, 3%	88%
9	**8c**	DCM	reflux	**2**, 5%	93%
10	**8c**	DCM	reflux	**2**, 7%	94%

[a] Of pure product.

This reaction product decomposed after few hours at room temperature. All attempts to isolate it were unsuccessful. In addition, no reaction was observed with the TBDMS-protected compound **8a** with any of the catalysts, probably because of steric hindrance of the substrate. We opted thus to react **7a** and protect the hydroxydiene in the crude mixture with a TBDMS group, obtaining **24a** with 50% yield after the two reaction steps (Scheme 7).

The rest of the examples selected yielded the desired products with, in general, good yields. The exception was **22**, which did not react, probably as a result of interaction with the unprotected amine. The reaction of the two ethers **21** using complex **1** gave only 50% conversion after

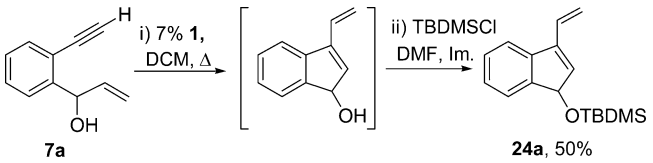
TABLE 2. Metathesis Reactions with Aromatic Enynes



entry	sub-strate	X	*n*	R	product	yield[a] (%) cat. **1**	cat. **2**	cat. **3**
1	**7a**	CHOH	0	H	**24a**	50[b]	nr	
2	**7b**	CHOH	1	H	**23b**	68	76	
3	**8a**	CHOTBDMS	0	H	**24a**	nr	nr	
4	**8b**	CHOTBDMS	1	H	**24b**	85	*c*	
5	**8c**	CHOTBDMS	2	H	**24c**	84	93	
6	**9**	CH_2	1	H	**25**	56	60	
7	**13**	CH_2	1	OCH_3	**26**	*c*	77	*c*
8	**20a**	$NCOCH_3$	1	H	**27a**	95	*c*	70
9	**20b**	$NCOCH_3$	2	H	**27b**	85	93	
10	**22**	NH	2	H	**28**	nr	nr	
11	**21a**	O	1	H	**29a**	65[d]	*c*,*e*	72
12	**21b**	O	2	H	**29b**	60[d]	*c*,*e*	70

[a] Of pure product with correct spectroscopic data. [b] Yield of protected compound **24a** after two steps. See Scheme 7. [c] The reaction did not complete. [d] 10% catalyst was added in four portions. [e] Partitioned addition of catalysts was also tried without reaching completion of the reaction.

SCHEME 7

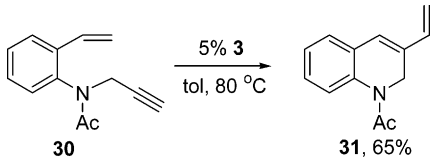


2 h, and it was not improved after 18 h. Thus, we added a total of 10% catalyst divided into four equal portions, which were added every 30 min. Before each addition, the reaction mixture was filtered trough Celite. With this procedure, the remaining starting material was reduced to less than 10% and we isolated the dienes **29** with good yields. When using catalyst **2** the results were similar with one portion of complex while it was not possible to complete the reaction using partitioned addition of the catalyst. The reaction did not complete when carried out in toluene at 80 °C or at reflux. In this latter case we obtained complex mixtures in the reaction of **21a**.

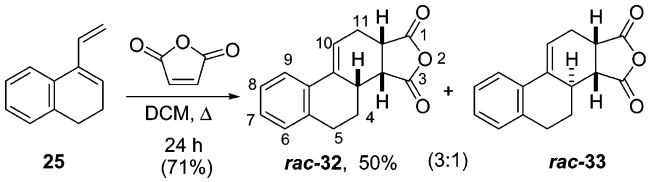
With respect to second-generation catalyst **2**, it is possible that this complex is more sensitive to steric hindrance as reactions with **8b**, **20a**, and **21a,b** gave conversions of only 50–65% in the crude ^{1}H NMR spectra. These results were not improved when changing solvents or temperatures or when adding the catalysts in portions. On the other hand, complex **2** improves the results with less hindered substrates such as **7b**, **8c**, **9**, **20b**, or **13**. The latter substrate yields compound **26**, the well-known Dane's diene.

Some of the substrates shown in Table 2 were also reacted with the Hoveyda–Grubbs catalyst, **3**. This complex has the advantage that it can be purified by column chromatography and recovered at the end of the reaction. It is also stable at higher temperatures. We tried to improve results with ethers **21a,b**. Metathesis reaction with enynes bearing oxygen are somewhat

SCHEME 8



SCHEME 9

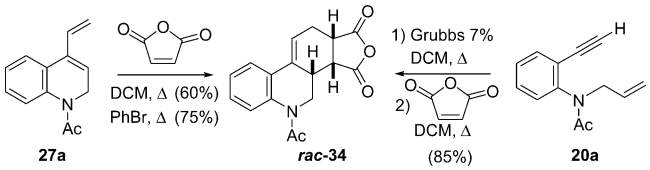


erratic: there are results in the literature in which this functionality seems to be beneficial, others in which no influence is observed, and in the majority of cases, a negative influence is reported.[17] A coordination of the oxygen with the catalyst is usually claimed as the reason for this result. In our hands, the reaction of compounds **21** with 5% complex **3** did not complete using DCM as solvent, even at reflux. Thus we used toluene at 80 °C, and we were pleased to observe total conversion with both ethers and a final yield of 72% and 70%, respectively. This result avoids the partitioned addition of the catalyst. The same conditions were used with enynes **13** and **20a**. Whereas the reaction of **13** did not complete after 12 h, compound **20a** gave 70% yield and total conversion, a worse result than when using catalyst **1** (see entry 8, Table 2).

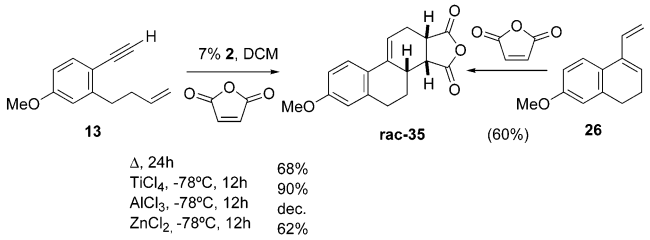
When designing the type of substrates used for these studies we had observed that when using compounds in which the double bond was conjugated with the aromatic ring, the cyclization did not occurr. We used compound **30** to test the previously optimized conditions.[18] Neither complexes **1** nor **2** were able to catalyze the cyclization. Starting material was recovered in both cases. On the other hand, compound **30** reacted with 5% **3** and was totally converted into **31**, which was isolated in 65% yield (Scheme 8).

Next we addressed the Diels−Alder reaction of some of these products. As a model we performed the cyclization of compound **25** with maleic anhydride (Scheme 9). We used toluene and DCM as solvents, at room temperature, observing in both cases after 3 days a 2:1 mixture of *rac*-**32** and *rac*-**33**. When using refluxing DCM, the reaction completed in 24 h and resulted in a 3:1 mixture of the same compounds (71% yield in mixture). The major adduct, *rac*-**32**, was isolated in 50% yield. These compounds were assigned as the stereoisomers depicted in

SCHEME 10



SCHEME 11



Scheme 9 by analogy with related structures described in the literature.[19]

The latter conditions were used with compound **27a** and with Dane's diene, **26**. Compound **27a** completed the reaction after 48 h (TLC), yielding 60% of compound *rac*-**34** (*endo* adduct). A minor isomer of this compound was detected in less than 10% in the ^{1}H NMR spectrum of the crude. The yield of this cyclization improved up to 75% when using refluxing bromobenzene as solvent. The relative configuration of this adduct was determined by analogy with previously reported compounds.[19] On the other hand, compound **26** reacted in 60% yield under standard conditions, giving *rac*-**35** as the only isomer.

We tried the one-pot obtention of these adducts from enynes **20a** and **13** by adding the dienophyle to the metathesis reaction mixture, once total conversion of the enyne was verified (TLC). Regarding compound *rac*-**34** the yield of the two-step one-pot process was 85%, after 36 h of reaction in refluxing dichloromethane. This result shows a possible beneficial action of the ruthenium complex in the Diels−Alder reaction (Scheme 10).[20]

Compound *rac*-**35** reached 68% yield, also improving the two-step procedure. As this latter case is a possible entry to new estradiol-related compounds, we tried to improve this result by adding a Lewis acid as cocatalyst. Scheme 11 shows the results obtained when adding 1 equiv of several Lewis acids jointly with the dienophile. $TiCl_4$ at low temperature gave the best results (90%).

At this point we thought it was worth trying this methodology to obtain indoles.[21] This would imply the synthesis of aromatic enamines or ynamines. Both approaches were addressed. We prepared enamine **36** and ynamine **37** following our previously reported procedure.[22] When reacting these compounds with catalyst **1**, no conversion was detected (TLC) and decomposition of starting material occurred when the reaction time was prolonged. Catalyst **2** gave the desired cyclization prod-

(17) (a) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263. (b) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633. (c) Paquette, L. A.; Efremov, I. *J. Am. Chem. Soc.* **2001**, *123*, 4492. (d) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255. (e) Krikstolaityte, S.; Hammer, K.; Undheim, K. *Tetrahedron Lett.* **1998**, *39*, 7595. In intermolecular enyne reactions coordination effects of oxygen atoms have also been identified sometimes with an accelerating result. See: Tonogaki, K.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 2235. Other authors circumvented this problem with adequate choice of the catalyst. Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271.

(18) Compound **30** was obtained from 2-iodoacetanilide by Stille reaction with tributylvinyltin and subsequent propargylation of the amide. See Supporting Information for details.

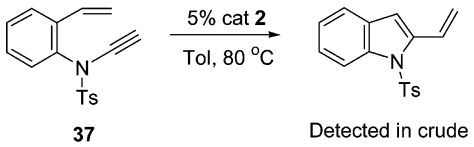
(19) (a) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697. (b) García Ruano, J. L.; Alemparte, C.; Martín Castro, A.; Adams, H.; Rodríguez Ramos, J. *J. Org. Chem.* **2000**, *65*, 7938.

(20) This would imply a nonmetathetic behavior of the ruthenium complex. See: Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1258.

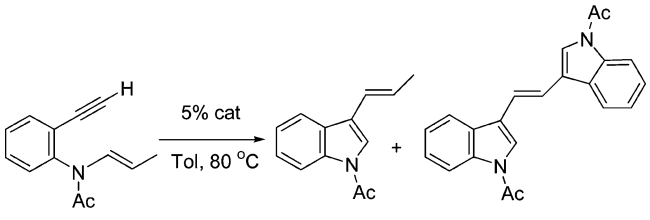
(21) The only example of indole synthesis using olefin RCM: Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem, Int. Ed.* **2002**, *41*, 4732.

(22) Domínguez, G.; Casarrubios, L.; Rodriguez-Noriega, J.; Pérez-Castells, J. *Helv. Chim. Acta* **2002**, *85*, 2856.

SCHEME 12



SCHEME 13

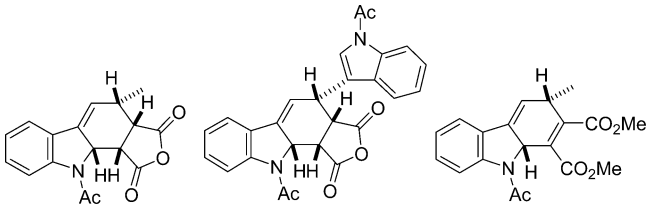


Cat	time	dil*	38	39
2	4h	40	36%	41%
3	4h	40	42%	53%
2	2h	100	60%	25%
3**	18h	20	20%	70%

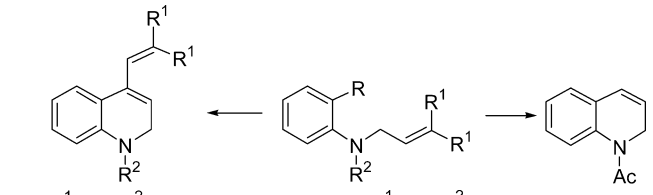
* in mL/mmol

** 5% + 2% addition after 4 h

CHART 2



SCHEME 14



ucts when toluene at 80 °C was used.[11a] Compound **37** gave a complex crude mixture in which *N*-tosyl-*2*-vinylindole was the major product. However, it was impossible to purify it probably as a result of instability of this product in the presence of traces of ruthenium species (Scheme 12).

On the other hand, compound **36** gave a clean conversion into a mixture of the vinylindole **38** and its dimmer **39**. As **38** is not a diene, a partial cross metathesis reaction had occurred after cyclization. When using catalyst **3** in the same conditions, yields improved for both products although there was a similar ratio of both. We were unable to find conditions that would allow the synthesis of only one of these products. When using catalyst **2**, high dilution (100 mL/mmol), and short reaction times (2 h) in toluene (80 °C) we reached 60% yield of **38** and 25% yield of **39**. With catalyst **3**, longer reaction time (18 h) and addition of a further 2% portion of catalyst, we reached 70% yield of **39** and 20% yield of **38** (Scheme 13).

One possible way to obtain only one reaction product would be performing a tandem RCM/Diels−Alder process in which the cycloaddition would be more rapid than the cross metathesis reaction. When carrying out the domino process from **36**, using maleic anhydride as dienophyle, we observed in the crude a (1:1.5) mixture of *rac*-**40** and *rac*-**41**, which could not be separated. On the other hand, with dimethyl acetylenedicarboxylate we were pleased to obtain only compound *rac*-**42** with 65% yield. This latter compound is related with carbazole alkaloids. Additionally, compounds **38** and **39** were separately reacted with maleic anhydride. They gave the corresponding adducts *rac*-**40** and *rac*-**41** in good yields (Chart 2).

To assign the relative configuration of these compounds, a single crystal of *rac*-**40** was submitted to X-ray diffraction analysis. This analysis shows a (3a*S**,3b*S**,-10*S**,10a*S**) relative stereochemistry for this compound in which all hydrogen atoms present in the stereogenic centers are positioned on the same face. We assume the same relative stereochemistry for compounds *rac*-**41** and *rac*-**42**.

From the results we have shown here it is clear that there is not a simple and predictable behavior of the three catalysts used. The claimed greater efficiency of second-generation complexes is true for substituted olefins and nonhindered substrates, whereas complex **1** gives better results with hindered ones. This differences may have their origin in the reaction course, which may be slightly or even completely different from one catalyst to another. To have more information on these reactions, we proceeded to follow some of them by ^{1}H NMR. The reactions were carried out with 25% catalyst in a 0.025 M solution of starting material.[19] We selected as starting materials compounds **20a**, **43**, and **44**. Compound **43** was synthesized to see the influence of substituted olefin fragments in the reaction, and **44** was selected as a parent olefin RCM substrate to check possible differences in the reaction course (Scheme 14).[23]

We registered a proton spectrum every 5 min during the first hour and every 15 min until total completion or 4 h of reaction. We followed the transformation of the starting material into the final product, the possible appearance of signals corresponding to styrene, and the changes in the signal of the carbene proton of the catalyst. The results are summarized in Table 3. We indicate the initial position of this carbene C−H signal and its eventual changes at the end of the reactions. We also made ^{1}H NMR spectra of complexes **1**, **2**, and **3** in the different solvents used for these reactions. The position of the carbene C−H signal in the spectra of the catalyst alone is also indicated.

When used, the first generation catalyst **1** produces styrene, and its carbenic signal disappears during the reaction (entries 1 and 6), any other carbenic species not being detectable at the end. During the enyne metathesis (entry 1) two new carbenic species are detected, a triplet (J = 4.3 Hz) at 18.28 ppm and a singlet at 20.7 ppm. As

(23) See Supporting Information for data on the synthesis of compounds **43** and **44**.

TABLE 3. Metathesis Reactions in NMR Tubes

								^{1}H NMR signal[a]		
entry	substrate	catalyst	solvent	temp	product	time (h)	conversion (%)	catalyst	initial	final
1	**20a**	**1**	$CDCl_3$	rt	**27a**[b]	3[c]	65	19.98	19.98	none
2	**20a**	**2**	$CDCl_3$	rt	**27a**	3[d]	>95	19.13	19.13	19.13
3	**20a**	**2**	C_6D_6	rt	**27a**	5	>95	19.63	19.62	19.62; 18.41
4	**20a**	**3**	$CDCl_3$	rt	**27a**	3[c]	83	16.56	16.57	16.57
5	**43**	**2**	CD_2Cl_2	rt	**45**	3	>95	19.07	19.07	19.07
6	**44**	**1**	$CDCl_3$	rt	**46**[b]	0.5	>95	19.98	19.98	none
7	**44**	**2**	$CDCl_3$	rt	**46**	1	>95	19.13	19.13	19.13
8	**44**	**2**	Xyl-d_{10}	rt	**46**	5	>95	19.22	19.22	19.22; 17.96
9	**44**	**2**	C_6D_6	rt	**46**	6	>95	19.63	19.62	18.41

[a] Position of the carbene C−H signal. [b] Styrene was formed in the reaction. [c] The reaction was not totally completed. [d] Some cross metathesis (dimeric) product is detected.

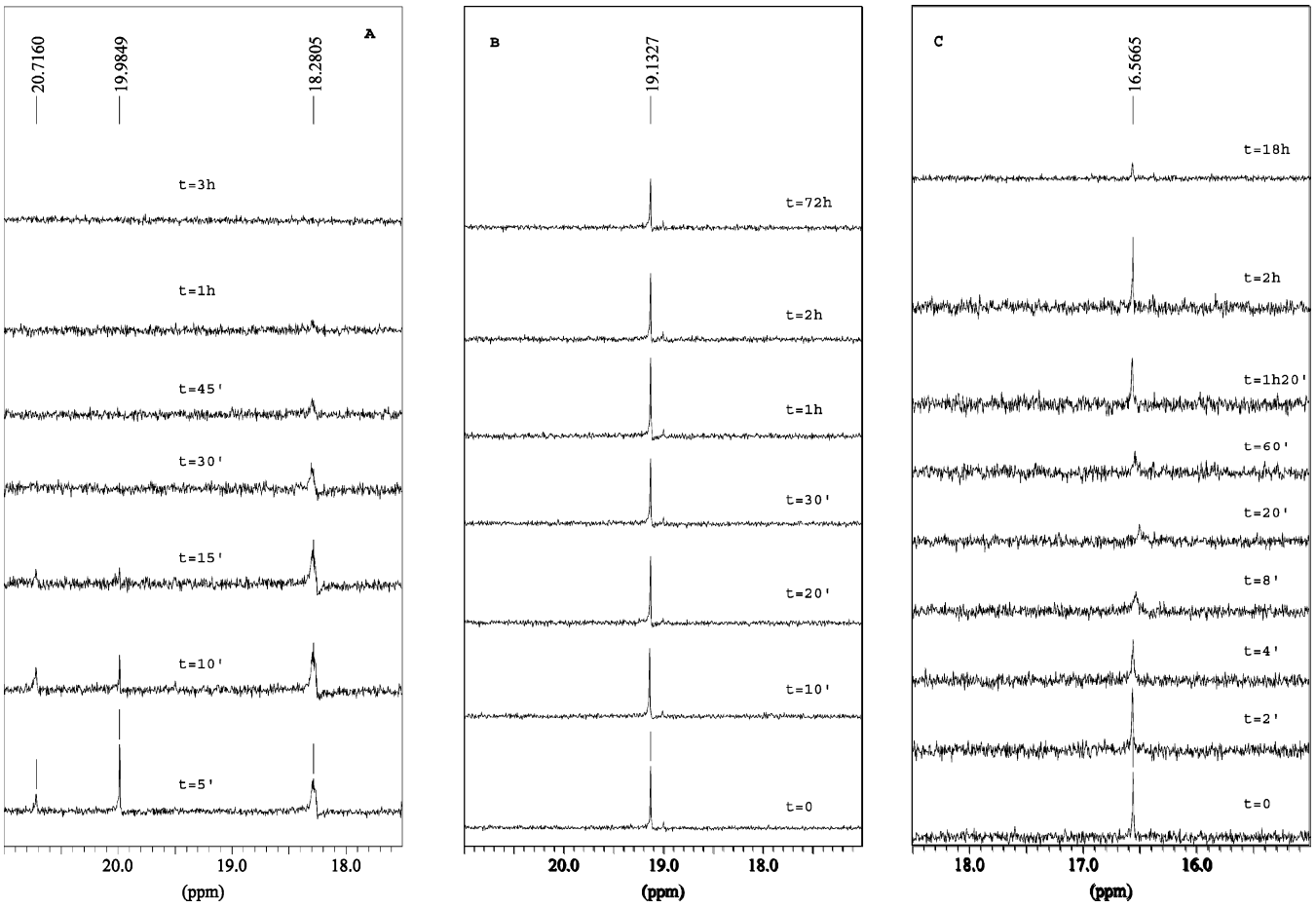


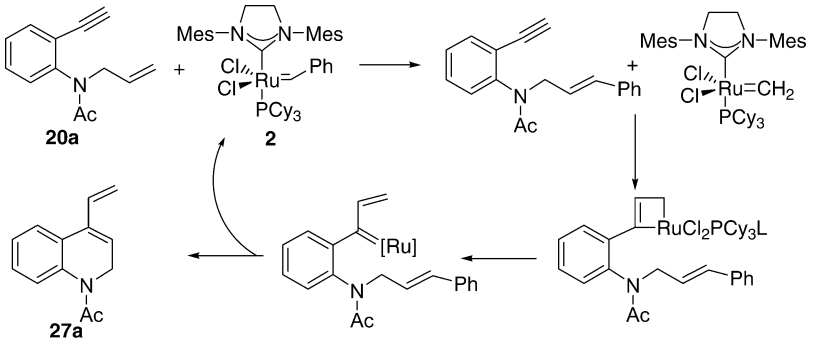
FIGURE 1. Comparative evolution of the carbenic signal of catalysts **1, 2** and **3** in the reactions of compound **20a** (entries 1, 2, and 4, Table 3).

Hoye has reported recently,[8] these signals may correspond with the carbenic species consistent with path a, Scheme 3, supporting that this reaction course is operating with catalyst **1,** although other paths may also operate at the same time. With catalyst **2**, the ruthenium complex remains apparently unaltered during the whole reaction when using CD_2Cl_2 or $CDCl_3$ (entries 2, 5, and 7) and is partially transformed into a new complex when using aromatic solvents (entries 3, 8, and 9). In all of these reactions no styrene was detected. This would discard path a and suggests path b is predominant. Finally the carbenic signal of complex **3** diminishes during the first hour (when final product is hardly detected) and reappears after 2 h. A comparative figure of the evolution of the low field signals of the reactions of entries 1, 2, and 4 from Table 3 is shown in Figure 1.[24]

The three reaction pathways generally discussed for enyne metathesis (paths a−c, Scheme 3) involve the formation of styrene (path a) or products with a pending phenyl that comes from the first catalytic cycle (paths b and c). We have seen styrene when using complex **1** but not with complexes **2** or **3**. This may be due to the fact that complex **2** may create active catalyst species to a lesser extent (not detectable by NMR), but that these give

(24) See Supporting Information for complete spectra of these reactions and of the rest of the Table 3 reactions.

SCHEME 15



more turnovers than the intermediate coming from **1**. This agrees with the values of the dissociation constants found by Grubbs and would explain that styrene is not detected.[7] One other possible explanation for this unchanging benzylidene signal would be that this catalyst begins transferring the benzylidene onto the substrate releasing a $Ru{=}CH_2$ complex. This methylidene would react with the alkyne to give a vinylcarbene that would ring close with the alkene (a 3-phenylallylamide), regenerating the benzylidene complex **2** in each turnover (Scheme 15).[25]

The apparent disappearance of the signal of catalyst **3** and its recovery after 1 h of reaction is something consistent with the ability of this complex to regenerate after the reactions. This has been shown in olefin metathesis reactions, and it also occurs in these enyne processes. As proposed by Hoveyda this complex reacts with the olefin (in alkene metathesis), releasing the corresponding styrene derivative. Upon consumption of the reactives, this styrene reacts with the metal carbene complex to regenerate the initial catalyst.[5b] According with our observations similar behavior is assumable with enyne reactions.

On the other hand, Mori has recently reported a new cyclization process catalyzed by ruthenium species in which a ruthenacyclopentene is proposed as intermediate.[26] Our observations in the reactions with complexes **2** and **3** may indicate that a possible reaction course in which this kind of metallocycles would be formed followed by cyclobutene formation and cyclorreversion may not be completely discarded.[27] It is clear that more evidence would be necessary, but this reaction course would also explain the behavior of complex **2**, which may be recovered after every cycle by recomplexation of the phosphine.

Also in olefin RCM reactions (entries 6 and 7) the same pattern is observed, catalyst **2** remaining unaltered in the reaction, while **1** produces styrene and disappears during the process.

Another interesting aspect of this experiments is the changes observed when switching the solvent to an aromatic one. When using xylene or benzene, new carbenic species are formed. It would be possible that these solvents interact with the metal, forming new complexes that also would be capable of catalyzing the metathesis reaction. No change in the spectrum was observed when heating the catalyst alone in xylene for 2 h at 40 °C. The reactions in aromatic solvents need more time to complete. We are investigating the nature of these species that may resemble the η^6 complexes described in the literature,[28] some of them reported as efficient catalyst for metathesis reactions.[29]

In conclusion, we have described the use of enynes connected through aromatic rings as substrates for the enyne metathesis reaction that affords quinoline, benzoazepine, chromane, hydronaphthalene, indole ,and other polycyclic derivatives. The reactivity of the most popular ruthenium complexes is studied and affords no exact rule for their preferable use, although second generation complexes give better results with monosubstituted olefins and worse with hindered substrates. Some polycyclic compounds are obtained in a tandem or stepwise RCM-Diels−Alder process. We have shown here some data on the enyne RCM reaction course. These data support the first complexation of the alkene with the ruthenium as has been proposed by other groups.[3a,m,8] They also point to possible differences in the reaction course when using the different catalysts.

Experimental Section

General Procedures for Metathesis Reaction. Method A. A 1 mmol portion of enyne was dissolved in 20 mL of dry dichloromethane under argon. To this solution was added 0.05−0.07 mmol of Grubbs catalyst (**1** or **2**), and the reaction was refluxed until completion (TLC). Filtration though Celite, evaporation of the solvent, and purification by column cromatography yielded the corresponding diene.

Method B. A 1 mmol portion of enyne was dissolved in 20 mL of dry dichloromethane under argon. To this solution was added 0.10 mmol of catalyst **2**, divided into four equal portions, which were added every 30 min, while the mixture was refluxed. Before each addition, the reaction mixture was cooled and filtered trough Celite. Evaporation of the solvent and purification by column chromatography yielded the corresponding diene.

Method C. A 1 mmol portion of enyne was dissolved in 50 mL of dry toluene under argon. To this solution was added 0.05 mmol of catalyst **3**, and the reaction was heated at 80 °C until completion (TLC). Evaporation of the solvent and purification by column chromatography yielded the corresponding diene.

(25) We thank one of the referees of this work for useful proposals on these mechanistic aspects.

(26) Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 5606.

(27) These ruthenium metalacycles have been proposed in cyclizations catalysed by noncarbene ruthenium(II) species: (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 714. (b) Chatani, N.; Kataoka, K.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 9104.

(28) Hansen, H. D.; Nelson, J. H. *Organometallics* **2000**, *19*, 4740.

(29) Cetinkaya, B.; Demir, S.; Ozdemir, I.; Toupet, L.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *New J. Chem.* **2001**, *25*, 519.

1-*tert*-Butyldimethylsilyloxy-3-vinyl-1*H*-indene (24a). Following method A, 150 mg (0.95 mmol) of **7a** and 55 mg (0.07 mmol) of **1** gave a crude mixture that was dissolved in 5 mL of DMF and treated with 162 mg (2.4 mmol) of imidazole and 286 mg (1.9 mmol) of *tert*-butyldimethylsilyl chloride. The resulting mixture was stirred for 2 h. The reaction was quenched with 20 mL of ice−H_2O/Et_2O (1:1). The organic layer was washed with abundant H_2O, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane) afforded 81 mg (50%) of **24a** as a yellow solid (mp 97−98 °C (EtAcO)). ^{1}H NMR: δ 0.09 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 5.28 (s, 1H), 5.40 (d, 1H, J = 11.5 Hz), 5.86 (d, 1H, J = 17.6 Hz), 6.33 (s, 1H), 6.68 (dd, 1H, J_1 = 17.6 Hz, J_2 = 11.5 Hz), 7.18−7.32 (m, 3H), 7.45 (t, 1H, J = 7.1 Hz). ^{13}C NMR: δ 174.0, 141.3, 141.1, 134.3, 130.0, 127.9, 126.1, 123.5, 120.2, 117.6, 76.6, 25.9, 18.3, −4.2. IR (neat): ν 1630, 1610 cm^{-1}. Anal. Calcd for $C_{17}H_{24}$OSi: C, 74.94; H, 8.88. Found: C, 74.69; H, 8.71.

1-*tert*-Butyldimethylsilyloxy-5-vinyl-2,3-dihydro-1*H*-benzocycloheptene (24c). Following method A, from 100 mg (0.33 mmol) of **8c** and 34 mg (0.02 mmol) of catalyst **2**, 93 mg (93%) of **24c** was obtained as a yellow oil. ^{1}H NMR: δ 0.00 (s, 3H), 0.03 (s, 3H), 0.92 (s, 9H), 1.68−1.79 (m, 1H), 1.83−1.99 (m, 2H), 2.33−2.46 (m, 1H), 4.69 (dd, 1H, J_1 = 9.9 Hz, J_2 = 7.7 Hz), 5.08 (d, 1H, J = 11.0 Hz), 5.13 (d, 1H, J = 18.1 Hz), 6.19 (dd, 1H, J_1 = 7.7 Hz, J_2 = 7.2 Hz), 6.52(dd, 1H, J_1 = 17.3 Hz, J_2 = 10.7 Hz) 7.23−7.35 (m, 3H), 7.71 (d, 1H, J = 7.2 Hz). ^{13}C NMR: δ 143.5, 140.4, 137.7, 133.8, 130.8, 127.8, 127.0, 125.8, 124.1, 114.6, 70.9, 43.5, 25.9, 23.2, 18.3, −4.9, −5.0. IR (neat): ν 1630, 1590 cm^{-1}. Anal. Calcd for $C_{19}H_{28}$OSi: C, 75.94; H, 9.39. Found: C, 76.26; H, 9.34.

7-Methoxy-4-vinyl-1,2-dihydronaphthalene (26). Following method A, from 200 mg (1.07 mmol) of **13** and 63 mg (0.07 mmol) of catalyst **2**, 174 mg (77%) of **26** was obtained as a colorless oil. ^{1}H NMR: δ 2.27−2.34 (m, 2H), 2.74 (t, 2H, J = 7.7 Hz), 3.82 (s, 3H), 5.19 (dd, 1H, J = 11.0 Hz, J = 1.6 Hz), 5.53 (dd, 1H, J_1 = 17.0 Hz, J_2 = 1.6 Hz), 6.08 (t, 1H, J = 5.0 Hz), 6.61 (dd, 1H, J_1 =18.1 Hz, J_2 = 11.0 Hz), 6.72−6.75 (m, 2H), 7.29 (d,1H, J = 8.8 Hz). ^{13}C NMR: δ 158.5, 138.4, 136.1, 135.7, 127.1, 125.0, 124.1, 114.9, 113.8, 110.8, 55.2, 28.7, 23.1. IR (neat): ν 3090, 2940, 1610, 1570 cm^{-1}. Anal. Calcd for $C_{13}H_{14}$O: C, 83.83; H, 7.58. Found: C, 83.91; H, 7.63.

1-Acetyl-4-vinyl-1,2dihydroquinoline (27a). Following method A, from 150 mg (0.75 mmol) of **20a** and 43 mg (0.05 mmol) of catalyst **1**, 143 mg (95%) of **27a** was obtained as pale yellow oil. ^{1}H NMR (DMSO-d_6, 80 °C): δ 1.52 (s, 3H), 3.72 (d, 2H, J = 4.3 Hz), 4.69 (d, 1H, J = 11.0 Hz), 5.47 (d, 1H, J = 17.7 Hz), 5.67 (t, 1H, J = 4.3 Hz), 6.05 (dd, 1H, J_1 = 17.7 Hz, J_2 = 11.0 Hz), 6.58−6.71 (m, 3H), 6.82 (d, 1H, J = 7.3 Hz).^{13}C NMR (DMSO-d_6, 80 °C): δ 168.2, 136.9, 134.0, 132.8, 128.1, 126.9, 124.7, 124.1, 124.0, 123.6, 116.3, 41.3, 21.6. IR (neat): ν 1660, 1600, 1490 cm^{-1}. Anal. Calcd for $C_{13}H_{13}$NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.01; H, 6.43; N, 6.90.

5-Vinyl-2,3-dihydrobenzo[*b*]oxepine (29b). Following method B, from 100 mg (0.58 mmol) of **21b**, 60 mg (60%) of **29b** was obtained as a colorless oil. ^{1}H NMR: δ 2.36 (q, 2H, J = 6.6 Hz), 4.43 (t, 2H, J = 6.0 Hz), 5.16 (dd, 1H, J_1 = 11.5 Hz, J_2 = 1.1 Hz), 5.33 (dd, 1H, J_1 = 17.6 Hz, J_2 = 1.1 Hz), 6.26 (t, 1H, J = 6.6 Hz), 6.56 (dd, 1H, J_1 = 17.6 Hz, J_2 = 11.0 Hz), 7.10−7.16 (m, 2H), 7.23−7.26 (m, 1H), 7.38 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz).^{13}C NMR: δ 156.8, 139.5, 138.1, 131.1, 129.7, 128.6, 128.5, 123.3, 122.2, 115.3, 77.8, 28.6. IR (neat): ν 1630, 1600 cm^{-1}. Anal. Calcd for $C_{12}H_{12}$O: C, 83.69; H, 7.02. Found: C, 83.51; H, 6.99.

1-Acetyl-3-vinyl-1,2-dihydroquinoline (31). Following method C, from 100 mg (0.50 mmol) of **30**, 65 mg (65%) of **31** was obtained as a pale yellow oil. ^{1}H NMR: δ 1.80 (s, 3H), 4.15 (dd, 1H, J_1 = 17.0 Hz, J_2 = 2.5 Hz), 4.75 (dd, 1H, J_1 = 17.0 Hz, J_2 = 2.7 Hz), 5.39 (dd, 1H, J_1 = 11.0 Hz, J_2 = 1.1 Hz), 5.80 (dd, 1H, J_1 = 17.6 Hz, J_2 = 1.1 Hz), 6.79 (dd, 1H, J_1 = 17.6 Hz, J_2 = 11.0 Hz), 7.26−7.29 (m, 2H), 7.33−7.43 (m, 2H), 7.67 (dd, 1H, J_1 = 7.7 Hz, J_2 = 1.6 Hz). ^{13}C NMR: δ 170.4, 139.3, 135.6, 131.4, 129.0, 128.9, 128.8, 126.3, 117.3, 78.5, 72.2, 37.7, 22.1. IR (neat): ν 2240, 1660, 1600, 1590 cm^{-1}. Anal. Calcd for $C_{13}H_{13}$NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.25; N, 6.85.

(3a*R,3b*S**,11a*S**)-3a,3b,4,5,11,11a-Hexahydrophenanthro[1,2-*c*]furan-1,3-dione (*rac*-32).** To a solution of 50 mg (0.32 mmol) of **25** in 4 mL of DCM was added 32 mg (32 mmol) of maleic anhydride, and the mixture was refluxed for 24 h. The reaction was concentrated giving a 3:1 mixture of *rac*-**32** and *rac*-**33** (^{1}H NMR). Crystallization of the mixture afforded 32 mg of *rac*-**32** as a white solid (50%, mp 217−218 °C (toluene)). ^{1}H NMR: δ 2.09−2.32 (m, 2H), 2.34−2.42 (m, 1H), 2.61−2.77 (m, 2H) 2.85 (dt, 1H, J_1 = 14.8 Hz, J_2 = 3.8 Hz), 2.98 (ddd, 1H, J_1 = 15.6 Hz, J_2 = 7.1 Hz, J_3 = 1.1 Hz), 3.47−3.58 (m, 2H), 6.40−6.44 (m, 1H), 7.11−7.21 (m, 3H), 7.47−7.50 (m, 1H). ^{13}C NMR: δ 174.3, 171.4, 138.6, 137.5, 133.0, 128.3, 127.7, 126.7, 123.5, 119.9, 44.4, 41.6, 36.2, 29.7, 24.9, 24.2. IR (KBr): ν 1840, 1770 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.79; H, 5.69.

(3a*R,3b*S**,11a*S**)-7-Methoxy-3a,3b,4,5,11,11a-hexahydrophenanthro[1,2-*c*]furan-1,3-dione (*rac*-35).** To a solution of 100 mg (0.54 mmol) of **13** in 20 mL of dry dichloromethane was added 32 mg (0.04 mmol) of catalyst **2**, and the mixture was refluxed for 6 h. After cooling to −78 °C, the reaction was treated with 53 mg (0.54 mmol) of maleic anhydride and 0.06 mL (0.54 mmol) of $TiCl_4$, which was added dropwise. The reaction was left to reach room temperature during 12 h, and stirring was continued at room temperature for 2 h. EtOAc/H_2O was added to the crude, which was extracted, dried, filtered, and concentrated. Purification by column chromatography (hexane/EtOAc 4:1 and hexane/EtOAc 2:1) gave 138 mg (90%) of *rac*-**35** as a white solid (mp 205−206 °C (toluene)). ^{1}H NMR: δ 2.10−2.21 (m, 1H), 2.27 (dd, 1H, J_1 = 12.4 Hz, J_2 = 3.6 Hz), 2.33−2.40 (m, 1H), 2.60−2.75 (m, 2H), 2.80 (dt, 1H, J_1 = 15.4 Hz, J_2 = 3.8 Hz), 2.95 (ddd, 1H, J_1 = 15.9 Hz, J_2 = 7.4 Hz, J_3 = 1.4 Hz), 3.45−3.56 (m, 2H), 3.80 (s, 3H), 6.26−6.28 (m, 1H), 6.65 (d, 1H, J = 2.8 Hz), 6.74 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 7.42 (d, 1H, J = 8.8 Hz).^{13}C NMR: δ 174.4, 171.5, 159.2, 139.1, 138.2, 126.0, 125.0, 117.3, 112.9, 112.8, 55.3, 44.4, 41.6, 36.1, 30.0, 24.9, 24.3. IR (neat): ν 1840, 1770, 1610 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.47; H, 5.64.

Preparation of 38 and 39. A 100 mg (0.50 mmol) portion of **36** was dissolved in 10 mL of dry toluene under argon. To this solution was added 16 mg (0.025 mmol) of **3**, and the reaction was heated to 80 °C. After 4 h, 6 mg (0.01 mmol) of catalyst **3** was added to the reaction, and it was heated to 80 °C for 14 h. Evaporation of the solvent and purification by column chromatography (hexane/EtOAc 9:1 and hexane/EtOAc 4:1) afforded 20 mg (20%) of **38** and 60 mg (70%) of **39** both as pale yellow oils.

(*E*)-1-Acetyl-3-prop-1-enylindole (38). ^{1}H NMR: δ 1.96 (dd, 3H, J_1 = 6.6 Hz, J_2 = 1.1 Hz), 2.63 (s, 3H), 6.30−6.41 (m, 1H), 6.50 (d, 1H, J = 15.9 Hz), 7.29−7.41 (m, 3H), 7.76 (d, 1H, J = 7.7 Hz), 8.47 (d, 1H, J = 7.7 Hz). ^{13}C NMR: δ 168.4, 127.3, 125.3, 123.7, 123.6, 121.6, 121.6, 120.9, 119.8, 119.0, 116.7, 24.0, 19.0. IR (neat): ν 3020, 1705, 1600, 1550 cm^{-1}. Anal. Calcd for $C_{13}H_{13}$NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.58; H, 6.32; N, 7.18.

(*E*)-1-Acetyl-3-[2-(1-acetylindol-3-yl)vinyl]-indole (39). ^{1}H NMR: δ 2.70 (s, 6H), 7.34 (s, 2H), 7.38−7.47 (m, 4H), 7.60 (s, 2H), 7.68 (dd, 2H, J_1 = 6.3 Hz, J_2 = 1.4 Hz), 8.52 (d, 2H, J = 7.7 Hz). ^{13}C NMR: δ 168.3, 136.4, 128.6, 125.7, 124.0, 122.7, 120.8, 120.6, 119.8, 116.8, 24.0. IR (neat): ν 1710, 1560, 1450, 1380 cm^{-1}. Anal. Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.01; H, 5.16; N, 8.03.

(3a*S,3b*S**,10*S**,10a*S**)-4-Acetyl-10-methyl-3b,4,10,10a-tetrahydro-3a*H*-furo[3,4-*a*]carbazole-1,3-dione (*rac*-40).** To a solution of 144 mg (0.72 mmol) of **38** in 40 mL of anhydrous toluene was added 62 mg (0.72 mmol) of maleic anhydride, and the mixture was refluxed for 20 h. The crude was concentrated and purified by flash chromatography (hexane/EtOAc 1:1), and 132 mg (62%) of *rac*-**40** was obtained as

a white solid (mp 272−273 °C (EtOAc)). ^{1}H NMR: δ 1.63 (d, 3H, J = 7.1 Hz), 2.54−2.61 (m, 1H), 2.61 (s, 3H), 3.33−3.39 (m, 1H), 4.63−4.69 (m, 1H), 4.89−4.91 (m, 1H), 6.06 (t, 1H, J = 3.8 Hz), 7.06−7.12 (m, 1H), 7.32−7.33 (m, 2H), 7.47 (d, 1H, J = 7.8 Hz). ^{13}C NMR: δ 170.6, 169.0, 168.7, 144.0, 136.5, 130.3, 126.6, 123.6, 121.7, 119.0, 114.3, 59.1, 43.6, 42.1, 32.1, 25.5, 16.6. IR (KBr): ν 1850, 1770, 1640, 1480, 1470 cm^{-1}. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.72; H, 5.13; N, 4.76.

(3a*S,3b*S**,10*S**,10a*S**)-4-Acetyl-10-(1-acetylindol-3-yl)-3b,4,10,10a-tetrahydro-3a*H*-furo[3,4-*a*]carbazole-1,3-dione (*rac*-41).** To a solution of 147 mg (0.43 mmol) of **39** in 20 mL of anhydrous toluene was added 37 mg (0.43 mmol) of maleic anhydride, and the mixture was refluxed for 20 h. The crude was concentrated and purified by flash chromatography (hexane/EtOAc 1:1), and 103 mg (55%) of **41** was obtained as a white solid (mp 261−262 °C (EtOAc)). ^{1}H NMR: δ 2.66 (s, 3H), 2.72 (s, 3H), 3.82−3.87 (m, 1H), 3.95−3.99 (m, 1H), 4.79−4.85 (m, 1H), 5.15−5.17 (m, 1H), 6.55 (t, 1H, J = 3.8 Hz), 7.12−7.18 (m, 1H), 7.34−7.47 (m, 3H), 7.39 (s, 1H), 7.53−7.60 (m, 3H), 8.52 (d, 1H, J = 7.7 Hz). ^{13}C NMR: δ 169.4, 169.1, 168.5, 168.1, 144.2, 138.0, 135.9, 130.9, 126.3, 125.8, 124.0, 123.8, 123.8, 122.1, 118.6, 117.8, 117.1, 117.1, 115.1, 114.5, 59.4, 43.0, 41.7, 34.2, 25.6, 24.2. IR (KBr): ν 1850, 1780, 1710, 1650, 1450, 1390 cm^{-1}. Anal. Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.55; H, 4.64; N, 6.31.

(3*S,9a*R**)-Dimethyl 9-Acetyl-3-methyl-9,9a-dihydro-3*H*-carbazole-1,2-dicarboxylate (*rac*-42).** To a solution of 200 mg (1.0 mmol) of **36** in 85 mL of anhydrous toluene was added 60 mg (0.07 mmol) of catalyst **2**, and the reaction was stirred at room temperature for 3 h. Then 0.12 mL (1.0 mmol) of dimethyl acetylenedicarboxylate was added, and the reaction was refluxed for 12 h. The mixture was concentrated and purified by flash chromatography (hexane/EtOAc 2:1), and 212 mg (65%) of *rac*-**42** was obtained as a white solid (mp 154−155 °C (EtOAc)). ^{1}H NMR: δ 1.38 (d, 3H, J = 7.1 Hz), 2.48 (s, 3H), 3.15−3.27 (m, 1H), 3.74 (s, 3H), 3.78 (s 3H), 5.13−5.17 (m, 1H), 6.03 (m, 1H), 7.10, (t, 1H, J = 7.7 Hz), 7.27−7.33 (m, 2H), 7.50 (d, 1H, J = 7.7 Hz). ^{13}C NMR: δ 170.2, 168.1, 129.5, 128.1, 123.8, 123.6, 123.3, 121.3, 120.6, 120.3, 115.0, 114.8, 60.4, 52.4, 52.2, 33.7, 25.0, 17.3. IR (KBr): ν 1730, 1670, 1600 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.60; H, 5.57; N, 4.03.

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Supporting Information Available: Full characterization of compounds **6a,b,c**, **7a,b,c**, **8a,b,c**, **9**, **10**−**13**, **17b**, **18**, **19**, **20b**, **21b**, **22**, **23b**, **24b**, **25**, **27b**, **29a**, **30**, *rac*-**34**, and **43**−**46**; ORTEP drawing for *rac*-**40**; spectra of reactions described in Table 3; and cif file with details on the X-ray analysis of compound *rac*-**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

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