Catalytic Rhodium-Mediated Tetraene Carbocyclizations

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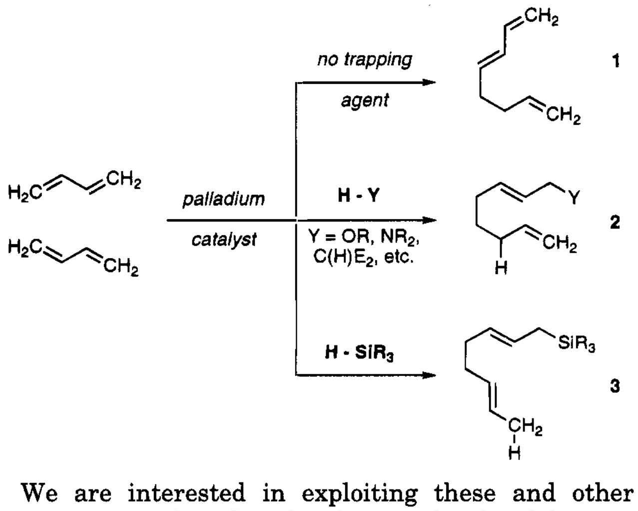
Certain rhodium complexes ([$RhCl_3$−2 Ar_3P], {[(1,5-COD)RhCl]$_2$−2 Ar_3P}, $(Ph_3P)_3RhCl$, [$(Ph_3P)_2Rh(NBD)$]PF_6) catalyze the cyclization−amine trapping of the prototypical tetraene **8**. The chemical yields are quite acceptable, up to 89% when one takes into account the unreacted tetraene recovered in reusable form. The best conversion is obtained in 2,2,2-trifluoroethanol (TFE, 75 °C) using $RhCl_3$ as the catalyst precursor. The stereochemistry of the products obtained via rhodium catalysis complements that obtained with palladium. The cyclization of **8**, promoted by the combination [$RhCl_3$−2 Ph_3P] in TFE (75 °C), affords the morpholine-trapped cyclopentane (67%) bearing a cis relative stereochemistry between the side chains and predominantly the *Z* geometry within the newly formed side chain (*i.e.*, a mixture of **9a** (minor component) and **9b** (major component)). In contrast, palladium catalysis affords predominantly the *trans*-cyclopentane derivative **9c**. The cyclization of **8**, promoted by the combination [$RhCl_3$−2 (p-Me_2N-C_6H_4)$_3P$] in TFE (75 °C), affords the morpholine-trapped cyclopentane **12** (63%), an isomer that may arise via the double-bond isomerization of **9a,b**. Rhodium-catalyzed cyclization and trapping by *N*-benzylmethylamine affords predominantly *cis*-**13a** (R^1 = CH_2Ph, R^2 = Me, 81%), and the reaction with diethylamine gives a 1:1 *cis−trans* mixture of **13b** (R^1 = R^2 = Et, 70% based on recovered **8**). Attempts to cyclize and trap tetraene **8** with benzylamine, diisopropylamine, phthalimide, and *N*-methyl-*p*-toluenesulfonamide were unsuccessful under the conditions of [$RhCl_3$−2 Ph_3P] catalysis in TFE.

Introduction

The groups of Smutny and Hagihara first reported the palladium-catalyzed linear telomerization of 1,3-butadiene in 1967.[1,2] Since that time, there have been many investigations into the *palladium-catalyzed* telomerizations of 1,3-butadiene, as evidenced by the more than 200 publications and several extensive reviews[3−8] on the subject. From these investigations into the linear telomerization of butadiene three principal types of bond constructions have emerged. These are illustrated by the formation of compounds **1−3** and arise via dimerization without trapping, dimerization with trapping by protic trapping agents, and dimerization with trapping by hydridic trapping agents.



We are interested in exploiting these and other transition-metal-mediated carbon−carbon bond-forming reactions that proceed by metal catalysis, developing their potential for application to complex molecule total synthesis. Toward this end, we have explored the *palladium-catalyzed* intramolecular dimerization of 1,3-dienes as a strategy for the formation of carbocyclic and certain heterocyclic rings, paying particular attention to important stereochemical aspects of the cyclization.[9−13]

In contrast to the large number of investigations into diene telomerizations catalyzed by palladium, there are only isolated reports using other transition-metal complexes.[3] Rhodium, cobalt, and/or iridium are of particular interest to us, since these metals can potentially form useful chiral complexes with chiral bidentate ligands and could therefore prove useful for the enantioselective carbocyclization of tetraene substrates. We are aware of few published reports of the *rhodium-catalyzed* linear telomerization 1,3-dienes with protic trapping reagents.[14] Baker and co-workers[15,16] reported that an ethanolic solution of $RhCl_3$ and Ph_3P catalyzed the

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(1) Smutny, E. J. *J. Am. Chem. Soc.* **1967,** *89,* 6793.
(2) Hagihara, N. *Tetrahedron Lett.* **1967,** 2451.
(3) Behr, A. *Aspects Homogeneous Catal.* **1984,** *5,* 3−73.
(4) Keim, W.; Behr, A.; Roper, M. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8; p 371.
(5) Keim, W.; Behr, A.; Roper, M. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: New York, 1982; Vol. 8; pp 430−462.
(6) Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985,** *24,* 283−295.
(7) Tsuji, J. *Adv. Organomet. Chem.* **1979,** *17,* 141−193.
(8) Smutny, E. J. *Ann. N. Y. Acad. Sci.* **1973,** *214,* 125.
(9) Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989,** *54,* 5193−5195.
(10) Takacs, J. M.; Zhu, J. *Tetrahedron Lett.* **1990,** *31,* 1117−1120.
(11) Takacs, J. M.; Chandramouli, S. V. *Organometallics* **1990,** *9,* 2877−2880.
(12) Takacs, J. M.; Zhu, J.; Chandramouli, S. *J. Am. Chem. Soc.* **1992,** *114,* 773−774.
(13) Takacs, J. M.; Chandramouli, S. *J. Org. Chem.* **1993,** *58,* 7315−7317.
(14) Behr, A.; He, R. *J. Organomet. Chem.* **1984,** *276,* C69.
(15) Baker, R.; Halliday, D. E. *Tetrahedron Lett.* **1972,** 2773−2776.

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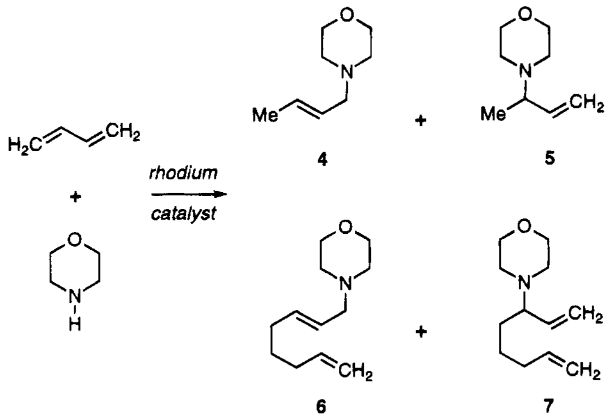
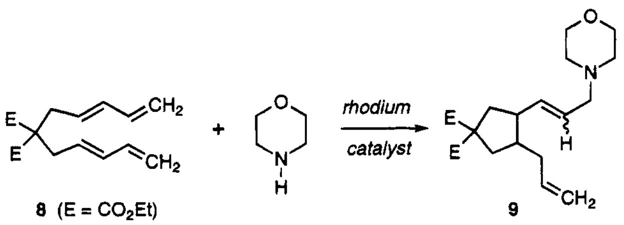
reaction of 1,3-butadiene with morpholine (75 °C, 15 h, 83% conversion) to afford a mixture of the C_4 amines **4** and **5** (27.5% of the mixture) and linear telomerization products, the C_8 amines **6** and **7** (62.5% of the mixture).



Using the preformed $(Ph_3P)_2Rh(CO)Cl$ complex, the percentage of telomerization product increased to 85% of the mixture, although under the reaction conditions reported (ethanol, 100 °C, 17 h) the conversion was only 43.5%. Using $(Ph_3P)_3RhCl$ (100 °C, 15 h, 68% conversion) telomerization accounted for only 30% of the product mixture with 70% of the C_4 amines.

Results and Discussion

On the basis of the rather modest precedents discussed above, we began an investigation into the rhodium-catalyzed reaction of tetraene **8** with morpholine and, eventually, with other amines. The effects of



catalyst precursor and reaction solvent are summarized in Table 1. All reactions use 3 mol % rhodium catalyst precursor and are run under otherwise similar reaction conditions (65–75 °C, 24 h). Comparing reaction solvents, we find that the reaction does not proceed to appreciable conversion in THF or acetonitrile, solvents which are quite acceptable in the corresponding palladium-catalyzed reaction. The reaction is better run in ethanol solvent (27–52% conversion of **8**), the reaction medium reported by Baker and co-workers, and is best run in 2,2,2-trifluoroethanol (TFE), the solvent employed by Livinghouse and co-workers[17] for rhodium-catalyzed [4 + 2] cycloadditions. Complete conversion of **8** is obtained in TFE at elevated reaction temperatures (ca 75 °C). An attempt to run the reaction at ambient temperature, but under conditions otherwise identical with those in entry 8, affords no cyclized product **9** even after 48 h. A complex mixture of isomerized products is isolated.

(16) Baker, R.; Onions, A.; Popplestone, R. J.; Smith, T. N. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1133–1138.
(17) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965–4966.

Table 1. Survey of Solvents and Catalyst Precursors for the Rhodium-Catalyzed Carbocyclization–Trapping of Tetraene 8 with Morpholine

entry no.	solvent	Rh complex[a]	% conv of **8**	% **9**[b]
1	THF	$[RhCl_3-2\ Ph_3P]$	7	5 (71)
2	THF	$(Ph_3P)_3RhCl$	22	
3	MeCN	$[RhCl_3-2\ Ph_3P]$	21	15 (71)
4	MeCN	$(Ph_3P)_3RhCl$	37	
5	EtOH	$[RhCl_3-2\ Ph_3P]$	52	38 (73)
6	EtOH	$(Ph_3P)_3RhCl$	27	21 (78)
7	TFE[c]	$[RhCl_3-2\ Ph_3P]$	100	67 (67)
8	TFE	$(Ph_3P)_3RhCl$	72	42 (58)
9	TFE	$(Ph_3)_2Rh(CO)Cl$	30	10 (33)
10	TFE	$[(1,5\text{-COD})RhCl-2\ Ph_3P]$[d]	68	42 (62)
11	TFE	$[(Ph_3P)_2Rh(NBD)]PF_6$	*e*	48 (48)

[a] Except where noted, reactions were run with 1 mmol of **8**, 5 mmol of morpholine, and 0.03 mmol of rhodium in 5 mL of solvent at approximately 75 °C for 24 h. [b] The numbers in parentheses are the percent yields corrected for the amount of recovered starting material. [c] TFE = 2,2,2-trifluoroethanol. [d] Charged as the rhodium dimer $[(1,5\text{-COD})RhCl]_2$. [e] Starting material was recovered (ca. 22%), but in impure form. The reaction was run for 48 h.

Of the three catalyst precursors reported by Baker and co-workers for the reaction of butadiene with morpholine ($[RhCl_3-Ph_3P]$, $(Ph_3P)_3RhCl$, and $(Ph_3P)_2Rh(CO)Cl$), we find that the combination $[RhCl_3-2\ Ph_3P]$ consistently gives higher conversion of substrate and better yield of trapped product **9**. In TFE, this combination effects complete consumption of substrate **8** and affords a 67% isolated yield of **9**. Two other catalyst precursors were screened. The rhodium dimer $[(1,5\text{-COD})RhCl]_2$ in combination with 2 equiv of Ph_3P per rhodium (Table 1, entry 10) affords a reasonably active catalyst, but the reaction fails to reach complete conversion after 24 h in TFE (75 °C). Further heating does not increase the extent of reaction. After 48 h (75 °C), the $[(Ph_3P)_2Rh(NBD)]PF_6$ complex (Table 1, entry 11) affords a 48% isolated yield of **9**.

Table 2 summarizes the results obtained by varying the ligand in the rhodium-catalyzed cyclization of **8** to **9**. Active rhodium catalysts are prepared in situ from $[(1,5\text{-COD})RhCl]_2$ and $RhCl_3$ in combination with 2 or 3 equiv of added phosphine. Without added ligand $[(1,5\text{-COD})RhCl]_2$ affords about 20% cyclized product after 24 h (entry 1). Entries 2, 3, 10, and 11 show that adding 3, or better 2, equiv of Ph_3P affords a more efficient catalyst. However, modifying $[(1,5\text{-COD})RhCl]_2$ with triphenyl phosphite or trifuranylphosphine[18] ligand decreases the extent of tetraene conversion (entries 4 and 5). Added tris(4-fluorophenyl)phosphine, tris(4-methoxyphenyl)phosphine, and tris(4-(dimethylamino)-phenyl)phosphine ligand (2 equiv) give catalysts that show a higher extent of substrate conversion over no added ligand, but efficiency slightly lower than that of triphenylphosphine. The last two ligands were reported to be particularly effective in the rhodium-catalyzed cyclization of hydroacylation of unsaturated aldehydes.[19] Using $RhCl_3$ as the rhodium source affords qualitatively similar results. Two equivalents of added triphenylphosphine are better than 3, and triphenylphosphine is somewhat superior to tris(4-methoxyphenyl)phosphine or tris(4-(dimethylamino)phenyl)phosphine. The chelating diphosphines 1,4-bis(diphenylphosphino)butane and 1,1′-bis(diphenylphosphino)ferrocene afford active cata-

(18) Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. 2* **1972**, 63.
(19) Larock, R. C.; Oertle, K.; Potter, G. F. *J. Am. Chem. Soc.* **1979**, *102*, 190.

Table 2. Influence of Phosphine Ligands and the Rhodium-Catalyzed Cyclization of 8 with Morpholine[a]

entry no.	ligand (amt (equiv per Rh))	% conv[b]	% 9[c]
	$[(1,5\text{-COD})RhCl]_2$ Complex[d]		
1	-	44	22 (50)
2	Ph_3P (2)	68	42 (62)
3	Ph_3P (3)	54[e]	34 (63)
4	$(PhO)_3P$ (2)	10	
5	$(furanyl)_3P$ (2)	27	18 (67)
6	$(p\text{-F-}C_6H_4)_3P$ (2)	57	35 (61)
7	$(p\text{-Me}_2N\text{-}C_6H_4)_3P$ (2)	54	34 (63)[f]
8	$(p\text{-MeO-}C_6H_4)_3P$ (2)	61	38 (62)
	$RhCl_3$ Complex		
9	-	27	21 (78)
10	Ph_3P (2)	100	67 (67)
11	Ph_3P (3)	100	54 (54)
12	$(o\text{-}CH_3C_6H_4)_3P$ (2)	6	4 (66)
13	$(p\text{-MeO-}C_6H_4)_3P$ (2)	75	57 (76)
14	$(p\text{-Me}_2N\text{-}C_6H_4)_3P$ (2)	73	63 (86)[f]
15	$(C_6H_{11})_3P$ (2)	14	13 (93)
16	Ph_3As (2)		
17	dppe[g]	14	
18	dppp[h]	6	5
19	dppb[i]	64	49 (77)
20	bdpf[j]	56	42 (75)

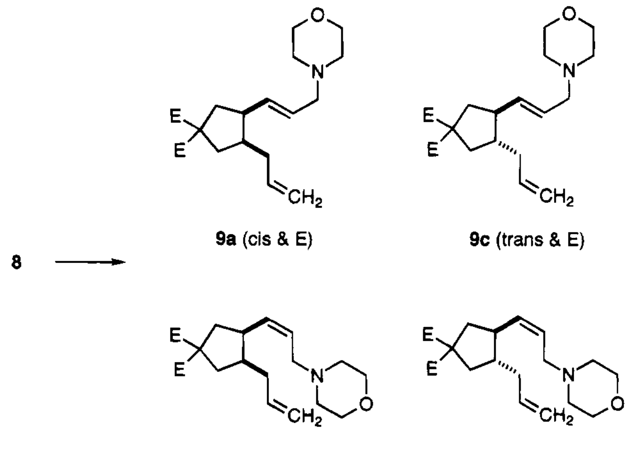
[a] Except where noted, reactions were run with 1 mmol of **8**, 5 mmol of morpholine, and 3 mol % of rhodium in 5 mL of TFE at approximately 75 °C for 24 h. [b] The percent conversion based on the amount of **8** recovered in reusable form. [c] The numbers in parentheses are the percent yields corrected for the amount of recovered starting material. [d] Charged as the rhodium dimer $[(1,5\text{-COD})RhCl]_2$. [e] Reaction run for 48 h. [f] An isomer of structure **9** is obtained (*vide infra*). [g] 1,2-Bis(diphenylphosphino)ethane.[h] 1,3-Bis(diphenylphosphino)propane. [i] 1,4-Bis(diphenylphosphino)butane. [j] 1,1′-Bis(diphenylphosphino)ferrocene.

lysts, while the corresponding bis(diphenylphosphino)-ethane and -propane do not.

Catalyst Turnover. We are puzzled as to why, with the exception of the $[RhCl_3/PPh_3]$ combination, the reaction does not proceed to completion. It is not simply a function of reaction time. Prolonged heating typically does not increase the extent of conversion. Monitoring the reaction at short reaction times indicates that there is an induction period prior to formation of an active catalyst and that the induction period is shortest with the $RhCl_3{-}PPh_3$ combination. Following the induction period there is a period of fairly rapid turnover; then the catalyst dies. Adding additional triphenylphosphine at this point does not regenerate an active catalyst. Attempts to monitor the course of the reaction more closely by ^{31}P NMR analysis (TFE solvent, 65 °C) reveal a complicated mixture of phosphine complexes and slow formation of triphenylphosphine oxide.

We carried out a number of experiments using the $[(1,5\text{-COD})RhCl]_2$ complex with triphenylphosphine in an attempt to define the cause of catalyst inactivation (Table 3). As described above, treatment of **8** with morpholine and 3 mol % of rhodium ($[(1,5\text{-COD})RhCl{-}2\ Ph_3P]$, TFE, 75 °C, 24 h) consumes 68% of the available tetraene substrate and on the basis of that conversion affords **9** in 62% yield (entry 1). Increasing the amount of rhodium from 3 to 6 mol % does not improve the yield of **9** (entry 2). Adding excess chloride in the form of tetraethylammonium chloride does not significantly affect the reaction (entry 3). Adding sodium tetraphenylborate with the intent of scavenging chloride (see also Table 1, entry 11) does not improve the conversion but does somewhat improve selectivity toward the formation of **9** (entry 4). Potentially, the cyclized product could inhibit the progress of the reaction, and to probe this possibility, we prepared **13b** via the rhodium-catalyzed reaction of **8** with diethylamine (*vide infra*). Adding 0.5 mmol of **13b** to the reaction mixture, prior to the addition of morpholine, does not inhibit formation of **9** (entry 5). Adding triphenylphosphine oxide, another potential source of product inhibition, at the start of the reaction only weakly inhibits the cyclization (entry 6).

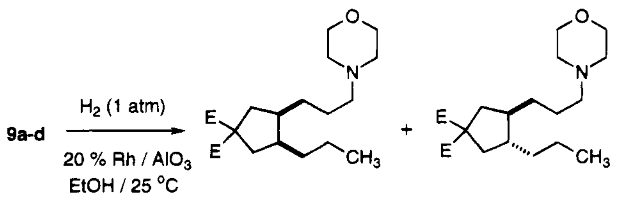
Stereochemical Aspects of the Rhodium-Catalyzed Cyclization–Trapping of 8. Cyclopentane **9**, the product of rhodium-catalyzed cyclization–morpholine trapping of tetraene **8**, contains two new stereochemical elements, the cis/trans relative stereochemistry between the two new ring substituents and the *E*/*Z* geometry of the newly formed disubstituted double bond. Thus for **9**, four diastereomeric structures (**a**–**d**) are possible. As we previously reported, the pal-



9a (cis & E) **9c** (trans & E) **9b** (cis & Z) **9d** (trans & Z)

ladium-catalyzed cyclization of tetraene **8** with morpholine (5 mol % Pd, acetonitrile, 75 °C, 2 h) affords predominantly **9c**.[9] **9c** possesses the trans relative stereochemistry between ring substituents and the *E* double bond geometry of the newly formed side chain.

The analysis of the product mixture obtained from rhodium-catalyzed cyclization–trapping is more complicated than in the palladium case. Depending on the exact reaction conditions, a mixture of two or more isomers of **9** is typically obtained. To simplify the analysis, the cis:trans ratio is first determined by hydrogenation of the mixture of diastereomers **9a**–**d** to a mixture of **10** and **11**, **9a,b** leading to **10** and **9c,d** leading to **11**. The **10**:**11** (*cis*-**9**:*trans*-**9**) ratio is conve-



10 (cis) **11** (trans)

niently determined by capillary GC analysis. In cases where *cis*-**9** (or *trans*-**9**) is strongly favored, an approximate **9a**:**9b** (or correspondingly **9c**:**9d**) ratio can usually be determined by careful analysis of the ^{13}C NMR spectrum of the product mixture.[20] For example, in the case of the palladium-catalyzed cyclization–trapping affording predominantly **9c** (5 mol % $Pd(OAc)_2$,

Table 3. Attempts To Probe the Cause of Catalyst Inactivation[a]

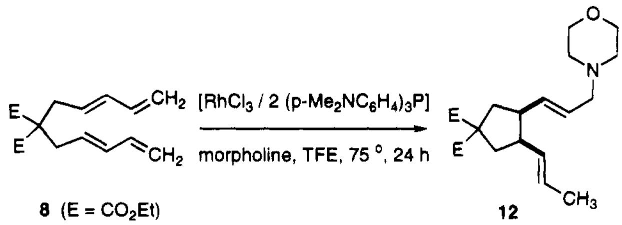
entry no.	addend	% conv[b]	% 9[c]
1	-	68	42 (62)
2	6 mol % Rh	64	28 (44)
3	2.5 equiv of Et_3NHCl	63	40 (63)
4	2.5 equiv of $NaBPh_4$	54	43 (80)
5	**13b**	64	39 (61)
6	3 equiv of $Ph_3P{=}O$	48	25 (52)

[a] Except where noted, reactions were run with 1 mmol of **8**, 5 mmol of morpholine, and 3 mol of rhodium in 5 mL of TFE at approximately 75 °C for 24 h. The catalyst was [(1,5-COD)RhCl−2 Ph_3P], charged as the rhodium dimer $[(1,5\text{-COD})RhCl]_2$. [b] The percent conversion based on the amount of **8** recovered in reusable form. [c] The numbers in parentheses are the percent yields corrected for the amount of recovered starting material.

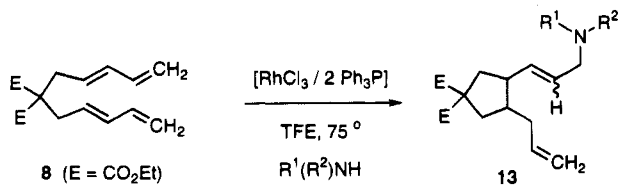
TFE, 75 °C, 24 h), hydrogenation of the product mixture affords mostly **11** (1:7 **10**:**11**). Careful consideration of the ^{13}C spectrum of the product mixture reveals an approximate 1:7 **9a**:**9c** mixture of products.

Stereochemical aspects of the palladium-catalyzed reaction and several of the rhodium-catalyzed reactions of tetraene **8** with morpholine are summarized in Table 4. Several trends are apparent. When the same ligand is employed, catalysts derived from $[RhCl(1,5\text{-COD})]_2$ and $RhCl_3$ give similar product mixtures, and in the case of triphenylphosphine as the ligand, $(Ph_3P)_3RhCl$ also gives a similar mixture (entries 2, 3, and 7). The catalyst precursors differ principally in the degree of substrate conversion, although generally $RhCl_3$ also gives a somewhat cleaner product mixture. The results suggest that a common active catalyst is formed from these precursors. In contrast to the palladium-catalyzed reaction (Table 4, entry 1), the triphenylphosphine-modified rhodium-catalyzed reaction affords products with predominantly the cis, rather than trans, relative stereochemistry of ring substituents. For example, the reaction catalyzed by the combination [$RhCl_3$−2 Ph_3P] affords a 26:1 *cis*-**9**:*trans*-**9** product ratio, as determined by the ratio of **10**:**11** after hydrogenation (entry 7). An approximate 1:2 ratio of the *cis* products **9a**:**9b** is formed under these conditions. Surprisingly, we find a remarkably large difference in catalyst selectivity between rhodium catalysts modified by soluble triphenylphosphine and those modified by polymer-bound triphenylphosphine. While the soluble triphenylphosphine ligand affords a high cis:trans product ratio (entries 2, 3, and 7), the rhodium catalyst modified by polymer-bound triphenylphosphine affords nearly a 1:1 ratio (entries 4 and 8). Rhodium catalysts modified by (soluble) tris(4-methoxyphenyl)phosphine (entries 5 and 9), dppb (entry 11), and bdpf (entry 12) give results similar to those obtained with (soluble) triphenylphosphine-modified catalysts.

The results obtained with the tris(4-(dimethylamino)-phenyl)phosphine-modified catalyst deserve special comment. The product obtained after hydrogenation is mostly the *cis* product **10** (entries 5 and 10); however, the product isolated after rhodium-catalyzed cyclization corresponds to neither **9a** nor **9b**. Structure **12** is the isolated product. The analysis of aliquots taken from the reaction mixture show that **9b** is the major diastereomer present at low conversion. Under the reaction conditions **9b** apparently isomerizes to the internal alkene and compound **12**.



The trapping of **8** by several other amines under the now standard [$RhCl_3$−2 Ph_3P] in TFE reaction conditions was briefly examined. Trapping by *N*-benzylmethylamine affords predominantly *cis*-**13a** (R^1 = CH_2-Ph, R^2 = Me) in 81% isolated yield (8:1 *cis:trans*) and 11% of unreacted **8**. The reaction with diethylamine



went to only 56% conversion under the standard conditions and gave a 1:1 *cis:trans* mixture of **13b** (R^1 = R^2 = Et) in 39% isolated yield (70% based on recovered **8**). Using the polymer-bound triphenylphosphine ligand, the isloated yield of diethylamine-trapped product improved to 46% (1.2:1 *cis:trans*). Attempts to cyclize and trap tetraene **8** with benzylamine, diisopropylamine, phthalimide, and *N*-methyl-*p*-toluenesulfonamide were unsuccessful under the conditions of [$RhCl_3$−2 Ph_3P]-catalysis in TFE.

Conclusions

Certain rhodium complexes catalyze the cyclization−trapping of the prototypical tetraene **8**. The chemical yields are quite acceptable, up to 89% when one takes into account the unreacted tetraene recovered in reusable form. Notably, the stereochemistry of the products obtained via rhodium catalysis complements that obtained with palladium. The cyclization of **8**, promoted by the combination [$RhCl_3$−2 Ph_3P] in TFE (75 °C), affords the morpholine-trapped cyclopentane bearing a cis relative stereochemistry between the side chains and predominantly the *Z* geometry within the newly formed side chain (*i.e.*, a mixture of **9a** and **9b**). In contrast, palladium catalysis affords predominantly **9c**. The cyclization of **8**, promoted by the combination [$RhCl_3$−2 (p-Me_2N-$C_6H_4)_3P$] in TFE (75 °C), affords the morpholine-trapped cyclopentane **12**, an isomer that may arise via the double bond isomerization of **9a**,**b**. The mechanism of the reaction is not clear at this point. In the absence of conflicting data, we assume a working model for the catalytic cycle akin to that proposed for the palladium-catalyzed reaction.[13] We are optimistic about the potential for future synthetic applications of this catalytic rhodium-mediated cyclization methodology in spite of the limited turnovers observed with the catalyst systems examined to date. Of particular promise are potential polycyclizations via intramolecular cyclization−intramolecular trapping, a novel transfor-

(20) The *E* geometry in **9a** and *Z* geometry in **9b** are assigned on the basis of the relatively downfield chemical shifts for the allylic methylene and methine carbons (δ 61.7 and 45.7 ppm, respectively) in the minor isomer **9a** compared to the major isomer **9b** (δ 56.1 and 40.4 ppm).

Table 4. Stereochemical Aspects of Metal-Catalyzed Cyclization–Morpholine Trapping of Tetraene 8

entry no.	metal complex[a]	ligand (amt (equiv per Rh))	% conv[b]	% **9**[c]	**10**:**11**[d]	**9a**:**9b**[e]
1	$Pd(OAc)_2$[f]	Ph_3P (2)	100	69 (69)	1:7	
2	$(Ph_3P)_3RhCl$		72	42 (58)	17:1	1:2
3	$[RhCl(1,5\text{-}COD)]_2$[g]	Ph_3P (2)	68	42 (62)	15:1	1:2
4	$[RhCl(1,5\text{-}COD)]_2$[g]	polymer–Ph_3P[h]	44	36 (82)	1.3:1	
5	$[RhCl(1,5\text{-}COD)]_2$[g]	$(p\text{-}MeO\text{-}C_6H_4)_3P$ (2)	61	38 (62)	12:1	1:2
6	$[RhCl(1,5\text{-}COD)]_2$[g]	$(p\text{-}Me_2N\text{-}C_6H_4)_3P$ (2)	54	34 (63)	10:1	*i*
7	$RhCl_3$	Ph_3P (2)	100	67 (67)	26:1	1:2
8	$RhCl_3$	polymer–Ph_3P[h]	52	43 (83)	1.6:1	
9	$RhCl_3$	$(p\text{-}MeO\text{-}C_6H_4)_3P$ (2)	75	57 (76)	12:1	1:2
10	$RhCl_3$	$(p\text{-}Me_2N\text{-}C_6H_4)_3P$ (2)	73	63 (86)	13:1	*i*
11	$RhCl_3$	dppb	64	49 (77)	18:1	
12	$RhCl_3$	bdpf	56	42 (75)	6:1	

[a] Except where noted, all reactions are run with 1 mmol of **8**, 5 mmol of morpholine, and 3 mol % of rhodium in 5 mL of TFE at approximately 75 °C for 24 h. [b] The percent conversion based on the amount of **8** recovered in reusable form. [c] The numbers in parentheses are the percent yields corrected for the amount of recovered starting material. [d] The **10**:**11** ratio determined after hydrogenation (Rh/AlO_3, EtOH, 1 atm of H_2, 25 °C). [e] The **9a**:**9b** ratio is estimated from the ^{13}C NMR spectrum. [f] Reaction run with 1 mmol of **8**, 5 mmol of morpholine, and 5 mol % of palladium in 5 mL of TFE at approximately 75 °C for 24 h. [g] Charged as the rhodium dimer $[(1,5\text{-}COD)RhCl]_2$. [h] 2% divinylbenzene cross-linked polystyrene bound triphenylphosphine; approximately 2 equiv of phosphine used in the reaction. [i] The major product corresponds to structure **12**.

mation that we have recently demonstrated with palladium catalysis.[13]

Experimental Section

General Procedures. NMR spectra were recorded with General Electric Omega 300 or 500 spectrometers. ^1H NMR spectral data are reported in ppm from the internal standard tetramethylsilane or residual chloroform. ^{13}C spectra are decoupled with Waltz-16 decoupling and reported in ppm from the internal standard chloroform. In some cases, ^{13}C NMR resonances are assigned by DEPT (distortionless enhancement by polarization transfer), HETCOR, and/or APT experiments. In such cases the number of attached protons is indicated in parentheses by s = quaternary carbon, d = methine, t = methylene, and q = methyl. Infrared spectra were obtained on an Analect RFX-65 FT-IR spectrometer from thin films using the Attenuated Total Reflectance (ATR) technique.[21] IR wavelengths are reported in cm^{-1}, and in some cases, peak intensities reported are in parentheses as percent absorbance. Combustion analyses were performed by M-H-W Analytical Labs, Phoenix, AZ. High resolution mass spectral determinations were performed by the Midwest Center for Mass Spectrometry, Lincoln, NE, on a Kratos MS-50 mass spectrometer. GC–MS analyses were performed on an HP 5890 Series II gas chromatograph equipped with 5972 mass selective detector and EI or CI source. 2,2,2-Trifluoroethanol (TFE) is degassed with nitrogen. Morpholine, diethylamine, and hexanes are purified by distillation. THF is distilled from sodium benzophenone ketyl. All other reagents received from commercial sources were used without further purification. All temperatures are reported in degrees Celsius and unless otherwise noted are externally measured. Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen. Rotary evaporators were used to concentrate reaction mixtures in vacuo at aspirator pressure.

Preparation of (E)-(2,4-Pentadienyl)propanedioic Acid Diethyl Ester. To a cooled (0 °C) solution of sodium hydride (1.70 g, 70 mmol) and DMSO (20 mL) in THF (250 mL) is added dropwise a solution of diethyl malonate (19.0 mL, 130 mmol) in THF (20 mL). After 1 h (0 °C), a solution of 2,4-pentadienyl chloride[22,23] (6.0 g, 60 mmol) in THF (15 mL) is added dropwise. The resulting mixture is warmed to ambient temperature, stirred (12 h), and then quenched by the addition of water (50 mL). The THF is removed in vacuo and the resulting oil partitioned between ether (300 mL) and water (100 mL). The organic layer is washed with water (3 × 50 mL) and then dried ($MgSO_4$) and concentrated. Chromatography on silica (200 g of EM Merck Kieselguhr 230–400 mesh, 92:8 Hex:EtOAc) affords (*E*)-(2,4–pentadienyl)propanedioic acid diethyl ester[24] (Registry No. 55693-36-2; 9.5 g, 70%): TLC analysis (92:8 Hex:EtOAc) R_f 0.2; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11–6.25 (m, 1H, C*H* = CH_2), 6.03–6.08 (m, 1H, =C*H*CH=CH_2), 5.54–5.64 (m, 1H, C*H*=CHCH=CH_2), 5.07 (d, J = 16.5 Hz, 1H, CH=C(H)H_{trans}), 4.96 (d, J = 9.5 Hz, 1H, CH=C(H_{cis})H), 4.15 (overlapping q's, J = 7.2 Hz, 4H, CO_2CH_2-CH_3), 3.36 (t, J = 7.4 Hz, 1H, C*H*CH_2CH=CH), 2.62 (dd, J = 7.4, 7.4 Hz, 2H, CHCH_2CH=CH–), 1.21 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (s, *C*=O), 137.2 (d, *C*H=CH_2), 134.4 (d, =*C*HCH=CH_2), 130.2 (d, *C*H=CH–CH=CH_2), 117.1 (t, –CH=CH_2), 62.0 (t, CO_2CH_2-CH_3), 52.5 (d, *C*HCH_2CH=CH), 32.4 (t, CHCH_2CH=CH–), 14.7 (q, $CO_2CH_2CH_3$); FT-IR (neat, ZnSe) 2980 (42%), 1747 (92%), 1730 (99%, C=O), 1475 (34%), 1466 (43%), 1446 (47%), 1390 (41%), 1368 (76%), 1335 (68%), 1297 (77%). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70%; H, 8.02. Found: C, 63.56; H, 7.87.

Preparation of (*E,E*)-Bis(2,4-pentadienyl)propanedioic Acid Diethyl Ester (8). To a cooled (0 °C) solution of sodium hydride (1.29 g, 50 mmol) and DMSO (18 mL) in THF (175 mL) is added dropwise a solution of (*E*)-(2,4-pentadienyl)-propanedioic acid diethyl ester (9.20 g, 40 mmol) in THF (20 mL). After 1 h (25 °C), the mixture is recooled (0 °C) and a solution of 2,4-pentadienyl chloride[22,23] (8.0 g, 80 mmol) in THF (15 mL) is added dropwise. The resulting mixture is warmed to ambient temperature, stirred (12 h), and then quenched by the addition of water (50 mL). The THF is removed in vacuo and the resulting oil partitioned between ether (300 mL) and water (100 mL). The organic layer is washed with water (3 × 50 mL) and then dried ($MgSO_4$) and concentrated. Chromatography on silica (200 g of EM Merck Kieselguhr 230–400 mesh, 92:8 Hex:EtOAc) affords **8**[25] (Registry No. 130408-54-7; 8.8 g, 75%): TLC analysis (92:8 Hex:EtOAc) R_f 0.3; ^1H NMR (300 MHz, $CDCl_3$) δ 6.20–6.33 (m, 2H, C*H*=CH_2), 6.03–6.11 (m, 2H, C*H*CH=CH_2), 5.46–5.56 (m, 2H, C*H*=CHCH=CH_2), 5.10 (d, J = 18.4 Hz, 2H, CH=C(H)H_{trans}), 4.96 (d, J = 9.5 Hz, 2H, CH=C(*H*)H_{cis}), 4.16 (q, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 2.64 (dd, J = 7.4, 7.6 Hz, 4H, CH_2CH=CH–), 1.23 (t, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (s, *C*=O), 137.2 (d, *C*H=CH_2), 135.7 (d, *C*HCH=CH_2), 128.5 (d, *C*H=CHCH=CH_2), 117.0 (t, CH=CH_2), 61.9 (t, $CO_2CH_2CH_3$), 58.3 (s, –O_2CCCO_2–), 36.6 (t, CH_2CH=CHCH=), 14.8 (q, CO_2-CH_2CH_3); FT-IR (neat, ZnSe) 2976 (42%), 1728 (98%, C=O), 1602 (36%), 1465 (39%), 1444 (47%), 1416 (30%), 1366 (53%),

(21) Wilks, P. A. *Am. Lab.* **1972**, *4*, 42.
(22) Prepared via the treatment of commercially available 1,4-pentadien-3-ol with thionyl chloride (1.2 equiv, methylene chloride, 0–25 °C, 2 h).
(23) Maruyama, K.; Nagai, N.; Naruta, Y. *J. Org. Chem.* **1986**, *51*, 5083–5092.
(24) Danishefsky, S.; Tsai, M. Y.; Dynak, J. *J. Chem. Soc., Chem. Commun* **1975**, *1*, 7–8.
(25) Wender, P. A.; Correia, C. R. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523–2525.

1300 (65%), 1281 (69%), 1261 (79%). Anal. Calcd for $C_{23}H_{24}O_4$: C, 70.03; H, 8.30. Found: C, 69.87; H, 8.02.

Catalytic Palladium-Mediated Cyclization–Morpholine Trapping of Tetraene 8 To Afford 9c. A solution of tetraene **8** (309.8 mg, 1.06 mmol), palladium diacetate (11.2 mg, 0.05 mmol), triphenylphosphine (65.0 mg, 0.15 mmol), and morpholine (436 mg, 5 mmol) in acetonitrile (5 mL) is stirred at elevated temperature (bath temperature ca. 75 °C) and the progress of the reaction monitored by TLC. After complete consumption of **8** (ca. 4 h), the reaction mixture is passed through a plug of silica (50:50:1 Hex:EtOAc:Et_3N) to remove the palladium and the effluent concentrated in vacuo. The residue is chromatographed on a column prepared from silica (55 g of EM Merck Kieselguhr 230–400 mesh, 50:50:1 Hex: EtOAc:Et_3N) and a top layer of neutral alumina (10 g, activity I, 150 mesh) to afford predominantly **9c** (277.0 mg, 69%) as a oil: TLC analysis (60:40:1 Hex:EtOAc:Et_3N) R_f 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69–5.80 (m, 1H, $CH_2CH{=}CH_2$), 5.41–5.55 (m, 2H, CHC*H*=C*H*CH_2), 4.95–5.04 (m, 2H, CH=CH_2), 4.18 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.70 (overlapping t's, J = 4.8 Hz, 4H, OCH_2CH_2N), 2.95 (d, J = 5.4 Hz, 2H, $NCH_2CH{=}$), 2.43–2.52 (m, 6H), 2.18–2.32 (m, 3H), 1.73–2.04 (m, 3H), 1.24 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (s, C=O), 137.2 (d, $-CH{=}CH_2$), 136.6 (d, $-CCH{=}CHCH_2-$), 127.9 (d, $-CCH{=}CHCH_2-$), 116.4 (t, $CH{=}CH_2$), 67.5 (t, CH_2OCH_2), 61.9 (t, $CO_2CH_2CH_3$), 61.7 (t, $NCH_2CH{=}$), 58.8 (s, $-O_2CCCO_2-$), 54.1 (t, CH_2NCH_2), 48.9 (**9c**, d, $CH_2CHCH{=}$), 45.3 (**9c**, d, CH_2CHCH_2), 41.2 (t, $CCH_2CHCH{=}$), 40.0 (t, CCH_2CHCH_2-), 37.7 (t, $CHCH_2CH{=}$), 14.6 (q, $CO_2CH_2CH_3$); FT-IR (neat, ZnSe) 2974 (39%), 1726 (97%, C=O), 1640 (28%, C=C), 1453 (52%), 1287 (64%), 1249 (91%), 1176 (81%), 1161 (76%). Anal. Calcd for $C_{21}H_{33}O_5N$: C, 66.46; H, 8.76. Found: C, 66.29; H, 8.53.

General Procedure for the Catalytic Rhodium-Mediated Carbocyclization of Tetraene 8 with Trapping by Dialkylamines. A solution of tetraene **8** (1 mmol), rhodium(III) chloride (6.4 mg, 0.03 mmol), phosphine ligand (0.06 mmol), and dialkylamine (5 mmol) in TFE (5 mL) is heated to 75 °C. After 24 h, the reaction mixture is passed through a plug of silica (50:50:1 Hex:EtOAc:Et_3N) to remove the rhodium, and the effluent is concentrated in vacuo. The residue is chromatographed on a column prepared from silica (55 g of EM Merck Kieselguhr 230–400 mesh, 50:50:1 Hex:EtOAc: Et_3N) and a top layer of neutral alumina (about 10 g, activity I, 150 mesh) to afford the cyclized and trapped product.

a. [$RhCl_3$–2 Ph_3P]-Catalyzed Carbocyclization–Morpholine Trapping To Afford 9a,b. Tetraene **8** (290.8 mg, 0.996 mmol), rhodium(III) chloride (6.4 mg, 0.03 mmol), triphenylphosphine (15.7 mg, 0.06 mmol), and morpholine (0.45 mL, 5.0 mmol) are treated according to the general cyclization procedure to afford after chromatography **9** (251.7 mg, 67%). The ^{13}C NMR spectrum reveals the presence of predominantly two diastereomers (**9a,b**) in an approximate 1:2 ratio: TLC analysis (60:40:1 Hex:EtOAc:Et_3N) R_f 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67–5.76 (m, 1H, $CH_2CH{=}CH_2$), 5.30–5.56 (m, 2H, CHC*H*=C*H*CH_2), 4.95–5.02 (m, 2H, $CH{=}CH_2$), 4.19 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.70 (t, J = 4.5 Hz, 4H, CH_2OCH_2), 2.92–3.10 (m, 3H, NCH_2-$CH{=}CHCHCH_2$), 2.34–2.52 (m, 6H), 1.87–2.23 (m, 5H), 1.22–1.28 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (s, C=O), 173.0 (s, C=O), 137.9 (d, $CH_2CH{=}CH_2$), 137.8 (d, $CH_2CH{=}CH_2$), 131.9 (d, $CHCH{=}CHCH_2$), 131.4 (d, $CHCH{=}CHCH_2$), 127.7 (d, $CHCH{=}CHCH_2$), 127.2 (d, $CHCH{=}CHCH_2$), 116.3 (t, $CH{=}CH_2$), 67.5 (t, CH_2OCH_2), 61.9 (t, $CO_2CH_2CH_3$), 61.7 (**9a**, t, NCH_2-$CH{=}$), 59.5 (s, $-O_2CCCO_2-$), 56.1 (**9b**, t, $NCH_2CH{=}$), 54.0 (t, $CH_2N(R)CH_2$), 45.7 (**9a**, d, $CH_2CHCH{=}$), 43.3 (overlapping **9b** and **9a**, d, CH_2CHCH_2), 40.7 (t, $CCH_2CHCH{=}$), 40.4 (**9b**, d, $CH_2CHCH{=}$), 39.1 (t, CCH_2CHCH_2-), 35.2 (t, $CHCH_2CH{=}$), 14.6 (q, $CO_2CH_2CH_3$); FT-IR (neat, ZnSe) 2936 (31%), 1726 (99%, C=O), 1640 (25%, C=C), 1453 (59%), 1444 (58%), 1366 (55%), 1327 (43%), 1290 (70%), 1250 (96%), 1175 (88%). Anal. Calcd for $C_{21}H_{33}O_5N$: C. 66.46; H, 8.76. Found: C, 66.63; H, 8.77.

b. [$RhCl_3$–2 (p-$Me_2NC_6H_4)_3P$]-Catalyzed Carbocyclization–Morpholine Trapping To Afford 12. Tetraene **8** (292.3 mg, 1.001 mmol), rhodium(III) chloride (7.9 mg, 0.04 mmol), tris(4-(dimethylamino)phenyl)phosphine (29.2 mg, 0.07 mmol), and morpholine (0.45 mL, 5.0 mmol) are treated according to the general cyclization procedure to afford after chromatography predominantly **12** (251.7 mg, 63%): TLC analysis (60:40:1 Hex:EtOAc:Et_3N) R_f 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25–5.55 (m, 4H), 4.19 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.70 (overlapping t's, J = 4.5 Hz, 4H, CH_2-OCH_2), 2.92–3.07 (m, 1H), 2.67–2.72 (m, 1H), 2.39–2.49 (m, 6H), 2.04–2.23 (m, 4H), 1.62 (d, J = 5.5 Hz, 3H, $=CHCH_3$), 1.25 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (s, C=O), 172.9 (s, C=O), 134.0 (d, $CHCH{=}CHCH_2$), 131.4 (d, $CHCH{=}CHCH_2$), 126.9 (d, $CHCH{=}CHCH_3$), 126.6 (d, $CHCH{=}CHCH_3$), 67.5 (t, CH_2OCH_2), 62.0 (t, $CO_2CH_2CH_3$), 59.8 (s, $-O_2CCCO_2-$), 56.2 (t, NCH_2-$CH{=}$), 54.1 (t, $CH_2N(R)CH_2$), 47.0 (d, $CH_2CHCH{=}CHCH_3$), 41.8 (d, $CH_2CHCH{=}$), 40.5 (t, $CCH_2CHCH{=}$), 39.9 (d, CH_2-$CHCH{=}CHCH_3$), 18.5 (q, $CHCH{=}CHCH_3$), 14.6 (q, CO_2-CH_2CH_3); FT-IR (neat, ZnSe) 2976 (47%), 2955 (47%), 2943 (43%), 1728 (99%, C=O), 1698 (32%), 1452 (64%), 1366 (58%), 1291 (73%), 1250 (97%), 1175 (90%). Anal. Calcd for $C_{21}H_{33}O_5N$: C, 66.46; H, 8.76. Found: C, 66.45; H, 8.76.

c. [$RhCl_3$–2 Ph_3P]-Catalyzed Carbocyclization–N-Benzylmethylamine Trapping To Afford 13a. Tetraene **8** (289.8 mg, 0.99 mmol), rhodium(III) chloride (6.4 mg, 0.03 mmol), triphenylphosphine (15.7 mg, 0.06 mmol), and N-benzylmethylamine (0.65 mL, 5.0 mmol) are treated according to the general cyclization procedure to afford after chromatography **13a** (274.1 mg, 81%). The ^{13}C NMR spectrum reveals the presence of predominantly two diastereomers (1.3:1 ratio; both cis diastereomers, as established by hydrogenation of the mixture to a single diastereomer): TLC analysis (90:10:1 Hex: EtOAc:Et_3N) R_f 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.31 (m, 5H, Ar H), 5.67–5.77 (m, 1H, $CH_2CH{=}CH_2$), 5.33–5.61 (m, 2H, CHC*H*=C*H*CH_2), 4.93–5.01 (m, 2H, $CH{=}CH_2$), 4.17 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.70 (m, 2H, NCH_2Ph), 2.95–3.04 (m, 3H), 2.73–2.77 (m, 2H, $CH_2CHCHCH_2$), 1.85–2.53 (m, 10H), 1.21–1.27 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3 (s, C=O), 173.2 (s, C=O), 139.6 (s, $NCH_2C_a{=}CH$), 138.1 (d, $CH_2CH{=}CH_2$), 138.0 (d, $CH_2CH{=}CH_2$), 133.9 (d, $CHCH{=}CHCH_2$), 132.8 (d, $CHCH{=}CHCH_2$), 129.7 (d, Ar), 128.8 (d, Ar), 127.6 (d, Ar), 116.3 (t, $CH{=}CH_2$), 62.5 (t, NCH_2-Ar), 62.0 (t, $CO_2CH_2CH_3$), 59.5 (s, O_2CCCO_2), 54.8 (t, NCH_2-$CH{=}$), 45.7 (d, $CH_2CHCH{=}$), 43.4 (d, CH_2CHCH_2), 42.8 (s, $CH_2CHCHCH_2$), 42.6 (q, NCH_3), 40.8 (t, $CCH_2CHCH{=}$), 40.5 (d, $CH_2CHCH{=}$), 39.9 (t, $CCH_2CHCH{=}$), 39.2 (t, CCH_2-$CHCH_2$), 35.5 (t, $CHCH_2CH{=}$), 35.3 (t, $CHCH_2CH{=}$), 14.7 (q, $CO_2CH_2CH_3$); FT-IR (neat, ZnSe) 2976 (37%), 2780 (23%), 1726 (98%, C=O), 1640 (24%, C=C), 1452 (58%), 1445 (59%), 1365 (60%), 1297 (59%), 1250 (95%), 1175 (87%). Anal. Calcd for $C_{21}H_{33}O_5N$: C, 72.61; H, 8.53. Found: C, 72.71; H, 8.76.

General Procedure for the Hydrogenation of Morpholine-Trapped Carbocyclization Products. The appropriate product (**9** or **12**) is added to a slurry of 20% rhodium on alumina in ethanol and the resulting mixture stirred under an atmosphere of hydrogen (hydrogen balloon). After complete consumption of alkene (about 18 h), the reaction mixture is filtered through a small plug of silica (EM Merck Kieselguhr 230–400 mesh, EtOAc). Analytical data are given below.

a. Hydrogenation of the Product Mixture 9a,b, Obtained via [Rhodium Chloride–Triphenylphosphine]-Catalyzed Carbocyclization. Capillary GC analysis (J&W Scientific DB-5, 150–275 °C at 5 °C/min): 16.8 (**11**, 3.7%), 17.3 min (**10**, 96.3%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.72 (overlapping t's, J = 4.8 Hz, 4H, H_2COCH_2), 2.44 (overlapping t's, J = 4.3 Hz, 4H, CH_2NCH_2), 2.28–2.35 (m, 4H), 1.99–2.06 (m, 4H), 1.31–1.42 (m, 5H), 1.24 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$), 1.10–1.19 (m, 3H), 0.89 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR of major isomer **11** (75 MHz, $CDCl_3$): δ 173.7 (s, C=O), 67.6 (t, CH_2OCH_2), 61.9 (t, $CO_2CH_2CH_3$), 59.9 (t, $NCH_2CH_2CH_2$), 59.5 (s, $C(CO_2Et)_2$), 54.4 (t, $CH_2N(R)CH_2$), 42.6 (d, $CH_2CHCHCH_2$), 42.4 (d, $CH_2CHCHCH_2$), 39.2 (t, $CHCH_2CH_2CH_2N$), 31.7 (t, CH_2CH_2N), 27.3 (t), 25.8 (t, $CH_2CH_2CH_3$), 21.9 (t, $CH_2CH_2CH_3$), 15.0 (q, $CH_2CH_2CH_3$), 14.7 (q, $CO_2CH_2CH_3$); FT-IR (neat, ZnSe) 2954 (58%), 28.52 (48%), 1728 (97%, C=O), 1465 (52%), 1457 (53%), 1445 (55%), 1365 (49%), 1298 (56%), 1250 (93%), 1205 (55%). Anal. Calcd for $C_{21}H_{33}O_5N$: C, 65.77; H, 9.72. Found: C, 65.96; H, 9.93.

b. Hydrogenation of the Product 9c, Obtained via Palladium-Catalyzed Carbocyclization. Capillary GC analysis (J&W Scientific DB-5, 150–275 °C at 5 °C/min): 16.6 min (**11**, 87.5%), 17.1 min (**10**, 12.5%). ^1H NMR (300 MHz, $CDCl_3$): δ 4.17 (overlapping q's, J = 7.2 Hz, 4H, $CO_2CH_2CH_3$), 3.72 (overlapping t's, J = 4.8 Hz, 4H, CH_2OCH_2), 2.54–2.44 (m, 6H), 2.33 (t, J = 7.4 Hz, 2H, $NCH_2CH_2CH_2$), 1.72–1.76 (m, 2H), 1.47–1.58 (m, 6H), 1.24 (overlapping t's, J = 7.2 Hz, 6H, $CO_2CH_2CH_3$), 1.10–1.12 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H, $CH_2CH_2CH_3$). ^{13}C NMR of major isomer **11** (75 MHz, $CDCl_3$): δ 173.5 (s, C=O), 67.6 (t, CH_2OCH_2), 61.3 (t, $CO_2CH_2CH_3$), 59.9 (t, $NCH_2CH_2CH_2$), 59.1 (s, $C(CO_2Et)_2$), 54.4 (t, CH_2NCH_2), 45.9 (d, $CH_2CHCHCH_2$), 45.7 (d, $CH_2CHCHCH_2$), 40.9 (t, $CH_2C(E_2)CH_2$), 36.7 (t, $CHCH_2CH_2CH_2N$), 32.1 (t, CH_2CH_2N), 25.8 (t, $CH_2CH_2CH_3$), 22.0 (t, CH_2CH_3), 15.0 (q, $CH_2CH_2CH_3$), 14.7 (q, $CO_2CH_2CH_3$). FT-IR (neat, ZnSe): 2850 (48%), 1728 (97%, C=O), 1465 (49%), 1455 (50%), 1444 (52%), 1365 (46%), 1297 (54%), 1251 (91%), 1206 (46%), 1178 (79%). Anal. Calcd for $C_{21}H_{33}O_5N$: C, 65.77; H, 9.72. Found: C, 65.66; H, 9.49.

c. Hydrogenation of the Product 12, Obtained via [Rhodium Chloride–Tris(*p*-(dimethylamino)phenyl)phosphine]-Catalyzed Carbocyclization. Capillary GC analysis (J&W Scientific DB-5, 150–275 °C at 5 °C/min): 16.6 min (**11**, 6.3%), 17.1 min (**10**, 93.7%). Spectral data are identical with those reported above for compound **10**.

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