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Palladium(II) Acetate−Tris(triphenylphosphine)rhodium(I) Chloride: A Novel Catalytic Couple for the Intramolecular Heck Reaction

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A series of crotyl ethers underwent intramolecular cyclizations in the presence of a novel catalytic couple, composed of tris(triphenylphosphine)rhodium(I) chloride and palladium(II) acetate, under Heck conditions initially described by Jeffery.[1] The data indicated that the combination of these two metal catalysts formed a synergistic interaction that mediated intramolecular couplings in a superior manner as compared to the use of palladium(II) acetate alone. When tris(triphenylphosphine)rhodium(I) chloride was added to the system, a distinct increase in rate and selectivity for the *endo*cyclic form of the bicyclic ether products was generally observed. In addition, changing parameters such as dilution and intial pot temperature appeared to significantly affect rate and selectivity in the experiments involving the catalytic couple, but not as drastically with those that were done only in the presence of palladium(II) acetate. Substitution of bis(triphenylphosphine)-palladium(II) acetate for palladium(II) acetate provided an outcome that slightly favored the *endo*cyclic form of the bicyclic ether, but when tris(triphenylphosphine)rhodium(I) chloride was added as a cocatalyst, the ratio clearly favored the *exo*cyclic isomer.

Introduction

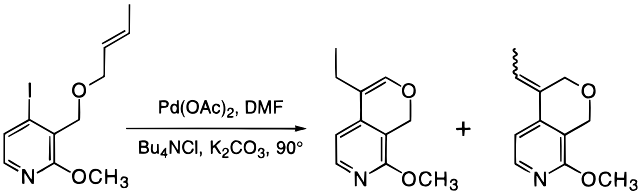
Coupling reactions between organic halides and olefins in the presence of a palladium catalyst were first introduced by Heck.[2] Since then, the Heck reaction has become one of the most versatile methods for carbon−carbon bond formations. It continues to attract interest as a route to simple coupling processes and intramolecular cyclizations.

The utilization of a cocatalyst in combination with palladium is not a new idea, and a prime example is the use of copper(I) iodide.[3] The addition of such a cocatalyst can enhance selectivity and/or rate in these coupling reactions.

Here, the use of a novel cocatalyst system, composed of a palladium(II) species {i.e., palladium(II) acetate or bis(triphenylphosphine)palladium(II) acetate} and tris-(triphenylphosphine)rhodium(I) chloride (Wilkinson's catalyst) is described. In general, it was observed that the presence of rhodium(I) in these reactions provided a product profile that was significantly more enriched in one form or the other as compared to those experiments that were done with palladium(II) acetate alone.

Results

Scheme 1



1 **2** **3**

~8 : 1

By heating a series of crotyl ethers (**1**, **13**, **16**, **19**) in *N*,*N*-dimethylformamide (DMF) at 90 °C in the presence of tetra-*n*-butylammonium chloride, potassium carbonate, and palladium(II) acetate (2.35 mol %) under an inert atmosphere,[1] bicyclic ethers were isolated as mixtures of *exo*- and *endo*cyclic isomers. For example, the reaction of crotyl ether **1** with palladium(II) acetate, under the conditions described, provided a bicyclic ether mixture with an *endo*:*exo*(*Z*) ratio as high as 8:1[4] (Scheme 1), although some experiments afforded ratios as low as 3:1. A minute amount of *exo*(*E*) isomer (~1%) also formed, but it was not possible to evaluate exact quantities due to an inability to separate its process control signals from those of a small, but unknown impurity.

The progress of these reactions was relatively slow, requiring between 16 and 20 h to reach completion, or near completion. In some instances, as previously mentioned, the ratios were more enriched in the *exo*cyclic form. Thus, it became necessary to investigate the use of an isomerization catalyst, since enol ether **2** was a desired intermediate for the preparation of a topoisomerase inhibitor.[4] Isomerization experiments with allylic ether **3** were conducted in the presence of three

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† Send questions or comments to the author at Bayer Corporation, 400 Morgan Lane, Pharmaceutical Division, Department of Chemistry Research, West Haven, CT 06516.

(1) For example, see: (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery T. *Synthesis* **1987**, 70. (c) Jeffery, T. *Tetrahedron Lett.* **1985**, *26(22)*, 2667.

(2) For reviews of the Heck reaction, see: (a) Heck, R. F. *Pure Appl. Chem.* **1978**, *50*, 691. (b) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (c) Heck, R. F. *Org. React.* **1982**, *27*, 345.

(3) For example, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Crisp, G. F.; Flynn, B. L. *J. Org. Chem.* **1993**, *58*, 6614. (c) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1854. (d) Robins, M. J.; Barr, P. J. *Tetrahedron Lett.* **1981**, *22*, 421. (e) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63(23)*, 8551.

(4) For example, see: (a) Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142. (b) Fang, F. G.; Bankston, D. D.; Huie, E. M.; Johnson, M. R.; Kang, M.-C.; LeHoullier, C. S.; Lewis, G. C.; Lovelace, T. C.; Lowery, M. W.; McDougald, D. L.; Meerholz, C. A.; Partridge, J. J.; Sharp, M. J.; Xie, S. *Tetrahedron* **1997**, 10953.

10.1021/jo982058q CCC: $18.00

Table 1. Attempted Isomerization of Allylic Ether 3 to Enol Ether 2 with Wilkinson's Catalyst, Iron Pentacarbonyl, and Collman's Reagent

entry	solvent	catalyst	mole %	reactn time (h)	*exo*:*endo*[f] (initial)	*exo*:*endo*[f] (final)
1	toluene	Rh(I)[a]	0.99	20	1:0.58	1:0.59
2	DMF	Rh(I)[a]	0.99	18	1:0.58	1:0.59
3	*n*-PrOH	Rh(I)[b]	3.83	15	1:2.30	1:8.50
4	*n*-PrOH	Fe[b]	3.83	3	1:2.30	1:13.6
5	*n*-PrOH	Fe[c]	3.83	10	1:2.30	1:9.40
6	*n*-PrOH	Na_2Fe[d]	<4.0	3	1:2.30	1:12.3
7	*n*-PrOH	Na_2Fe[e]	4.0	3	1:2.30	1:13.2
8	*n*-PrOH	Na_2Fe[e]	4.0	3	1:2.30	1:13.7

[a] Reaction done in the presence of n-Bu_4NCl (0.5 equiv) and K_2CO_3 (2 equiv) at 90 °C under nitrogen. [b] Reaction done in the presence of K_2CO_3 (2 equiv) at reflux temperature. [c] Reaction done at reflux temperature under nitrogen. [d] Reagent handled in open air and reaction done at reflux temperature under nitrogen. [e] Reagent handled under an inert atmosphere and reaction done at reflux temperature under nitrogen. [f] *Exo* isomer indicated as the *Z*-form. Fe = iron pentacarbonyl; Rh(I) = Wilkinson's catalyst; Na_2Fe = Collman's reagent.

Table 2. Modified Heck Conditions Using a Palladium(II)−Rhodium(I) Couple

entry	crotyl ether **1** (g)	*exo*:*endo* (crude)	*exo*:*endo* (distilled)	enol ether **2** (yield, %)	reactn time (h)
1	135.0[a]	1:12.79	1:14.5	68	4
2	228.0[a]	1:12.79	1:14.3	68	4
3	175.0[b]	1:12.40			4
4	228.8[b]	1:12.70			4.5
5	5.0[c]	1:8.5			14

[a] Reaction conditions: palladium(II) acetate (2.35 mol %), tris(triphenylphosphine)rhodium(I) chloride (0.8 mol %), potassium carbonate (2 equiv), and tetra-*n*-butylammonium chloride (0.5 equiv) in DMF (15 mL/g of **1**) at 90 °C under nitrogen. The catalysts were added to the reaction medium at 17 °C. [b] The 175.0 and 228.8 g batches were combined and distilled for a yield of 63% and an *exo*:*endo* ratio of 1:14.1. [c] Reaction conditions: palladium(II) acetate (2.35 mol %), triphenylphosphine (1.0 mol %), potassium carbonate (2 equiv), and tetra-*n*-butylammonium chloride (0.5 equiv) in DMF (15 mL/g of **1**) at 90 °C under nitrogen. The catalyst was added to the reaction medium at 17 °C.

different catalysts: Wilkinson's catalyst,[5] iron pentacarbonyl,[6] and Collman's reagent.[7] Isomerization experiments were attempted in several solvents, but significant results were only obtained in *n*-propanol (Table 1). Iron pentacarbonyl proved to be a superior isomerization catalyst, especially in the presence of potassium carbonate. The presence of potassium carbonate during this reaction probably generated dipotassium tetracarbonylferrate, a form of Collman's reagent.[7] Indeed, Table 1 confirms that isomerization experiments in the presence of disodium tetracarbonylferrate (Collman's reagent) provided results that were essentially the same as those conducted in the presence of iron pentacarbonyl/potassium carbonate. In general, Wilkinson's catalyst does not require the presence of base to act as an isomerization agent,[5] but in these particular experiments double-bond migration was not observed when potassium carbonate was absent from the reaction mixture. Potassium carbonate alone would not effect olefin isomerization of **3**.

A major consideration at this point was to determine a more selective and reproducible method for the synthesis of **2**, and other enol ethers, that would also offer an enhancement in rate. Utilization of copper(I) iodide[3] as a cocatalyst with palladium(II) acetate appeared promising, but the results were not reproducible. Quite unexpectedly, Wilkinson's catalyst (0.8 mol %) appeared to act synergistically in combination with palladium(II) acetate (2.35 mol %) to mediate an intramolecular coupling of **1** with greater selectivity for enol ether **2**, and at a much faster rate than observed in experiments without the presence of rhodium(I). A separate experiment with triphenylphosphine (1.0 mol %) and palladium(II) acetate (2.35 mol %) provided results similar to those observed with palladium(II) alone (Table 2, entry 5). This result indicated that rhodium(I) played a significant role in these particular coupling experiments and that triphenylphosphine was not a major contributor.

A series of experiments were conducted to determine if the rhodium(I) catalyst, in conjunction with palladium(II), or acting alone, actually isomerized the cyclized material, isomerized the crotyl ether prior to cyclization, or acted only as a cocatalyst, which in combination with palladium(II) formed a synergistic interaction that exceeded the capabilities of either complex used alone. Wilkinson's catalyst did not mediate intramolecular couplings of the various crotyl ether substrates used in this study, albeit, it is known[8] to effect such closures with certain substrates. As mentioned earlier, Wilkinson's catalyst did not isomerize allylic ether **3** to desired enol ether **2** in DMF under the standard reaction conditions employed, although it did induce double-bond movement of **3** in propanol (Table 1, entry 3). In addition, rhodium(I) did not isomerize crotyl ether **1** in DMF, THF, or propanol, but neither did iron pentacarbonyl. Nevertheless, the reaction of iron pentacarbonyl with crotyl ether **1** did generate a dark red mixture in both THF and *n*-propanol, and this indicated complex formation. Supposedly, crotyl ether **1** preferentially forms a stable η^4-metal complex with both metals and that would obviate an isomerization pathway (Scheme 2). Complex formation of **1** with rhodium(I) could also enhance reactivity of the crotyl ether toward cyclization in the presence of palladium(II) and subsequent isomerization to **2**. It is fairly certain that rhodium(I) alone does not act as an isomerization agent, or as a Heck reagent under the conditions employed, but as emphasized earlier, the addition of Wilkinson's catalyst to these reactions provides a more reproducible outcome and a faster rate. Finally, it appears that isomerization does not occur before cyclization, because for that to happen a five-membered-ring species (**25**) would be generated via a 5-*exo-trig* process,[9] and in order for desired enol ether **2** to form, crotyl ether **22**

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(5) (a) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehrmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102. (b) Biellman, J. and Jung, M. *J. Am. Chem. Soc.* **1968**, *90*, 1673. (c) Birch, A.; Rao, G. *Tetrahedron Lett.* **1968**, 3797. (d) Uematsu, T.; Kawakami, F.; Saitho, F.; Miura, M.; Hashimoto, H. *J. Mol. Catal.* **1981**, *12*, 11. (e) Augustine, R. L.; Van Peppen, J. F. *J. Chem. Soc., Chem. Commun.* **1970**, 495. (f) Blum, J.; Pickholtz, Y. *Israel J. Chem.* **1969**, *7*, 723.

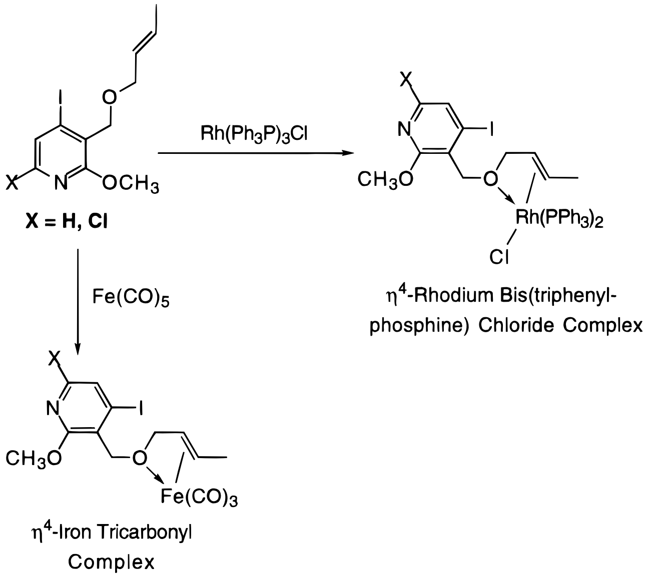
(6) Emerson, G.; Pettit, R. *J. Am. Chem. Soc.* **1962**, *84*, 4591.

(7) For example, see: (a) Collman, J.; Winter, S.; Clark, D. *J. Am. Chem. Soc.* **1972**, *94*, 1788. (b) Collman, J. *Acc. Chem. Res.* **1975**, *8*, 342 (c) Collman, J.; Finke, R.; Cawse, J.; Brauman, J. *J. Am. Chem. Soc.* **1977**, *99*, 2515. (d) Collman, J.; Winter, S.; Komoto, R. *J. Am. Chem. Soc.* **1973**, *95*, 249.

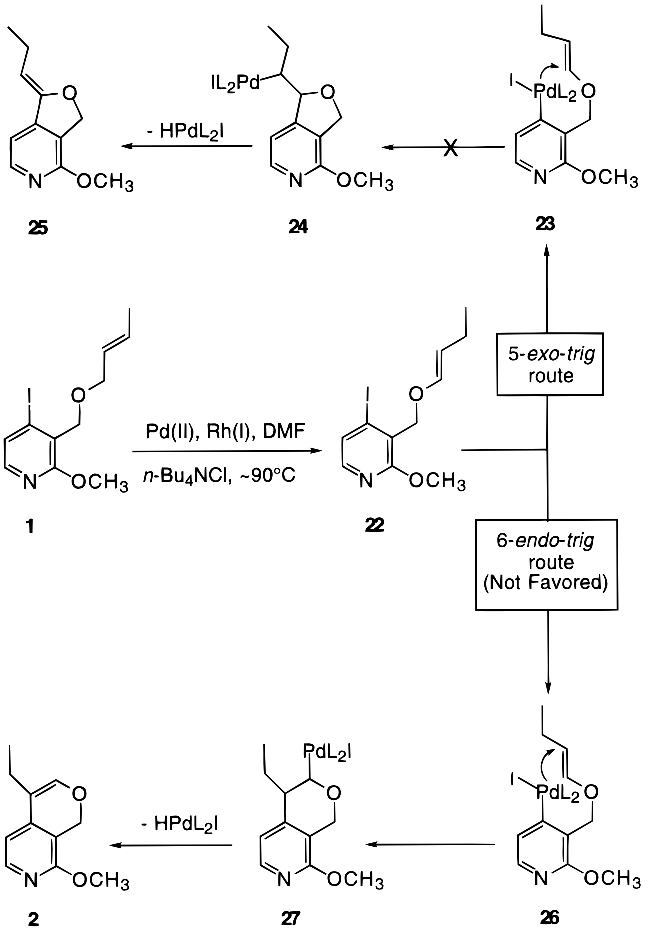
(8) For example, see: (a) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073. (b) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc. Chem. Soc., Chem. Commun.* **1985**, 971. (c) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44(15)*, 4967. (d) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44-(7)*, 2049. (e) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46(11)*, 4003. (f) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44(7)*, 2033.

(9) For definitions and rules regarding ring closure, see: Baldwin, J. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

Scheme 2

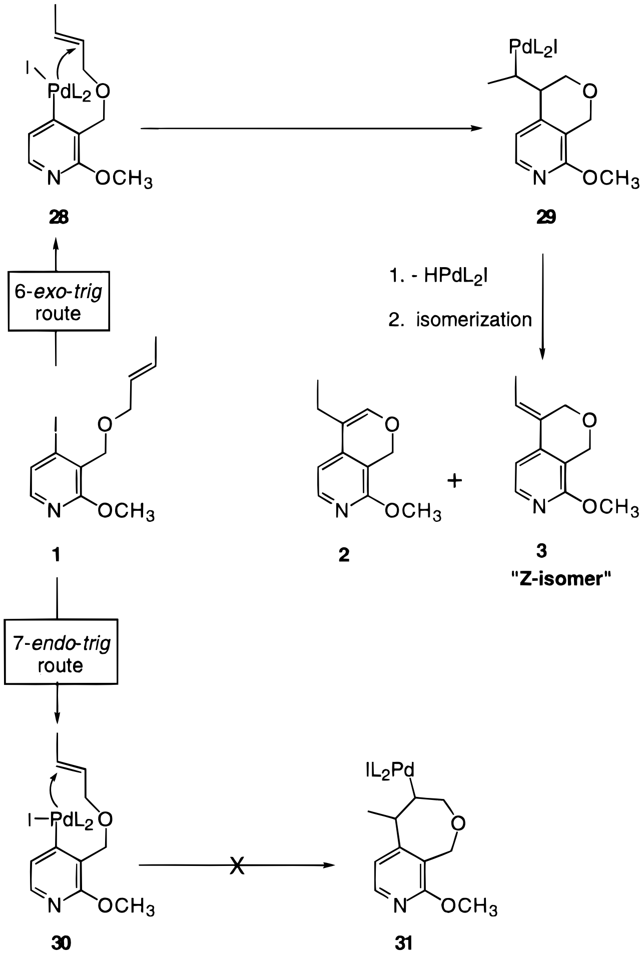


Scheme 3



would have to proceed through a less favored 6-*endo-trig* route (Scheme 3). The regiochemical outcomes of intramolecular Heck reactions generally favor a 5-*exo-trig* pathway in those cases where a competition exists between 6-*endo-* and 5-*exo-trig* closures.[10] Aliquot analysis over time by HPLC and NMR methods only indicated the presence of unreacted crotyl ether **1**, along with various ratios of enol ether **2** and allylic ether **3** (mostly *Z-* with a minute amount of *E*-congener). A five-membered-ring product (**25**) and its precursor (**22**) were never detected or isolated. Even if the less-favored 6-*endo-trig* closure was the major route followed, one would expect to isolate a minor amount of product formed from a 5-*exo-trig* process. Although the reactions of *N*-acryloyl-7-bromoindolines[11] selectively provided 6-*endo-trig* products in the presence of palladium(II) acetate, this unexpected result probably occurred because a 5-*exo-trig* closure would produce strain through approach of the palladium species to the α position of the double bond of these acrylamides. Nevertheless, experimental observation here supports intramolecular cyclization of these crotyl ethers via a 6-*exo-trig* route, followed by isomerization of the *exo*cyclic products to their *endo*cyclic form (Scheme 4).

Scheme 4



Closer inspection of this reaction indicated that the product profile and rate could be modified further by changing parameters such as solvent volume and temperature. Data from Table 3 supports the conclusion that variance in solvent volume and initial pot temperature (prior to addition of the catalysts) significantly affected the outcomes of these experiments. Introduction of pal-

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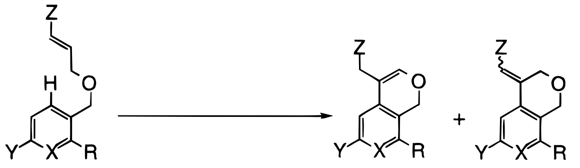
[10] For example, see: (a) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *44(11)*, 3557. (c) Grigg, R.; Sridharan, V.; Sukirthalingam, S.; Workun, T. *Tetrahedron* **1989**, *30(9)*, 1139.

[11] (a) Dankwardt, J.; Flippin, L. Presented at the 209th National Meeting of the American Chemical Society (Anaheim, CA, April 2–6, 1995). (b) Dankwardt, J.; Flippin, L. *J. Org. Chem.* **1995**, *60*, 2312.

Table 3. Effect of Solvent Volume and Internal Pot Temperature on *Exo*:*Endo* Ratio[a]



entry/pot temp (°C)	cat.	solvent (g/mL)	reactn time (h)	*exo*:*endo* (final)	X	Y	Z	R	H
1: 17−90	Pd	1/16	16	1:7.7	N	H	Me	OMe	I
2: 17−90	Pd + Rh	1/16	3.5	1:12.3	N	H	Me	OMe	I
3: 32−90	Pd + Rh	1/16	3.5	1:20.7	N	H	Me	OMe	I
4: 17−90	Pd	1/10	9.5	1:8	N	H	Me	OMe	I
5: 30−90	Pd	1/10	14	1:8.4	N	H	Me	OMe	I
6: 22−90	Pd + Rh	1/10	2	1:14.3	N	H	Me	OMe	I
7: 26−90	Pd + Rh	1/10	2	1:16.3	N	H	Me	OMe	I
8: 26−90	Pd + Rh	1/10	2	1:16.7	N	H	Me	OMe	I
9: 32−90	Pd + Rh	1/10	2	1:28.6	N	H	Me	OMe	I
10: 17−90	Pd	1/15	20	1:7.2	N	Cl	Me	OMe	I
11: 17−90	Pd + Rh	1/15	4	1:11.6	N	Cl	Me	OMe	I
12: 27−90	Pd	1/10	9	1:6	N	Cl	Me	OMe	I
13: 26−90	Pd + Rh	1/10	2.5	1:19.3	N	Cl	Me	OMe	I
14: 17−90	Pd	1/14	7	8.7:1	C	H	Ph	H	I
15: 17−90	Pd + Rh	1/14	2.5	46.4:1	C	H	Ph	H	I
16: 17−90	Pd	1/14	17	1:6.9	C	H	Me	H	I
17: 30−90	Pd	1/10	7	1:8.8	C	H	Me	H	I
18: 30−90	Pd + Rh	1/10	2	1:18.4	C	H	Me	H	I
19: 17−90	Pd + Rh	1/10	2	1:12.6	C	H	Me	H	I
20: 17−90	Pd + Rh	1/10	3	1:12.6	C	H	Me	H	Br

[a] Typical reaction conditions: crotyl ether, potassium carbonate (2 equiv), palladium(II) acetate (2.35 mol %), tetra-*n*-butylammonium chloride (0.5 equiv), Wilkinson's catalyst (0.8 mol %), and DMF (10−16 mL/g) heated to 90 °C under nitrogen. The reaction medium was purged of air with a stream of nitrogen for 20 min prior to addition of the catalyst(s) at the initial temperatures reflected in the table. **1:** X = N; Y = H; R = OMe; H = I; Z = Me. **2**, **3:** X = N; Y = H; R = OMe; Z = Me. **13:** X = N; Y = Cl; R = OMe; H = I; Z = Me. **14**, **15:** X = N; Y = Cl; R = OMe; Z = Me. **16a,b:** X = C; Y = R = H; Z = Me; H = Br, I. **17**, **18:** X = C; Y = R = H; Z = Me. **19a,b:** X = C; Y = R = H; Z = Ph; H = Br, I. **20**, **21:** X = C; Y = R = H; Z = Ph.

ladium(II) acetate to 16 volumes[14] of DMF (containing **1**) at 17 °C, and heating the contents to 90 °C for 16 h, provided a product profile with an *exo*:*endo* ratio of 1:7.7 (entry 1). Under the same conditions, in the presence of Wilkinson's catalyst, the ratio was shown to be 1:12.3 (entry 2) by NMR analysis, and the reaction was complete in only 3.5 h! When the Pd(II)−Rh(I) couple was added to 16 volumes of DMF (containing **1**) at 32 °C, the product profile reflected a new ratio of 1:20.7 after 3.5 h at 90 °C (entry 3). The variance of solvent volume, in conjunction with initial pot temperature, did not appear to affect *exo*:*endo* ratios of those reactions of **1** done in the presence of palladium(II) alone, and expected changes in rate did not occur. In two experiments in which palladium(II) acetate was added to **1** in 10 volumes of DMF at 17 °C (entry 4) and 30 °C (entry 5), respectively, the *exo*:*endo* ratios were essentially identical (1:8 vs 1:8.4), but the rates were unexpectedly different. Although the first experiment was complete after 9.5 h when the catalyst was added to the flask at 17 °C, the second one, in which the catalyst was introduced to the flask at 30 °C, required more than 14 h to totally consume crotyl ether **1**. Addition of the cocatalyst system to the flask containing **1** in 10 volumes of DMF at 22, 26, and 32 °C provided *exo*:*endo* ratios of 1:14.3 (entry 6), 1:16.7 (entry 8), and 1:28.6 (entry 9), respectively, after only 2 h at 90 °C. These comparison studies suggest that the presence of rhodium(I) played a significant role in the outcomes of these experiments in selectivity, rate, and reproducibility.

Significant differences in rate and selectivity were also observed when the cocatalyst system was added to other substrates (such as crotyl ether **13**) that contained additional substitution to the pyridine ring. For example, addition of the cocatalyst system to **13** in 15 volumes of DMF at 17 °C afforded an *exo*:*endo* ratio of 1:11.6 in 4 h at 90 °C (Table 3, entry 11), but when the catalysts were added to the same substrate in 10 volumes of DMF at 26 °C, the ratio became 1:19.3 in 2.5 h at 90 °C (entry 13). Addition of palladium(II) acetate alone to **13** in 15 volumes of DMF at 17 °C generated an *exo*:*endo* ratio of only 1:7.2 after 20 h at 90 °C (entry 10).

Similar results were noted for crotyl ethers in which X = C. Treatment of crotyl ether **16b** (H = I) with palladium(II) acetate in 10 volumes of DMF at 30 °C effected intramolecular closure that resulted in an *exo*:*endo* ratio of 1:8.8 in 7 h at 90 °C (Table 3, entry 17). However, a ratio of 1:18.4 was observed under the same conditions in the presence of the cocatalyst system in only 2 h at 90 °C (entry 18). Exchanging iodide for bromide in **16** did not alter selectivity in the presence of the cocatalyst system, but the bromide (**16a**) did require a slightly longer reaction time than the iodide (**16b**).[12]

Crotyl ether **19** (Z = Ph) provided an *exo*:*endo* ratio of 8.7:1 after 7 h at 90 °C when that starting material was treated with palladium(II) acetate at 17 °C (Table 3, entry 14). Of course, conjugation of the *exo*cyclic double bond of **21** to the phenyl ring would explain its resistance to isomerize. However, when this reaction proceeded in the presence of the Pd(II)−Rh(I) cocatalyst, under the same conditions, a ratio of 46.4:1 was realized after 2.5 h (entry 15), which demonstrated a profound difference in rate accompanied by a higher selectivity for the *exo*cylic form. This experiment was reproducible, with a product profile consistently containing only 2.1−2.5% of *endo*cyclic material. It is not clear, however, why so little isomerization occurred in this experiment, but a synergistic interaction between the two metals must be responsible.

The combination of bis(triphenylphosphine)palladium(II) acetate and Wilkinson's catalyst propagated quite different results than those observed with the palladium(II) acetate−tris(triphenylphosphine)rhodium(I) chloride cocatalyst system (Table 4). When a mixture of crotyl ether **1** and the bis(triphenylphosphine)palladium(II) acetate−tris(triphenylphosphine)rhodium(I) chloride cocatalysts was heated to 90 °C for 2.5 h, the isolated product profile provided an *exo*:*endo* ratio of 1:0.5 (entry 2). Clearly, this system afforded a product profile that favored the *exo*cyclic isomer; but, if the cocatalyst was added to the flask at 32 °C, and the mixture was heated to 90 °C for 2 h, the ratio was more enriched in the *endo*cyclic form. In the absence of Wilkinson's catalyst, bis(triphenylphosphine)palladium(II) acetate converted **1** to a mixture of isomers with an *exo*:*endo* ratio of 1:3.2 (entry 1). The low ratio with respect to the *endo*cyclic form can be rationalized by steric factors, since the

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[12] For example, see: (a) Mori, M.; Chiba, K.; Ban, Y. *Tetrahedron Lett.* **1977**, 1037. (b) Plevyak, J.; Dickerson, J.; Heck, R. *J. Org. Chem.* **1979**, *44*, 4078. (c) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. *J. Org. Chem.* **1980**, *45*, 2710.

[13] Comins, D.; Baevsky, M.; Hong, Hao *J. Am. Chem. Soc.* **1992**, *114(27)*, 10971.

[14] A "volume" is a development term that refers to the number of grams of starting material per mL; thus, a 10-volume experiment would indicate that each gram of starting material was suspended or dissolved in 10 mL of solvent.

Table 4. Modified Heck Conditions Using a Bis(triphenylphosphine)Palladium(II)−Rhodium(I) Couple[a]

entry	internal pot temp (°C)	catalyst	solvent (g/mL)	reactn time (h)	*exo*:*endo*
1	17−90	Pd	1/10	6	1:3.2
2	17−90	Pd + Rh	1/10	2	1:0.5
3	32−90	Pd + Rh	1/10	2	1:1.1

[a] Typical reaction conditions: crotyl ether **1**, potassium carbonate (2 equiv), bis(triphenylphosphine)palladium(II) acetate (2.35 mol %), tetra-*n*-butylammonium chloride (0.5 equiv), tris(triphenylphosphine)rhodium(I) chloride (0.8 mol %), and DMF (10 mL/g) heated to 90 °C under nitrogen. The reaction medium was purged of air with a stream of nitrogen for 20 min prior to addition of the catalyst(s) at the initial temperatures reflected in the table.

isomerization step involves a much bulkier metal due to the presence of triphenylphosphine groups. In addition, the bis(triphenylphosphine)palladium(II) acetate−tris(triphenylphosphine)rhodium(I) chloride cocatalyst probably operated in tandem during the isomerization stage, and this hindered system would be expected to work much slower than either palladium(II) acetate or its bis(triphenylphosphine) derivative. Addition of the cocatalyst system to the flask at elevated temperature (32 °C) obviously provided the energy necessary to push the isomerization step further, prior to decomposition of the metal reagents.

A closer examination of this chemistry will be forthcoming to determine its efficacy with other substrates. Perhaps further scrutiny of the conditions employed will more aptly explain the mechanics behind the synergy demonstrated by these two catalysts when they are used in tandem.

Conclusions

In conclusion, tris(triphenylphosphine)rhodium(I) chloride acted synergistically with palladium(II) acetate to mediate intramolecular closures of a set of crotyl ethers in DMF solvent with greater selectivity, at a faster rate and with greater reproducibility than observed with Heck chemistry performed in the presence of palladium(II) acetate alone. It is proposed that initial complex formation between rhodium(I) and any of the crotyl ethers would explain an enhanced rate of cyclization in the presence of palladium(II), a higher degree of selectivity for the enol ether through subsequent isomerization, and a reproducibility of results not observed with those reactions conducted without Wilkinson's catalyst. In general, it appears that parameters, such as initial pot temperatures, prior to the addition of the catalysts, and dilution, have significant effects on the overall selectivity and rates of these reactions, especially in the presence of the catalytic couple.

Higher yields of the *exo*cyclic isomer were realized when bis(triphenylphosphine)palladium(II) acetate was substituted for palladium(II) acetate, with or without the presence of Wilkinson's catalyst. It is assumed that the bulkiness of the triphenylphosphine-substituted species slowed the progress of the isomerization step, especially when tris(triphenylphosphine)rhodium(I) chloride was incorporated as a cocatalyst. Finally, it was shown that iron pentacarbonyl was a superior isomerization catalyst (as compared to Wilkinson's catalyst) for the bicyclic allylic ethers, especially in the presence potassium carbonate.

Experimental Section

General. Combustion analyses were obtained from Atlantic Microlabs, Inc. Anhydrous solvents were purchased from Aldrich (THF, methanol, toluene, methylene chloride, and chloroform), and all other solvents were purchased from EM Science and used without further purification. High-grade tris(triphenylphosphine)rhodium(I) chloride (99.99%), copper(I) iodide (99.99%), bis(triphenylphosphine)palladium(II) acetate (99%) and palladium(II) acetate (98%) were all obtained from Aldrich. Crotyl ether starting materials were synthesized from known procedures.[4,13]

Preparation of Enol Ether 2 and Allylic Ether 3 via Standard Heck Conditions. A mixture of crotyl ether **1** (30.0 g, 94.0 mmol), potassium carbonate (26.0 g, 188.12 mmol, 2 equiv), and tetra-*n*-butylammonium chloride (13.10 g, 47.14 mmol, 0.5 equiv) in DMF (500 mL) was purged of air with a brisk stream of nitrogen below the medium surface for 20 min prior to addition of palladium(II) acetate (0.495 g, 2.20 mmol, 2.35 mol %) at 17 °C. The mixture was heated to 90 °C for 16 h under nitrogen, cooled to ambient temperature, and filtered over a pad of Celite. The pad was washed with methyl *tert*-butyl ether (MTBE, 300 mL), and the filtrate was sequentially washed with water (3 × 400 mL). The organic layer was dried (sodium sulfate) and concentrated to a dark yellow oil that possessed an *exo*(*Z*):*endo* ratio of 1:7.7 as determined by NMR analysis. The crude sample was vacuum distilled (88−90 °C, 6 Torr) to provide purified enol ether **2** (13.87 g, 72.53 mmol, 77%) as a pale-yellow oil (*exo*:*endo* ratio = 1:10.5).

Preparation of Enol Ether 2 and Allylic Ether 3 with Modified Heck Conditions. A mixture of crotyl ether **1** (228.0 g, 714.40 mmol), potassium carbonate (200.0 g, 1.45 mol, 2.03 equiv), and tetra-*n*-butylammonium chloride (100.0 g, 359.82 mmol, 0.50 equiv) in DMF (3700 mL) was degassed with a brisk stream of nitrogen below the medium surface for 20 min prior to the addition of palladium(II) acetate (3.75 g, 16.70 mmol, 2.34 mol %) and tris(triphenylphosphine)rhodium(I) chloride (5.31 g, 5.74 mmol, 0.80 mol %) at 17 °C. The mixture was heated to 90 °C for 4 h, cooled to 47 °C, and filtered over a pad of Celite. The pad was washed with MTBE (2000 mL) and the filtrate was washed sequentially with water (3 × 2000 mL). The organic layer was dried over sodium sulfate and concentrated to a dark oil that was shown to possess an *exo*(*Z*):*endo* ratio of 1:12.79 by NMR analysis. The crude sample was vacuum distilled (84−97 °C, 6 Torr) to provide purified enol ether **2** (92.84 g, 485.46 mmol, 68%) as a pale-yellow oil that contained an *exo*(Z):*endo* ratio of 1:14.3. Allylic ether **3** was not isolated. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.12 (t, $J = 7.40$ Hz, 3H, $-CH_3$); 2.30 (q, $J = 7.40$ Hz, 2H, $-CH_2-$); 3.94 (s, 3H, $-OCH_3$); 5.04(s, 2H, $-CH_2O-$); 6.54 (s, 1H, olefinic); 6.63 (d, 1H, $J = 5.4$ Hz, aromatic); 8.03 (d, 1H, $J = 5.40$ Hz, aromatic). Anal. Calcd for $C_{11}H_{13}NO_2\cdot 0.15\ H_2O$: C, 68.13; H, 6.91; N, 7.22. Found: C, 68.16; H, 6.94; N, 7.11. Mass spectrum (EI^+): *m/e* 191 (M^+).

Isolation of Allylic Ether 3 (*Z*-isomer). A mixture of the bicyclic ethers (2.20 g, 11.50 mmol; *exo*:*endo* = 1:4) was chromatographed on silica gel 60 that was equilibrated in hexanes. The desired product was eluted with 50% hexanes/dichloromethane to provide pure *exo*cyclic *Z*-isomer (0.067 g, 0.35 mmol, 3%) as a waxy, white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.82 (d, $J = 7.17$ Hz, 3H, $-CH_3$); 3.94 (s, 3H, $-OCH_3$); 4.48 (s, 2H, $-CH_2O-$); 4.68 (s, 2H, $-CH_2-$); 6.33 (q, $J = 7.17$ Hz, $-CH-$); 7.03 (d, $J = 5.62$ Hz, 1H, aromatic); 7.96 (d, $J = 5.62$ Hz, 1H, aromatic). Anal. Calcd for $C_{11}H_{13}NO_2\cdot 0.2\ H_2O$: C, 67.81; H, 6.93; N, 7.19. Found: C, 67.80; H, 6.78; N, 7.22. Mass spectrum (EI^+); *m/e* 191 (M^+); 176 ($M - CH_3$); 162 ($M - CH_2CH_3$). The stereochemistry of this purified material was confirmed to be the *Z*-isomer by 1DNOEDIFF experiments. A separate fraction (0.208 g) was collected that contained both *E*- and *Z*-isomers in a ratio of 1:2.7. ^{1}H NMR ($CDCl_3$, 300 MHz, *E*-isomer): δ 2.04 (d, $J = 7.35$ Hz, 3H, $-CH_3$); 3.95 (s, 3H, $-OCH_3$); 4.21 (s, 2H, $-CH_2O-$); 4.75 (s, 2H, $-CH_2O-$); 5.85, (q, $J = 7.35$ Hz, 1H, olefinic); 7.08 (d, $J = 5.54$ Hz, 1H, aromatic); 8.04 (d, $J = 5.54$ Hz, 1H, aromatic).

Isomerization of Allylic Ether 3 to Enol Ether 2 with Iron Pentacarbonyl. A mixture of the bicyclic ethers (0.40 g, 2.09 mmol, *exo*(*Z*):*endo* = 1:2.3) in *n*-propanol (6 mL) was purged of air with a brisk stream of nitrogen below the medium surface for 20 min prior to the addition of iron pentacarbonyl (0.16 g, 0.08 mmol, 3.83 mol %). The solution was heated to reflux for 10 h under a nitrogen atmosphere, filtered over a pad of Celite, and concentrated to a dark oil (0.39 g, 2.04 mmol, 98%) by a stream of nitrogen pressure; at that time, NMR analysis showed an *exo*(*Z*):*endo* ratio of 1:9.4.

Isomerization of Allylic Ether 3 to Enol Ether 2 with Iron Pentacarbonyl/Potassium Carbonate. A mixture of the bicyclic ethers (0.4 g, 2.09 mmol, *exo*(*Z*):*endo* = 1:2.3) and potassium carbonate (0.5 g, 3.62 mmol, 1.73 equiv) in *n*-propanol (6 mL) was purged of air with a brisk stream of nitrogen below the medium surface for 20 min prior to the addition of iron pentacarbonyl (0.16 g, 0.08 mmol, 3.83 mol %). The solution was heated to reflux for 3 h under a nitrogen atmosphere, diluted with chloroform (2 mL), and then filtered over a pad of Celite. The resultant solution was concentrated to a dark oil (0.35 g, 88%) by a stream of nitrogen pressure; at that time, NMR analysis showed an *exo*(*Z*):*endo* ratio of 1:13.6.

Isomerization of Allylic Ether 3 to Enol Ether 2 with Collman's Reagent. A mixture of the bicyclic ethers (0.4 g, 2.09 mmol; *exo*(*Z*):*endo* = 1:2.3) was placed in a nitrogen bag and treated with disodium tetracarbonylferrate·1.5 dioxane (0.04 g, 0.084 mmol, 4 mol %). The mixture was treated with degassed *n*-propanol (6 mL) via syringe, and the contents were heated to reflux for 3 h, diluted with chloroform (5 mL), and filtered over a pad of Celite. The resultant solution was concentrated to a dark oil (0.33 g, 82%) by a stream of nitrogen pressure; at that time, NMR analysis showed an *exo*(*Z*):*endo* ratio of 1:13.7.

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Supporting Information Available: Copies of NMR spectra and additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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