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Transannular vs Intramolecular Insertion Reactions of Transition Metal Carbenes: Evaluation of a Transannular Approach to Cyclooctane Ring Synthesis

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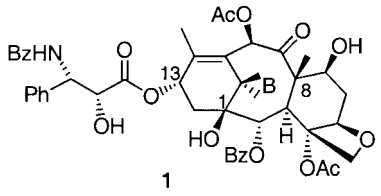
Abstract—The efficacy of closing cyclooctane rings via transannular metal-stabilized carbene insertion reactions within an 11-membered macrocyclic lactone ring was explored. The impact of performing these reactions in a transannular fashion was evaluated via a comparative study of closely analogous intramolecular (but not transannular) processes. Closure of a γ-lactone ring via intramolecular cyclopropanation on a moderately electron-deficient alkene proceeded in good yield under $Cu(acac)_2$ catalysis, whereas analogous transannular cyclopropanation was thwarted by competitive β-hydride migration. In contrast, use of a more electron-rich methoxy-substituted alkene resulted in successful transannular cyclopropanation to afford the desired cyclooctane ring-containing product.

Introduction

In ongoing studies aimed at the synthesis of selectively functionalized analogs of the anticancer diterpene alkaloid paclitaxel (**1**),[1] we have previously demonstrated the viability of a macrolactonization/transannular aldol condensation approach for the construction of the mediocyclic taxane B ring (Scheme 1).[2] More recently, we have reported a cyclopropanation/reductive cleavage protocol using Corey's sulfur ylide chemistry on model furanone **2** (Scheme 2) that has some potential for installation of the taxane C-8 methyl group.[3] One limitation of this latter chemistry was the need for 20 equiv. of sulfur ylide in what amounted to a two pot cyclopropanation step. In addition, only modest yields of the propellane adduct **3** were obtained. Therefore, we sought to develop alternate transannular routes that would allow *direct* access to propellane **3**, fused furanone **4**, or other adducts where a C-8 methyl group equivalent can be installed *directly* in the transannular reaction step. In this paper, we report on our explorations toward these goals using transannular metal-stabilized carbene insertion methods.[4]



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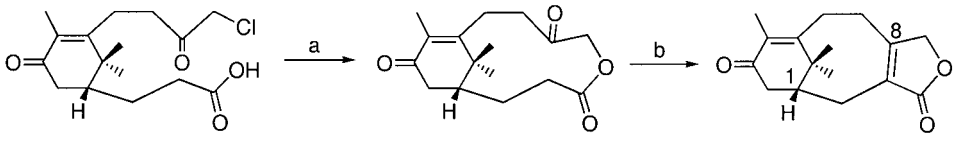
Intramolecular π-bond and unactivated C–H bond insertion reactions of transition metal-stabilized carbenes have become powerful methods for ring construction due to the often predictable and reliable chemo-, regio- and stereoselectivity of such transformations.[5] These reactions typically involve the use of α-diazo carbonyl precursors and most commonly proceed via Rh(II)- or Cu(I)-stabilized carbene species. In stark contrast, very little is known about *transannular* metal carbene insertion reactions. Very few examples of transannular metal carbene cyclopropanation[6]



Scheme 1. (a) NaOH, DMSO, 100°C (59%). (b) NaH, DMSO, 70–90°C, then aq NH_4Cl (51%).

Keywords: transannular reactions; cyclooctanes; carbenes and carbenoids; cyclopropanation.
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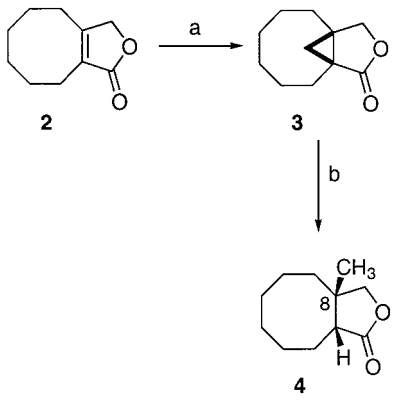
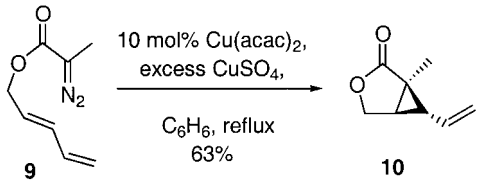


Scheme 2. (a) 2×10 equiv. $Me_2S(O)=CH_2$, DMSO, 50°C, 60 h (53%). (b) 2 equiv. Li, NH_3, −78 to −63°C (92%).

or C–H insertion[7] have previously been reported, and none of these reactions have led to medium-sized ring formation.[7c] We envisaged that a transannular cyclopropanation strategy, utilizing the model alkenyl α-diazo lactone **5** as a source of the metal-stabilized carbene **6** (Scheme 3), could potentially furnish the desired cyclooctane-fused furanone **3** (path a). In this way, a taxane C-8 methyl group surrogate would be established *directly* in the transannulation step. It was recognized that there was the potential for competition from a transannular 1,5-secondary C–H bond insertion pathway (path b to give **7**) as well as from a β-hydride migration (path c to give **8**), thus allowing for a study of the chemoselectivity of such metal carbene-mediated reactions. Our expectation that it should be possible to favor cyclopropanation over β-hydride migration was based on a report by Hudlicky[8] (Eq. (1)), who found that dienyl α-diazo ester **9** afforded γ-lactone **10** in reasonable yield when proceeding via a copper carbene intermediate and did not report the formation of any products resulting from β-hydride migration.[9]



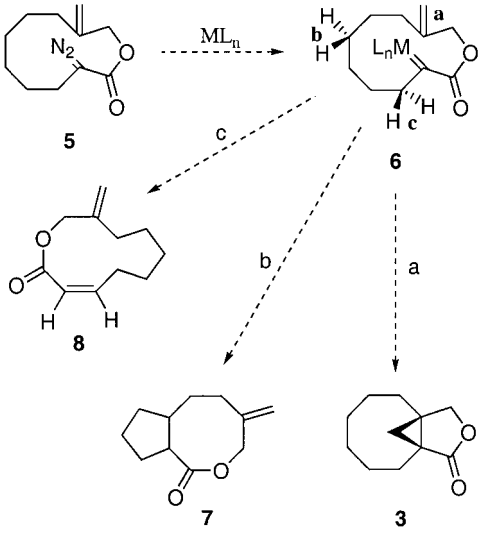
(1)

We also planned to explore metal carbene C–H insertion reactions using the saturated α-diazo lactone **11** (Scheme 4), where successful transannular metal carbene tertiary C–H bond insertion (path a) would yield the cyclooctane-fused furanone **4** directly. Once again, it was of interest to examine the chemoselectivity of this process, given that competition from transannular 1,5-secondary C–H bond insertion (path b to give **12**) and/or β-hydride migration (path c to give **13**) would also be possible.

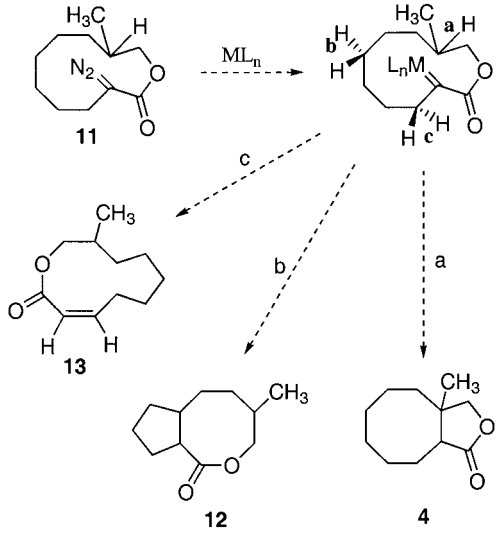
We were particularly interested in evaluating the impact of performing the above alkene and C–H insertion reactions in a transannular fashion. We wished to determine if the potential entropic advantage associated with performing *transannular* carbene insertion reactions (due to the higher level of conformational preorganization present in the macrocyclic substrates for these reactions) would facilitate such reactions over analogous intramolecular (but not transannular) processes. This was done by performing a comparative study using metal carbenes derived from the acyclic α-diazo esters **15** (Scheme 5) and **20** (Scheme 6).

Synthesis of α-diazo lactones and esters 5, 11, 15 and 20[10]

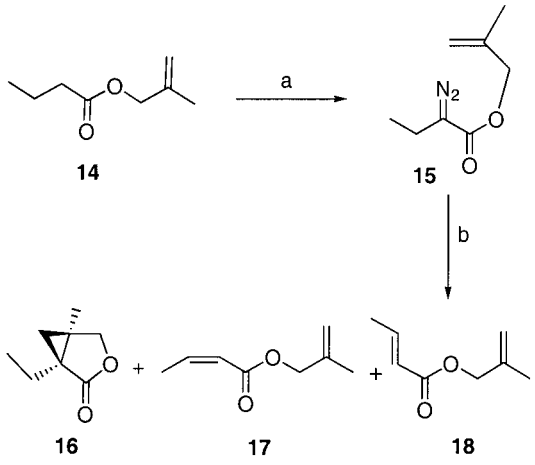
The requisite lactone precursors **25** and **26** were prepared in good overall yield as shown in Scheme 7. Multigram quantities of the macrocyclic keto lactone **24** were accessed via a facile four step synthetic sequence previously developed in our



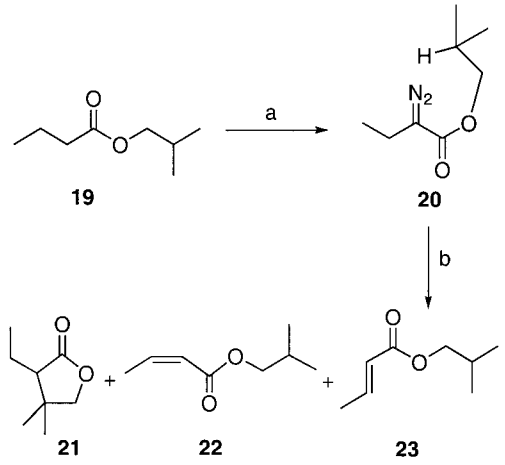
Scheme 3. (a) Cyclopropanation. (b) 2° C–H bond insertion. (c) β-Hydride migration.



Scheme 4. (a) 3° C–H bond insertion. (b) 2° C–H bond insertion. (c) β-Hydride migration.



Scheme 5. (a) Diazo transfer (Table 1). (b) ML_n (Table 2).

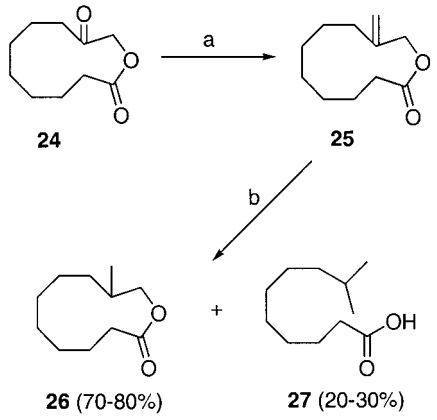


Scheme 6. (a) Diazo transfer (Table 1). (b) ML_n.

laboratory.[11] This material was methylenated using standard Wittig technology[12] to give the alkenyl lactone **25** in good yield. The corresponding saturated lactone **26** was prepared by the catalytic hydrogenation of **25** utilizing Adam's catalyst[13] in acceptable yield along with the hydrogenolysis byproduct **27** in an approximately 3:1 ratio.[†] The corresponding ester precursors **14** and **19** (Schemes 5 and 6 respectively) were prepared via standard literature procedures.[14]

Initial attempts to prepare alkenyl α-diazo lactone **5** from **25** proceeded via Regitz's one pot formylation/diazo transfer protocol,[15] however, none of the desired product was obtained. Instead, based on chromatographic and NMR analysis, we obtained what appeared to be a mixture of oligomeric products. It is likely that these were formed by a transesterification (lactone ring-opening) chain reaction initiated by ethoxide ion (the byproduct in the initial Claisen condensation step) and propagated by the alkoxide ion generated on opening the lactone ring.[16] Thus, it was necessary to employ a protocol that did not generate nucleophilic

[†] Use of Pd/C in ethanol (60 psi H_2) afforded only small amounts of **26**; the major product in this case was the hydrogenolysis product **27**.



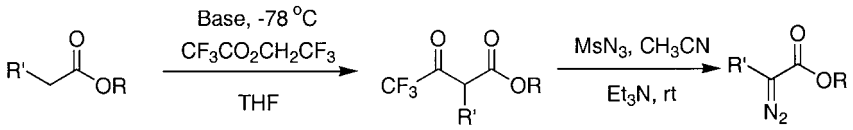
Scheme 7. (a) $Ph_3P^+CH_3Br^-$, KHMDS, C_6H_6, 0°C to rt (75%). (b) H_2, PtO_2, EtOH, 20 min.

alkoxide ion as a byproduct. The trifluoroacetylation/diazo transfer protocol developed by Danheiser[17] for the preparation of base-sensitive α-diazo ketones was appealing in this regard, since the weakly nucleophilic trifluoroethoxide ion generated during this chemistry was not expected to open the lactone ring in our system. Although this chemistry has recently been sporadically used for the preparation of some α-diazo esters,[18] no systematic study of its use in the preparation of nucleophile-sensitive α-diazo esters and lactones has been reported.

Initial attempts to prepare alkenyl α-diazo lactone **5** from **25** via Danheiser's methodology, utilizing LiHMDS as the base (Table 1, entry 1), proceeded in very poor yield (<10%). Once again, evidence for dimeric and oligomeric byproducts was observed by both GC and ^1H NMR analysis of the crude reaction product. It seems likely that the inability of LiHMDS to rapidly and completely deprotonate lactone **25**[19] allowed for self-Claisen condensation side reactions leading to dimeric and (via transesterification reactions of the alkoxide ion released during the Claisen condensation) oligomeric products. We postulated that such problems could be averted by use of a stronger base. Indeed, we found that when LDA[20] was substituted for LiHMDS (Table 1, entry 2), with very slow addition of the substrate to the base solution at −78°C, the requisite α-trifluoroacetyl lactone intermediate could be prepared in good yield. This is especially noteworthy in light of Danheiser's observation that LiHMDS is a superior base to LDA for the preparation of base sensitive α-diazo ketones.[17a] Subjection of the isolated crude α-trifluoroacetyl lactone to diazo transfer conditions afforded the desired α-diazo lactone in 68% overall yield for the two step process.[‡] Following the same protocol, the saturated α-diazo lactone **11** and the α-diazo esters **15** and **20** were obtained in 71–79% yield (Table 1, entries 3–5). These results represent a successful extension of Danheiser's trifluoroacetylation/diazo transfer methodology to the

[‡] Column chromatography allowed for only partial purification of the α-trifluoroacetyl lactone, contaminated by small amounts of unwanted self-Claisen condensation byproducts. Conversion of this partially purified material to the α-diazo lactone proceeded in 67% overall yield for the two step process.

Table 1. Preparation of α-diazo lactones and esters



Entry	Ester/lactone	Base	Yield of α-trifluoroacetyl ester (%)[a]	Yield of α-diazo ester (%)[b]	Overall isolated yield of α-diazo ester[c]
1	**25**	LiHMDS	<10	–	–
2	**25**	LDA	85	79 (**5**)	68 (67%)
3	**26**	LDA	75	83 (**11**)	79 (62%)
4	**14**	LDA	75	77 (**15**)	71 (58%)
5	**19**	LDA	65	93 (**20**)	73 (61%)

[a] Isolated yield of α-trifluoroacetyl ester after column chromatography (contaminated by small amounts of self-Claisen condensation byproducts).
[b] Isolated yield of α-diazo lactone or ester from chromatographed α-trifluoroacetyl ester intermediate.
[c] Overall yield for the two step process *without* purification of the α-trifluoroacetyl ester intermediate. Yields in parentheses show the overall yield *with* purification of the α-trifluoroacetyl ester intermediate.

general preparation of a series of nucleophile-sensitive α-diazo esters and lactones.

Metal-stabilized carbene insertion reactions using saturated α-diazo ester 20 and α-diazo lactone 11

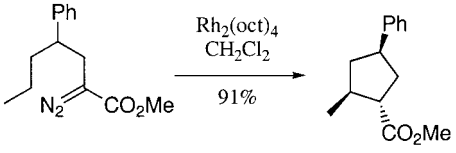
With α-diazo lactone **11** in hand, we were set to evaluate the propensity for transannular 1,5-C–H bond insertion vs β-hydride migration (Scheme 4). The impact of performing these reactions in a transannular fashion within this conformationally constrained system was probed by pursuing analogous chemistry using the acyclic α-diazo ester **20** (Scheme 6).

Attempts to perform the desired 1,5-C–H bond insertion reaction using α-diazo ester **20** (Scheme 6) were pursued under thermal as well as transition metal-catalyzed reaction conditions; however, none of the desired 1,5-tertiary C–H insertion product **21** was ever observed. In every case, β-hydride migration to give enoates **22** and/or **23** dominated.[21] In the thermally mediated reaction (xylenes, 130°C) and with Pd(II) ($Pd(OAc)_2$ or $PdCl_2(PhCN)_2$) and $Cu(acac)_2$ catalysts, mixtures of *Z*:*E* enoates **22** and **23** were obtained with *Z*:*E* ratios ranging from 86:14 to 50:50. With several Rh(II) catalysts bearing ligands of varying electron-withdrawing power as well as polarizability ($Rh_2(OAc)_4$, $Rh_2(oct)_4$ and $Rh_2(cap)_4$), reactions proceeded diastereoselectively to give the thermodynamically least stable *Z*-enoate **22** (as determined by NOE difference ^1H NMR spectroscopy). Where evaluated, variations in the solvent (CH_2Cl_2 or C_6H_6) or temperature (room temperature or reflux) has no observable impact on the reaction outcome.

Failure to afford the desired γ-lactone **21** may be attributed to two factors. In general, insertion of a metal carbene into a tertiary C–H bond should be enthalpically favored over insertion into a secondary C–H bond;[22] however, this preference may be attenuated by the proximate electron-withdrawing oxygen substituent in **20**,[22c,d,23] such that the entropically most facile pathway (β-hydride migration to give **22** and/or **23**) dominates. This observation could also be a manifestation of a late transition state whereby formation of **21** is precluded due to an unfavorable steric interaction between the ethyl and *gem*-dimethyl groups on the newly forming C–C bond.

A *priori*, we had anticipated more success with α-diazo lactone **11**, where the potential for a templating effect by the macrocyclic ring might offer a significant entropic advantage for the desired transannular C–H insertion reaction leading to **4** (Scheme 4). Unfortunately, only the *Z*-enoate **13** derived from β-hydride migration was isolated using a variety of Rh(II) ($Rh_2(OAc)_4$, $Rh_2(oct)_4$ and $Rh_2(cap)_4$) catalysts and with $Cu(acac)_2$. The complete *Z*-stereoselectivity observed with $Cu(acac)_2$ is in stark contrast to the analogous reaction with the acyclic α-diazo ester **20**, which afforded a 1.2:1 mixture of *Z*- and *E*-isomers **22** and **23**. This result may give some indication of the relative conformational rigidity of the macrocyclic ring in the metal carbene derived from **11**.

Perhaps most surprising is the fact that no product of transannular 1,5-secondary C–H bond insertion (**12**, Scheme 4) was ever observed in these reactions. This is especially remarkable because Taber has successfully performed a very analogous intramolecular (but not transannular) cyclization (Eq. (2)) with no report of complications from a competing β-hydride migration pathway.[23b]



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Metal-stabilized carbene insertion reactions using alkenyl α-diazo ester 15 and alkenyl α-diazo lactones 5 and 31

We next evaluated the propensity for transannular alkene cyclopropanation to compete with the entropically favorable β-hydride migration pathway observed above. Initially,

Table 2. Metal-stabilized carbene insertion reactions using unsaturated α-diazo ester 15 (see Scheme 5)

Entry	Catalyst[a]	Solvent[b]	**17**:**18**:**16**[c,d]	Isolated yield of **16**
1	–	Xylenes	50:50:0	–
2	$PdCl_2$	CH_2Cl_2	82:18:0	–
3	$PdCl_2$	C_6H_6	75:25:0	–
4	$PdCl_2(PhCN)_2$	CH_2Cl_2	55:45:0	–
5	$PdCl_2(PhCN)_2$	C_6H_6	100:0:0	–
6	$Pd(OAc)_2$	CH_2Cl_2	80:20:0	–
7	$Pd(OAc)_2$	C_6H_6	74:26:0	–
8	$Rh_2(OAc)_4$	CH_2Cl_2	100:0:0	–
9	$Rh_2(oct)_4$	CH_2Cl_2	95:0:5	–
10	$Rh_2(oct)_4$	C_6H_6	93:0:7	–
11	$Rh_2(cap)_4$	CH_2Cl_2	85:0:15	18%
12	$Rh_2(cap)_4$	CH_2Cl_2[e]	94:0:6	–
13	$Rh_2(cap)_4$	C_6H_6	95:0:5	–
14	$Cu(acac)_2$	CH_2Cl_2	20:15:65	60%
15	$Cu(acac)_2$	CH_2Cl_2[f]	62:38:0	–
16	$Cu(acac)_2$	C_6H_6	30:22:48	53%
17	$Cu(acac)_2$[g]	C_6H_6	31:20:49	–

[a] Two mol% of all Rh(II) catalysts and 10 mol% of all other catalysts were employed.
[b] The final reaction concentration after addition of the diazo compound was 30 mM.
[c] Unless otherwise stated, all reactions were performed at reflux and were complete within 2 h.
[d] Ratio of products determined by GC using calculated response factors. A small amount of carbene dimer (<10% products) was also produced in every case. These byproducts were not considered in the product ratios.
[e] This reaction was performed at rt and was complete within 2 h as indicated by ^1H NMR analysis.
[f] This reaction was performed at rt. After 24 h, ^1H NMR indicated the presence of 66% unreacted **15**.
[g] Reaction performed in the presence of 4.4 equiv. of anhydrous $CuSO_4$.

this was explored using the alkenyl α-diazo lactone **5** (Scheme 3). Once again, the analogous intramolecular chemistry was explored, using the acyclic alkenyl α-diazo ester **15** (Scheme 5).

The results of our attempts to achieve cyclopropanation using the acyclic alkenyl α-diazo ester **15** are summarized in Table 2. As before, the thermally mediated reaction did not produce any of the desired cyclopropyl γ-lactone **16** but rather only a 1:1 mixture of *Z* and *E* enoates **17** and **18** (entry 1). Likewise, using a variety of Pd(II) catalysts generally afforded only mixtures of enoate products (entries 2–7). The use of $Rh_2(OAc)_4$ also led to the clean formation of *Z*-enoate **17** as the only observable product (entry 8); however, use of the more electron-rich and polarizable $Rh_2(oct)_4$ and $Rh_2(cap)_4$ finally afforded small amounts of the desired γ-lactone **16** along with *Z*-enoate **17** (entries 9–13). We obtained significantly better results using $Cu(acac)_2$ as the catalyst (entries 14–17). A respectable 60% isolated yield of lactone **16** was obtained when the reaction was performed in refluxing CH_2Cl_2 (entry 14). The yield of γ-lactone **16** fell markedly if the reaction was performed at room temperature (compare entries 11 and 12, entries 14 and 15) or in refluxing benzene (compare entries 11 and 13, entries 14 and 16). The above results are in contrast to some related intramolecular copper carbene cyclopropanation studies reported by Hudlicky and coworkers.[8a] They found that the use of only *catalytic* amounts of $Cu(acac)_2$ did not give 'useful yields' of insertion product **10**, which they attributed to deleterious complexation of the metal catalyst with the ester oxygen (Eq. (1)). They were able to achieve the desired cyclopropanation reaction by the addition of several equivalents of $CuSO_4$ to the reaction mixture. In our case, the desired cyclopropanation proceeded smoothly even using *catalytic* $Cu(acac)_2$; the addition of anhyd $CuSO_4$ offered no advantage in this system (entry 17).

We next turned our attention to the analogous transannular cyclopropanation reaction using alkenyl α-diazo lactone **5** (Scheme 3). Not surprisingly, only *Z*-enoate **8** (path c) was observed when using $Rh_2(OAc)_4$ as catalyst, however, we were disappointed to find that, with $Rh_2(cap)_4$ and $Cu(acac)_2$, transannular cyclopropanation (path a) competed to only a very small extent (<5%); again, *Z*-enoate **8** was the major product (>95%). This was in stark contrast to the analogous intramolecular chemistry, where these catalysts had afforded significant amounts of cyclopropanation product (Table 2, entries 11–17).

It appears that the macrocyclic ring in **5** is actually hindering cyclopropanation rather than providing the entropic advantage we had sought! Carbene lactone **6** presumably favors the stereoelectronically preferred *syn* conformation ($\mathbf{6}_{syn}$) about the ester C–O bond, where the alkene and metal carbene center are held a considerable distance apart (Fig. 1).[24] In order for a successful transannular cyclopropanation reaction to take place, the carbene lactone must adopt the somewhat less stable *anti* conformation $\mathbf{6}_{anti}$. Extensive conformational searching using MM3 calculations by Saunders revealed that the lowest energy *anti* conformer in decanolactone is ca 12 kcal/mol less stable than the global minimum (*syn*) conformer in the gas phase.[25] This is in contrast to a gas phase energy difference of only 8–10 kcal/mol for *syn* and *anti* conformers in simple acyclic esters.[24] Assuming that similar arguments apply in solution, this supports the notion that the *anti* conformer of the metal carbene ($\mathbf{6}_{anti}$) may be relatively inaccessible, such that facile β-hydride migration can outcompete conformational interconversion to the *anti* conformer required for transannular cyclopropanation. In contrast, the greater accessibility of the *anti* conformer in the acyclic metal carbene ($\mathbf{28}_{anti}$) would allow for cyclopropanation to effectively compete with β-hydride migration in that case. In the acyclic metal carbene **28**, the use of a more polar solvent

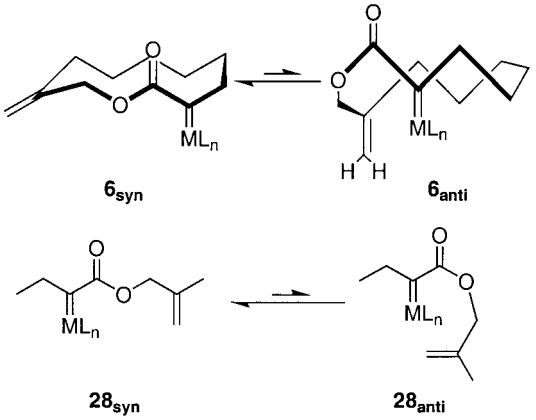
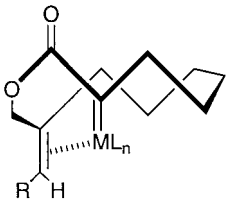


Figure 1. *Syn*/*anti* conformational equilibria for **6** and **28**.



R = H (**6**) or R = OMe

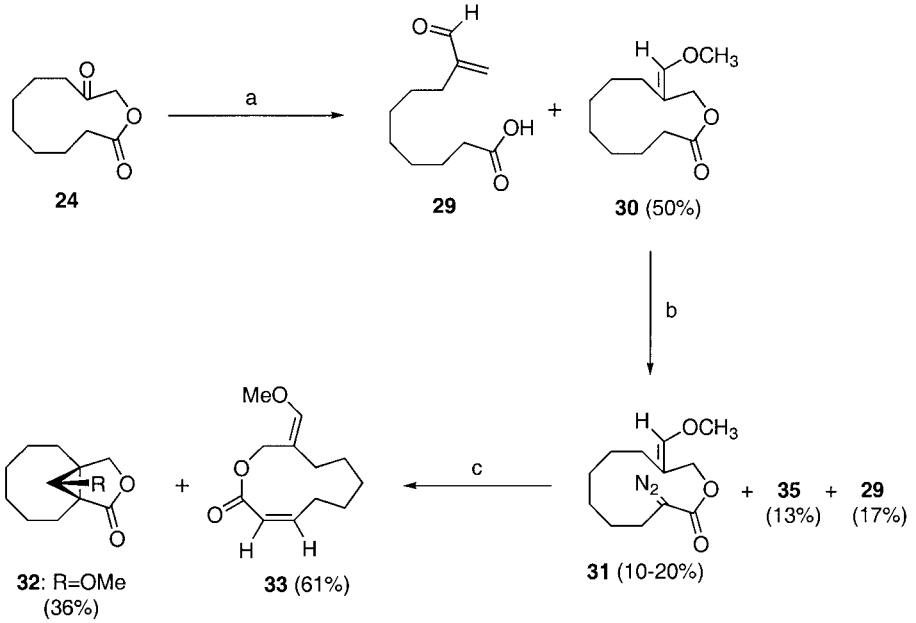
Figure 2. Metal-alkene precoordination prior to cyclopropanation.

(CH_2Cl_2 rather than benzene) presumably facilitated access to the more polar $\mathbf{28}_{anti}$ conformer needed for cyclopropanation,[26] which allowed this pathway to compete more effectively with the entropically favored β-hydride migration (Table 2, compare entries 11 and 13, entries 14 and 16). Unfortunately, such an effect was not observed in the corresponding transannular cyclopropanation reaction involving metal carbene **6**.

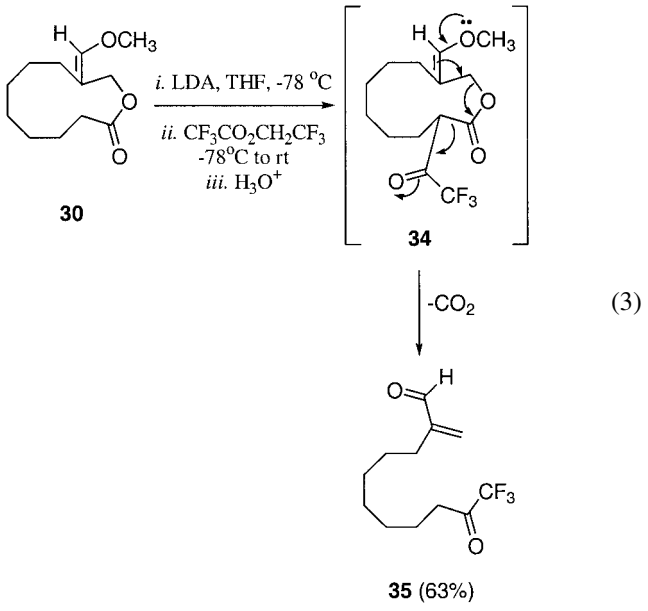
We considered that transannular cyclopropanation might be facilitated if we could achieve precoordination of the alkene to the metal center prior to π-bond insertion (Fig. 2).[27] It may be that the alkene moiety in metal carbene **6** is not sufficiently electron-rich to effectively coordinate to the metal, due to the presence of the β-electron-withdrawing lactone ring oxygen. We felt that use of a more electron-rich alkene might favor such an interaction, orienting the metal carbene in a conformation where transannular cyclopropanation could then effectively compete with β-hydride migration. Vinyl ethers are a class of highly electron-rich alkenes which should more effectively achieve this desired metal precomplexation. Direct intermolecular competition experiments have shown vinyl ethers to be an order of magnitude more reactive than simple alkenes toward metal carbene insertion.[28] Thus, we synthesized methoxymethylenyl α-diazo lactone **31** to see if transannular cyclopropanation was viable in this more favorable substrate (Scheme 8).[29]

Alkenylation of keto lactone **24** using the ylide derived from (methoxymethyl)triphenylphosphonium chloride under standard Wittig conditions[12] gave the *Z*-vinyl ether **30** (as determined by NOE difference ^{1}H NMR spectroscopy) in 50% yield after column chromatography. The major byproduct of this reaction was the ring-opened ω-carboxy enal **29**; interestingly, no *E*-vinyl ether was obtained. It appears that the *E*-vinyl ether was formed during the Wittig reaction but underwent hydrolytic fragmentation, perhaps during workup, to give **29**. In contrast to the *E*-isomer, the *Z*-vinyl ether is not stereoelectronically predisposed to undergo a lactone C–O bond cleavage, and so it was isolated as a single geometric isomer at the end of the reaction.[30]

Z-Vinyl ether **30** was next elaborated to the key intermediate methoxymethylenyl α-diazo lactone **31** using the trifluoroacetylation/diazo transfer protocol employed previously for the preparation of other nucleophile-sensitive α-diazo esters and lactones (vide supra). Initial attempts to perform the Claisen condensation step of the protocol did not yield any of the desired α-trifluoroacetyl lactone **34**, but instead afforded ω-trifluoroacetyl enal **35** in 63% yield (Eq. (3)). This product was presumably generated via a 1,4-elimination reaction from the initially generated product **34**. It may be that the added driving force of decarboxylation (due to the presence of the α-trifluoroacetyl group) is sufficient to facilitate this pathway, while a similar reaction is not seen with *Z*-vinyl ether **30** (where there is no possibility of a decarboxylation step).



Scheme 8. (a) $Ph_3P^+CH_2OMe\ Cl^-$, KHMDS, C_6H_6, 0°C to rt. (b) *i*. LDA, THF, −78°C; *ii*. $CF_3CO_2CH_2CF_3$, 2 h; *iii*. MsN_3, Et_3N −78°C to rt. (c) 10 mol% $Cu(acac)_2$, CH_2Cl_2, reflux.



(3)

Since we were unable to isolate the α-trifluoroacetyl lactone intermediate **34** required for the subsequent diazo transfer step, we elected to perform the diazo transfer reaction directly on the in situ generated α-trifluoroacetyl lactone at low temperature (Scheme 8). Thus, after addition of $CF_3CO_2CH_2CF_3$ to the preformed lactone enolate, the reaction was maintained at −78°C for 2 h. Additional amine base (Et_3N or i-Pr_2NH) was then added along with mesyl azide, and the reaction was allowed slowly to warm to rt. In this way, we were able to access the desired methoxymethylenyl α-diazo lactone **31**, albeit in a disappointing 10–20% yield. Also isolated from the reaction were two ring opened products **29** (17%) and **35** (13%).

The methoxymethylenyl α-diazo lactone **31** proved thermally unstable, undergoing nitrogen elimination with β-hydride migration to give the *Z*-enoate **33**, and so it was used immediately in the transannular cyclopropanation chemistry. As seen with the previous cyclopropanation reactions (vide supra), the use of a rhodium (II) catalyst led to only *Z*-enoate **33**. However, with $Cu(acac)_2$ we were pleased to obtain the desired propellane **32**, albeit in a relatively modest 36% isolated yield, along with 61% *Z*-enoate **33** (Scheme 8). The conservation of olefin geometry in going from α-diazo lactone **31** to propellane **32** was established on the basis of a ^{1}H NMR 2D NOESY experiment.

The relative facility of transannular cyclopropanation using methoxymethylenyl α-diazo lactone **31** (Scheme 8) compared with the less electron-rich alkenyl α-diazo lactone **5** (Scheme 3) suggests that the chelated pseudometallocycle shown in Fig. 2 may form prior to cyclopropanation in the presence of an electron-rich alkene (R=OMe), allowing cyclopropanation to compete effectively with the very favorable β-hydride migration pathway. If alkene–copper complexation occurred *after* copper carbene formation, it would be difficult to reconcile the dramatic increase in cyclopropanation product formation. Presumably, the difficulties outlined above in accessing the requisite *anti* conformer would still exist with the copper carbene generated from uncomplexed vinyl ether **31**, and β-hydride migration should again be expected to outcompete cyclopropanation. That cyclopropanation is a major pathway suggests that alkene–copper complexation may occur *prior* to reaction of copper at the diazo moiety. This is consistent with a mechanism previously proposed by Salomon and Kochi[27a] for copper carbene cyclopropanation reactions.

Conclusion

We have demonstrated that transannular insertion of a metal carbene species into an alkene π-bond or tertiary C–H bond within the constraints of an 11-membered lactone ring is considerably more challenging than the analogous intramolecular (but not transannular) chemistry leading to closure of a 5-membered lactone ring. The challenge of accessing the presumably less favored *anti* conformation around the lactone C–O bond appears to be the major stumbling block associated with this chemistry. However, it was demonstrated that use of an electron-rich alkene (**31**) does allow for transannular cyclopropanation to effectively compete with the highly favorable β-hydride migration side reaction that was dominant when attempts were made to achieve transannulation into a less electron-rich alkene (**5**).

Experimental

All reactions were performed in oven-dried (125°C) glassware under Ar or N_2 using standard inert atmosphere techniques and were monitored by GC. IR spectra were recorded on an FT-IR or a grating IR spectrophotometer; only major diagnostic bands are reported. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or at 200 and 50 MHz. Mass spectra were obtained by GC/MS with electron impact ionization; only selected peaks are reported. Combustion analyses were performed on purified samples by Atlantic Microlabs, Inc., Norcross, Georgia. All anhydrous solvents were purified according to standard procedures.[31] $Rh_2(OAc)_4$ was either prepared according to the method of Rempel et al.[32] or was purchased from Aldrich. $Rh_2(cap)_4$ was either prepared by the method of Doyle[22c] or was purchased from Regis Technology (Morton Grove, IL). $Rh_2(oct)_4$ was purchased from Strem (Newburyport, MA). $Rh_2(pfb)_4$ was generously donated by Dr Mark McMills (Ohio University). All other catalysts utilized for the metal carbene chemistry were purchased from Aldrich. All the catalysts were heated to 40–50°C under high vacuum (<5 mmHg) for 24 h immediately prior to use.[§] **CAUTION:** Extreme care should be exercised when either preparing or handling MsN_3 as it is potentially explosive! There are published warnings of the relative dangers of isolating and using organic azides such as MsN_3 that contain more than 25% by weight nitrogen.[33] Nevertheless, we have prepared,[17b] isolated, stored (for up to six months) and used this reagent on many occasions without incident. We recommend that the reagent be prepared in less than 10 g

[§] The presence of residual water can lead to the formation of alcohol byproducts during metal carbene insertion reactions due to competitive O–H insertion.

batches, that small amounts of the reagent (<10 g) be stored at or below 0°C when not in use, and that excess cerium (IV) ammonium nitrate or Sn/conc. HCl be kept on hand to destroy reaction residues, and/or old samples of the reagent.[34]

10-Methylene-1-oxacycloundecan-2-one (25). To a slurry of methyltriphenylphosphonium bromide (427 mg, 1.2 mmol, 1.1 equiv.) in anhyd C_6H_6 (3.25 mL) was added KHMDS (0.5 M solution in toluene: 2.18 mL, 1.1 mmol, 1.0 equiv.) to give an opaque bright yellow solution. After 1 h, the reaction mixture was cooled to 0°C, a solution of 1-oxacycloundeca-2,10-dione (**24**)[11] (200 mg, 1.09 mmol, 1.0 equiv.) in C_6H_6 (5 mL) was slowly added and the resulting mixture was allowed to warm up to rt overnight. After 18 h, the reaction mixture was heated to 55°C and left to stir for an additional 22 h. The crude reaction mixture was then cooled to rt and diluted with ether (250 mL). The resulting solution was washed with H_2O (4×30 mL), brine (2×30 mL) and stored over anhyd $MgSO_4$. The solution was filtered and concentrated in vacuo to remove the bulk of the volatile extraction solvent, yielding a yellow oil (487 mg).[¶] Purification by column chromatography (hexanes:ether, 7:1) revealed 2 fractions. *Fraction 1* (R_f=0.30) was identified as the title compound (150 mg, 76%, bp 60°C at 0.5 mmHg). IR (Neat, cm^{-1}) ν 3077, 2947, 1732, 1646, 1451; ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (m, 1H), 5.08 (m, 1H), 4.61 (br s, 2H), 2.36 (app t, J=6.0 Hz, 2H), 2.15 (app t, J=6.0 Hz, 2H), 1.80–1.70 (m, 2H), 1.60–1.40 (m, 4H), 1.40–1.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 144.6, 117.7, 68.2, 35.1, 30.8, 27.3, 27.1, 24.2, 23.3, 21.2. Anal Calcd for $C_{11}H_{18}O_2$: C, 72.49%; H, 9.96%. Found: C, 72.55%; H, 10.00%. *Fraction 2* was identified by ^1H NMR spectroscopy as recovered ketone **24** (18 mg).

10-Methyl-1-oxacycloundecan-2-one (26). A 25 mL flask fitted with an addition port was charged with 10-methylene-1-oxacycloundecan-2-one (**25**) (145 mg, 0.8 mmol, 1 equiv.), PtO_2 (13.5 mg, 0.060 mmol, 7.5 mol%) and EtOAc (16 mL). A helium quality party balloon was wired onto the addition port neck and the system was filled with H_2 gas on four occasions so that the balloon inflated to about half capacity (~6 inches in diameter) and each time the H_2 gas was removed via vacuum. Finally, the flask and balloon were filled with H_2 gas and the reaction was allowed to continue for 45 min. (This reaction must be carefully monitored by GC. The reaction must be stopped *immediately* after the complete consumption of starting material in order to minimize formation of hydrogenolysis byproduct **27**.) Then, the H_2 gas was vented and the solvent was remove in vacuo to yield a heterogeneous oil. Purification by dry column chromatography using a gradient elution technique (hexane:ether 7:1 to 1:1) gave two fractions. *Fraction 1* (R_f=0.40) was identified as the title compound (104 mg, 71%). IR (neat, cm^{-1}) ν 2950, 1728, 1464; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (app t, J=10.5 Hz, 1H), 3.89 (dd, J=3.5, 10.9 Hz, 1H), 2.44 (ddd, J=3.2, 6.8, 14.9 Hz, 1H), 2.25 (ddd, J=3.2, 11.2, 14.8 Hz, 1H) 2.10–1.90 (m, 1H), 1.85–1.10 (m, 12H), 0.91 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 69.4, 34.9, 32.7, 30.6, 25.7, 24.4, 23.9, 23.4, 21.7, 18.8. Anal Calcd for $C_{11}H_{20}O_2$: C, 71.69%; H, 10.94%. Found: C, 71.70%; H, 10.97%. *Fraction 2* (R_f=0.01) was identified by ^1H NMR as 9-methyldecanoic acid (**27**)[35] (36 mg, 24%). ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (t, J=7.5 Hz, 2H), 1.71–1.56 (m, 2H), 1.51 (nonet, J=6.6 Hz, 1H), 1.40–1.10 (m, 10H), 0.86 (d, J=6.6 Hz, 6H).

General procedure for diazo transfer

(2-Methyl-2-propenyl) 2-diazobutanoate (15). To a solution of *i*-Pr_2NH (4.4 mL, 33.8 mmol, 1.6 equiv.) in anhyd THF (21 mL) cooled to 0°C was added dropwise *n*-butyl lithium (2.0 M solution in hexanes: 15.8 mL, 31.7 mmol, 1.5 equiv.). After 15 min, the LDA solution was cooled to −78°C and a solution of (2-methyl-2-propenyl) butanoate (**14**) (3.0 g, 21.1 mmol, 1 equiv.) in THF (15 mL) was added via syringe pump at a rate of 6.5 mL/h. After 30 min (2,2,2-trifluoroethyl) trifluoroacetate (4.2 mL, 31.7 mmol, 1.5 equiv.) was added in one portion to the transparent bright yellow reaction mixture and a white smoke was evolved. The reaction was then allowed to slowly warm up to rt overnight. Next, the crude red-brown mixture was poured onto 5% aq HCl (200 mL) and was extracted with ether (4×200 mL). The combined ether extracts were washed with brine (1×200 mL) and stored over anhyd Na_2SO_4. The solution was filtered and concentrated in vacuo to give a brown oil (9.41 g). The crude product was immediately dissolved in anhyd CH_3CN (30 mL) and Et_3N (4.0 mL, 28.7 mmol, 1.4 equiv.) was added to give a transparent red-amber solution. After 15 min a solution of mesyl azide (1.8 mL, 22.0 mmol, 1.04 equiv.) in anhyd CH_3CN (20 mL) was added dropwise. After 5 h, the red-brown reaction mixture was diluted with ether (800 mL) and washed with 5% aq NaOH (3×100 mL), H_2O (1×150 mL), brine (1×200 mL) and stored on anhyd Na_2SO_4. The solution was filtered and concentrated in vacuo to reveal a crude brown oil (4.02 g). Purification by flash column chromatography (hexanes:ether, 14:1) gave the title compound (**15**) as a bright yellow oil (2.51 g, 71%). IR (neat, cm^{-1}) ν 3083, 2974, 2082, 1698, 1660; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (m, 1H), 4.92 (m, 1H), 4.59 (br s, 2H), 2.37 (q, J=7.5 Hz, 2H), 1.76 (br s, 3H), 1.15 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ[‖] 167.1, 140.1, 112.5, 67.7, 19.4, 16.6, 11.9; Anal Calcd for $C_8H_{12}N_2O_2$: C, 57.12%; H, 7.19%; N, 16.55%. Found: C, 57.60%; H, 7.23%; N, 16.74%.

(2-Methylpropyl) 2-diazobutanoate (20). Reaction of (2-methylpropyl) butanoate (**19**) (3.0 g, 21.1 mmol, 1.0 equiv.) with LDA (31.2 mmol, 1.5 equiv.) and (2,2,2-trifluoroethyl) trifluoroacetate (4.2 mL, 31.7 mmol, 1.5 equiv.) in anhyd THF (32 mL) according to the general procedure provided a crude black oil (7.14 g). Half of this material (3.69 g) was then treated with Et_3N (2.6 mL, 18.75 mmol, 2.3 equiv.) and MsN_3 (1.65 mL, 20.0 mmol, 2.4 equiv.) in anhyd CH_3CN (40 mL) at rt for 15 h according to the general procedure to yield a crude brown oil (2.26 g). Column chromatography (hexanes:ether, 14:1)

[¶] Complete removal of the solvent afforded a tan solid which was insoluble in the chromatography solvent, complicating product purification.

[‖] The diazo-bearing carbon resonance was not seen in the ^{13}C NMR spectrum.

gave the title compound as a bright yellow oil (1.32 g, 73%). IR (neat, cm^{-1}) ν 2967, 2081, 1696, 1660, 1470; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, J=6.3 Hz, 2H), 2.34 (q, J=7.5 Hz, 2H), 1.92 (app septet, J=6.7 Hz, 1H), 1.12 (t, J=7.5 Hz, 3H), 0.91 (d, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 70.6, 49.3, 27.9, 18.9, 16.5, 11.9. Anal Calcd for $C_8H_{14}N_2O_2$: C, 56.44%; H, 8.29%; N, 16.46%. Found: C, 56.81%; H, 8.35%; N, 16.48%.

3-Diazo-10-methylene-1-oxacycloundecan-2-one (5). Reaction of 10-methylene-1-oxacycloundecan-2-one (**25**) (500 mg, 2.74 mmol, 1.0 equiv.) with LDA (4.11 mmol, 1.5 equiv.) and (2,2,2-trifluoroethyl) trifluoroacetate (0.55 mL, 4.11 mmol, 1.5 equiv.) in anhyd THF (4.7 mL) according to the general procedure provided a crude brown oil (1.17 g). This crude material was then treated with Et_3N (0.40 mL, 2.86 mmol, 1.1 equiv.) and MsN_3 (0.36 mL, 4.38 mmol, 1.6 equiv.) in anhyd CH_3CN (10 mL) at rt for 6 h according to the general procedure to yield a crude yellow oil (533 mg). Column chromatography (hexanes: EtOAc, 14:1) gave the title compound as a bright yellow oil (385 mg, 68%). IR (neat, cm^{-1}) ν 3077, 2942, 2086, 1731, 1682, 1648, 1458; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (d, J=0.9 Hz, 1H), 5.05 (d, J=0.9 Hz, 1H), 4.57 (br s, 2H), 2.40 (app t, J=6.0 Hz, 2H), 2.04 (t, J=6.0 Hz, 2H), 1.62–1.50 (m, 2H), 1.45–1.20 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 145.1, 116.8, 69.6, 57.0, 30.0, 28.5, 27.2, 23.2, 22.7, 21.2. Anal Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44%; H, 7.74%. Found: C, 63.83%; H, 8.01%.

3-Diazo-10-methyl-1-cycloundecan-2-one (11). Reaction of 10-methyl-1-oxacycloundecan-2-one (**26**) (350 mg, 1.90 mmol, 1.0 equiv.) with LDA (2.85 mmol, 1.5 equiv.) and (2,2,2-trifluoroethyl) trifluoroacetate (0.38 mL, 2.85 mmol, 1.5 equiv.) in anhyd THF (3.3 mL) according to the general procedure provided a crude amber oil (771 mg). This crude material was then treated with Et_3N (0.45 mL, 3.23 mmol, 1.7 equiv.) and MsN_3 (0.25 mL, 3.0 mmol, 1.6 equiv.) in anhyd CH_3CN (7 mL) at rt for 6 h according to the general procedure to yield a crude yellow oil (409 mg). Column chromatography (hexanes: EtOAc, 14:1) gave the title compound as a bright yellow oil (315 mg, 79%). IR (neat, cm^{-1}) ν 2922, 2086, 1694, 1683, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ 4.11 (app t, J=11.4 Hz, 1H), 3.70 (dd, J=3.3, 10.8 Hz, 1H), 2.50 (ddd, J=5.0, 10.1, 15.6 Hz, 1H), 2.26 (dt, J=15.5, 4.1 Hz, 1H), 1.85–1.70 (m, 1H), 1.70–1.10 (m, 10H), 0.90 (d, J=7.1 Hz, Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 70.9, 57.2, 32.0, 31.7, 27.4, 27.0, 23.1, 22.7, 21.2, 18.7.

(*Z*)-10-[Methoxymethylene]-1-oxacycloundecan-2-one (30). To a slurry of (methoxymethyl)triphenylphosphonium chloride (2.42 g, 7.06 mmol, 1.3 equiv.) in anhyd C_6H_6 (17 mL) was added dropwise NaHMDS (1.0 M solution in THF; 7.1 mL, 7.1 mmol, 1.3 equiv.) to give an opaque brown solution. After 45 min, the ylide solution was cooled to 0°C and a solution of 1-oxacycloundeca-2,10-dione (**24**) (1.00 g, 5.43 mmol, 1 equiv.) in C_6H_6 (17 mL) was slowly added. When the addition was complete, the resulting mixture was allowed to warm up to rt. After 24 h, the crude reaction mixture was partitioned between H_2O (100 mL) and ether (500 mL). The ether layer was washed with H_2O (3×50 mL), brine (1×150 mL) and stored on anhyd Na_2SO_4. The solution was filtered and condensed in vacuo to yield a red–brown oil (5.59 g). Purification by flash column chromatography (hexanes:ether, 10:1) yielded 3 fractions. *Fraction 1* (R_f=0.30), a clear colorless oil, was identified as the title compound **30** (572 mg, 50%). IR (neat, cm^{-1}) ν 2941, 1728, 1672, 1558; ^1H NMR (200 MHz, $CDCl_3$) δ 5.99 (br s, 1H), 4.70 (s, 2H), 3.58 (s, 3H), 2.32 (m, 2H), 1.99 (br t, J=6.0 Hz, 2H), 1.74–1.58 (m, 2H), 1.48–1.18 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.5, 148.8, 112.1, 60.4, 60.3, 36.0, 29.4, 26.4, 25.9, 25.5, 23.1, 21.7. Anal. Calcd for $C_{12}H_{18}O_3$: C, 67.89%; H, 9.50%;. Found: C, 67.33%; H, 9.52%. The (*Z*)-stereochemistry of **30** was established on the basis of the following ^1H NMR nOe enhancements [signal irradiated (signals enhanced)]: δ 3.58 (5.99, 4.70), 5.99 (3.58, 1.99). *Fraction 2* (R_f=0.30–0.10) was identified as a mixture of the title compound, recovered starting material and other unidentified compounds (643 mg). *Fraction 3* (R_f=0.05, stripped off the column with ethyl acetate) was identified as an impure sample of 9-methylene-10-oxodecanoic acid (**29**) (443 mg). IR (neat, cm^{-1}) ν 3600–2500, 2931, 2853, 2696, 1710, 1630, 1462, 1414; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 6.23 (s, 1H), 5.98 (s, 1H), 2.32 (t, J=7.5 Hz, 2H), 2.21 (t, J=7.5 Hz, 2H), 1.71–1.50 and 1.50–1.20 (m, 10H).

Attempted preparation of (*Z*)-10-[methoxymethylene]-3-trifluoroacetyl-1-oxacycloundecan-2-one (34). A 15 mL round bottom flask was charged with anhyd THF (2.2 mL) and *i*-Pr_2NH (0.44 mL, 3.34 mmol, 1.6 equiv.). The resulting mixture was cooled to 0°C and *n*-butyl lithium (2.5 M solution in hexanes: 1.3 mL, 3.13 mmol, 1.5 equiv.) was added dropwise with intense stirring to yield a transparent light yellow solution. After 15 min, the LDA solution was cooled to −78°C and a solution of (*Z*)-10-[1-(methoxy)-methylene]-1-oxacycloundecan-2-one (**30**) (460 mg, 2.1 mmol, 1 equiv.) in THF (1.5 mL) was added via syringe pump at a rate of 1.7 mL/h. When the addition was complete, the reaction mixture was stirred for 45 min to ensure complete enolate formation. (2,2,2-Trifluoroethyl) trifluoroacetate (0.42 mL, 3.13 mmol, 1.5 equiv.) was then added in one portion to the transparent amber reaction mixture and a white smoke was evolved. The reaction was allowed to slowly warm up to rt overnight. Then the crude red-brown reaction mixture was poured onto 5% aq HCl (100 mL) and extracted with ether (4×90 mL). The combined ether extracts were washed with brine (1×100 mL) and stored over anhyd Na_2SO_4. The solution was filtered and concentrated in vacuo to give a red-brown oil (840 mg). Purification by flash column chromatography (hexanes:ether, 4:1) revealed only 2-(9,9,9-trifluoro-8-oxononyl)acrolein (**35**) (331 mg, 63%). IR (neat, cm^{-1}) ν 3088, 2931, 2859, 2700, 1764, 1695, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 6.22 (br s, 1H), 5.96 (br s, 1H), 2.68 (t, J=7.2 Hz, 2H), 2.20 (br t, J=7.5 Hz, 2H), 1.70–1.55 (m, 2H), 1.50–1.20 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 191.5 (q, J=34.5 Hz), 150.2, 134.0, 115.5 (q, J=290.0 Hz), 36.2, 28.9, 28.8, 28.5, 27.63, 27.58, 22.2. Anal Calcd for $C_{12}H_{17}F_3O_2$: C, 57.59%; H, 6.86%. Found: C, 57.75%; H, 6.71%.

(*Z*)-3-Diazo-10-[methoxymethylene]-1-oxacycloundecan-2-one (31). To a solution of *i*-Pr_2NH (0.48 mL, 3.63 mmol,

1.8 equiv.) in anhyd THF (2.4 mL) cooled to 0°C was slowly added *n*-butyl lithium (2.5 M solution in hexanes: 1.2 mL, 3.0 mmol, 1.5 equiv.). After 15 min, the LDA solution was cooled to −78°C and a solution of (*Z*)-10-[1-(methoxy)methylene]-1-oxacycloundecan-2-one (**30**) (445 mg, 2.1 mmol, 1 equiv.) in THF (1.4 mL) was added via syringe pump at a rate of 2.7 mL/h. After 45 min (2,2,2-trifluoroethyl) trifluoroacetate (0.41 mL, 3.1 mmol, 1.6 equiv.) was added in one portion to the transparent orange reaction mixture and a white smoke was evolved. After 1 h, Et_3N (0.45 mL, 3.2 mmol, 1.6 equiv.) was added to give a red–brown reaction mixture. After an additional 15 min, mesyl azide (0.83 mL, 10.1 mmol, 5.1 equiv.) was added and the resulting milky white solution was allowed to slowly warm up to rt. After 12 h the resulting orange reaction mixture was diluted with ether (350 mL) and washed with 5% aq NaOH (3×50 mL), brine (1×100 mL) and stored on anhyd Na_2SO_4. The solution was filtered and concentrated in vacuo to reveal a crude yellow–brown oil (1.68 g). Purification by flash column chromatography (hexanes:ether, 14:1) gave 3 fractions. *Fraction 1* (R_f=0.30; a yellow oil) was identified as the title compound **31** (95 mg, 20%). IR (neat, cm^{-1}) ν 2925, 2084, 1726, 1681, 1461; ^1H NMR (200 MHz, $CDCl_3$) δ 6.02 (br s, 1H), 4.75 (br s, 2H), 3.60 (s, 3H), 2.40 (t, *J*=6.0 Hz, 2H), 1.96 (br t, *J*=6.4 Hz, 2H), 1.80–1.00 (m, 8H). On standing, this compound underwent elimination to afford the (*Z*)-enoate **33**. Therefore, it was used immediately in the next step. *Fraction 2* (R_f=0.25 to 0.15, 49 mg) and *fraction 3* (resulting from stripping the column with a solvent mixture of ethyl acetate:ether (1:1), 102 mg) each contained a mixture of compounds. ^1H NMR analysis indicated that both fractions 2 and 3 contained 2-(9,9,9-trifluoro-8-oxononyl)acrolein (**35**) and fraction 3 also contained 9-methylene-10-oxodecanoic acid (**29**). Other unidentified minor components were also present in each fraction. The two fractions were combined, dissolved in ether, extracted with 10% aq $NaHCO_3$ (2×15 mL), brine and stored on anhyd Na_2SO_4. The drying agent was removed and the solution was concentrated in vacuo to give an amber oil (68 mg) identified as compound **35** (13%) by comparison of its ^1H NMR spectrum with an authentic sample which had been independently prepared (vide supra). The base extracts from above were acidified and extracted with ether. The combined ether extracts were washed with brine and stored over anhyd Na_2SO_4. The drying agent was removed and the solution was concentrated in vacuo to give an amber oil (70 mg) identified as 9-methylene-10-oxodecanoic acid (**29**) (17%) by comparison of its ^1H NMR spectrum with an authentic sample which had been independently prepared (vide supra).

General procedure for attempted intramolecular C–H bond insertion reactions

To a refluxing solution of catalyst (2 mol% for all Rh(II) catalysts or 10 mol% for all other catalysts) in anhyd CH_2Cl_2 (enough to make a 0.75 mM solution for all Rh(II) catalysts or a 3.8 mM solution for all other catalysts) was added a 0.15 M solution of diazo compound (1 equiv.) in anhyd CH_2Cl_2 via syringe pump at a rate of 0.10 mL/min. After 2 h, the reaction mixture was cooled to rt, concentrated in vacuo and the crude product was purified by flash column chromatography.

Diazo decomposition of (2-methylpropyl) 2-diazobutanoate (20)

a. $Rh_2(cap)_4$, CH_2Cl_2, Δ. Using the general procedure a solution of (2-methylpropyl) 2-diazobutanoate (**20**) (50 mg, 0.29 mmol) in CH_2Cl_2 (1.9 mL) was added to a refluxing solution of $Rh_2(cap)_4$ (3.8 mg, 5.8×10^{-3} mmol, 2 mol%) in CH_2Cl_2 (7.7 mL). Purification by flash column chromatography (hexanes:ethyl acetate, 14:1) yielded a clear, colorless liquid (34 mg, 82%). ^1H NMR analysis was consistent with that of previously prepared samples of (2-methylpropyl) (*Z*)-2-butenoate (**22**).[36] ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (dq, *J*=11.4, 7.2 Hz, 1H), 5.77 (dq, *J*=11.5, 1.5 Hz, 1H), 3.86 (d, *J*=6.6 Hz, 2H), 2.10 (dd, *J*=1.8, 7.2 Hz, 3H), 1.92 (nonet, *J*=6.7 Hz, 1H), 0.91 (d, *J*=6.6 Hz, 6H). The (*Z*)-stereochemistry was unequivocally established by ^1H NMR nOe difference spectroscopy [signal irradiated (signals enhanced)]: δ 0.91 (6.28), 6.28 (0.91, 5.77).

b. $Cu(acac)_2$, CH_2Cl_2, Δ. Using the general procedure a solution of (2-methylpropyl) 2-diazobutanoate (**20**) (50 mg, 0.29 mmol) in CH_2Cl_2 (1.9 mL) was added to a refluxing solution of $Cu(acac)_2$ (0.29 mmol, 10 mol%) in CH_2Cl_2 (7.7 mL). Purification by flash column chromatography (hexanes:ethyl acetate, 14:1) gave a clear, colorless liquid (30 mg, 73%). ^1H NMR analysis indicated the material was a 1.2:1 mixture of *Z*:*E* (2-methylpropyl) 2-butenoate (**22**:**23**). ^1H NMR (300 MHz, $CDCl_3$) of (2-methylpropyl) (*E*)-2-butenoate (**23**):[37] δ 6.94 (dq, *J*=15.5, 6.9 Hz, 1H), 5.82 (dq, *J*=15.4, 1.9 Hz, 1H), 3.87 (d, *J*=6.9 Hz, 2H), 1.92 (nonet, *J*=6.7 Hz, 1H), 1.84 (dd, *J*=1.7, 7.1 Hz, 3H), 0.91 (d, *J*=6.6 Hz, 6H).

Diazo decomposition of 3-diazo-10-methyl-1-oxacycloundecan-2-one (11). Using the general procedure a solution of 3-diazo-10-methyl-1-oxacycloundecan-2-one (**11**) (100 mg, 0.48 mmol) in CH_2Cl_2 (3.2 mL) was added to a refluxing solution of $Rh_2(cap)_4$ (6.3 mg, 9.6×10^{-3} mmol, 2 mol%) in CH_2Cl_2. Purification by flash column chromatography (hexanes:ethyl acetate, 4:1) revealed (*Z*)-10-methyl-1-oxacycloundec-3-en-2-one (**13**) (70 mg, 80%). IR (neat, cm^{-1}) ν 3030, 2946, 1712, 1626; ^1H NMR (300 MHz, $CDCl_3$) δ 6.27 (ddd, *J*=8.1, 10.1, 11.7 Hz, 1H), 5.80 (br d, *J*=11.7 Hz, 1H), 4.67 (dt, *J*=10.8, 1.8 Hz, 1H), 3.53 (t, *J*=10.5 Hz, 1H), 3.05–2.80 (m, 1H), 2.09 (ddd, *J*=4.2, 8.3, 12.3 Hz, 1H), 2.00–1.70 (m, 2H), 1.62–1.15 (m, 7H), 0.87 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 147.3, 123.0, 69.6, 35.1, 30.5, 26.8, 25.0, 24.6, 22.3, 18.6; Anal Calcd for $C_{11}H_{18}O_2$: C, 72.49%; H, 9.96%. Found: C, 72.30%; H, 9.97%.

General procedure for intramolecular cyclopropanation reactions

To a solution of catalyst (2 mol% for all Rh(II) catalysts or 10 mol% for all other catalysts) in anhyd CH_2Cl_2 (enough to make a 0.75 mM solution for all Rh(II) catalysts or a 3.7 mM solution for all other catalysts) heated to reflux was added a 0.15 M solution of diazo compound

(1 equiv.) in anhyd CH_2Cl_2 via syringe pump at a rate of 0.10 mL/min. After 2 h, the reaction mixture was cooled to rt, concentrated in vacuo and the crude product was purified by flash column chromatography.

Diazo decomposition of (2-methyl-2-propenyl) 2-diazobutanoate (15)

a. $Cu(acac)_2$, CH_2Cl_2, Δ. Using the general procedure a solution of (2-methyl-2-propenyl) 2-diazobutanoate (**15**) (200 mg, 1.11 mmol) in CH_2Cl_2 (8 mL) was added to a refluxing solution of $Cu(acac)_2$ (31.1 mg, 0.12 mmol, 10 mol%) in CH_2Cl_2 (32 mL). Purification by flash column chromatography (hexanes:ether, 3:1) yielded two fractions. *Fraction 1* (R_f=0.80) was identified by ^1H NMR analysis to be a 1.2:1 mixture of *Z*:*E* (2-methyl-2-propenyl) 2-butenoate (**17:18**) (59 mg, 35%).[38] *(Z)-Isomer* (**17**): ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (dq, *J*=11.4, 7.2 Hz, 1H), 5.75 (dq, *J*=11.4, 1.8 Hz, 1H), 4.89 (br s, 1H), 4.83 (br s, 1H), 4.44 (s, 2H), 2.05 (dd, *J*=1.8, 7.2 Hz, 3H), 1.67 (s, 3H). *(E)-Isomer* (**18**): ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (dq, *J*=15.5, 6.8 Hz, 1H), 5.89 (dq, *J*=15.5, 1.7 Hz, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 4.55 (s, 2H), 1.89 (dd, *J*=1.8, 6.9 Hz, 3H), 1.77 (m, 3H). *Fraction 2* (R_f=0.30) was identified as 3-ethyl-5-methyl-1-oxabicyclo[3.1.0]hexan-2-one (**16**) (100 mg, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 4.14 (d, *J*=9.0 Hz, 1H), 3.95 (d, *J*=9.0 Hz, 1H), 1.87 (dq, *J*=14.7, 7.4 Hz, 1H), 1.39 (dq, *J*=14.7, 7.3 Hz, 1H), 1.31 (s, 3H), 1.02 (t, *J*=7.4 Hz, 3H), 0.93 (d, *J*=4.5 Hz, 1H), 0.82 (d, *J*=4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 73.0, 32.2, 28.3, 23.3, 19.7, 14.5, 11.8; Anal Calcd for $C_8H_{12}O_2$: C, 68.54%; H, 8.63%. Found: C, 68.70%; H, 8.59%.

b. $Rh_2(cap)_4$, CH_2Cl_2, Δ. Using the general procedure a solution of (2-methyl-2-propenyl) 2-diazobutanoate (**15**) (25 mg, 0.15 mmol) in CH_2Cl_2 (1.6 mL) was added to a refluxing solution of $Rh_2(cap)_4$ (2.0 mg, 3.0×10^{-3} mmol, 2 mol%) in CH_2Cl_2 (6.5 mL). Purification by flash column chromatography (hexanes:ether, 3:1) gave two fractions. *Fraction 1* (R_f=0.80) was found to be an impure sample of (2-methyl-2-propenyl) (*Z*)-2-butenoate (**17**) (16 mg, ∽76%). *Fraction 2* (R_f=0.30) was identified as 3-ethyl-5-methyl-1-oxabicyclo[3.1.0]hexan-2-one (**16**) (3.8 mg, 18%).

Diazo decomposition of 3-diazo-10-methylene-1-oxacycloundecan-2-one (5). Using the general procedure a solution of 3-diazo-10-methylene-1-oxacycloundecan-2-one (**5**) (50 mg, 0.24 mmol) in CH_2Cl_2 (1.6 mL) was added to a refluxing solution of $Cu(acac)_2$ (6.3 mg, 0.024 mmol, 10 mol%) in CH_2Cl_2 (6.9 mL). Purification by flash column chromatography (hexanes:ethyl acetate, 5:1) gave 2 fractions. *Fraction 1*(R_f=0.70) was identified as (*Z*)-10-methylene-1-oxacycloundec-3-en-2-one (**8**) (30 mg, 71%). IR (neat, cm^{-1}) ν 3030, 2940, 1709, 1645, 1626; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (dt, *J*=11.8, 9.2 Hz, 1H), 5.77 (br d, *J*=11.7 Hz, 1H), 5.17 (br s, 1H), 5.02 (br s, 1H), 4.72 (s, 2H), 2.51 (dt, *J*=8.9, 6.4 Hz, 2H), 2.23 (t, *J*=6.3 Hz, 2H), 1.70–1.61 (m, 2H), 1.53–1.40 (m, 2H), 1.30–1.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 147.4, 142.7, 122.9, 119.5, 67.0, 34.9, 26.5, 25.3, 24.6, 23.1. Anal Calcd for $C_{11}H_{16}O_2$: C, 73.30%; H, 8.95%. Found: *C*, 73.08%; H, 8.90%. *Fraction 2* (R_f=0.30) was identified as an impure sample of 10-oxa[6.3.1]propellane-9-one (**3**) (10 mg) by comparison of its ^1H NMR spectrum with that previously reported by another worker in our group.[3]

Diazo decomposition of (*Z*)-3-diazo-10-[1-(methoxy)-methylene]-1-oxacycloundecan-2-one (31). Using the general procedure a solution of (*Z*)-3-diazo-10-[1-(methoxy)-methylene]-1-oxacycloundecan-2-one (**31**) (60 mg, 0.25 mmol) in CH_2Cl_2 (1.7 mL) was added to a refluxing solution of $Cu(acac)_2$ (6.5 mg, 0.025 mmol, 10 mol%) in CH_2Cl_2 (7.5 mL). Purification by flash column chromatography (hexanes:ethyl acetate 4:1) gave 2 fractions. *Fraction 1* (R_f=0.70) was identified as an impure sample of (*Z*)-10-[1-(methoxy)methylene]-1-oxacycloundec-3-en-2-one (**33**) (32 mg, 61%). An analytically pure sample of **33** was obtained by additional column chromatography (hexanes:ethyl acetate, 14:1). IR (neat, cm^{-1}) ν 3029, 2936, 1714, 1671, 1461; ^1H NMR (300 MHz, $CDCl_3$) δ 6.23 (dt, *J*=11.7, 9.0 Hz, 1H), 5.88 (t, *J*=0.6 Hz, 1H), 5.79 (br d, *J*=11.7 Hz, 1H), 4.87 (s, 2H), 3.57 (s, 3H), 2.44 (dt, *J*=9.0, 6.5 Hz, 2H), 2.03 (dt, *J*=0.8, 6.2 Hz, 2H), 1.66–1.53 (m, 2H), 1.51–1.40 (m, 2H), 1.30–1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 146.8, 146.2, 123.0, 111.9, 60.1, 59.8, 29.9, 26.5, 25.2, 25.1, 23.5. Anal Calcd for $C_{12}H_{18}O_3$: C, 68.54%; H, 8.63%. Found: C, 68.18%, H, 8.55%. *Fraction 2* (R_f=0.30) was identified as (1*S**,2*R**, 6*R**)-1-methoxy-4-oxa[6.3.1]propellan-5-one (**32**) (16 mg, 36%). IR (neat, cm^{-1}) ν 2927, 1762; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, *J*=15.3 Hz, 1H), 4.23 (d, *J*=15.3 Hz, 1H), 3.40 (s, 3H), 3.14 (s, 1H), 2.65 (dt, *J*=15.3, 3.5 Hz, 1H), 2.48 (dt, *J*=15.3, 3.8 Hz, 1H), 1.70–1.00 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 68.9, 65.2, 58.6, 37.8, 37.2, 26.0, 25.6, 25.5, 25.3, 24.7. Anal Calcd for $C_{12}H_{18}O_3$: C, 68.54%; H, 8.63%. Found: C, 68.90%, H, 8.69%. The relative stereochemistry of **32** was established on the basis of a ^1H NMR 2D NOESY experiment, which included the following cross-peaks: δ 3.40/4.25, 3.40/3.14, 3.14/some portion of the δ 1.70–1.00 region.

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