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Features and Applications of $[Rh(CO)_2Cl]_2$-Catalyzed Alkylations of Unsymmetrical Allylic Substrates

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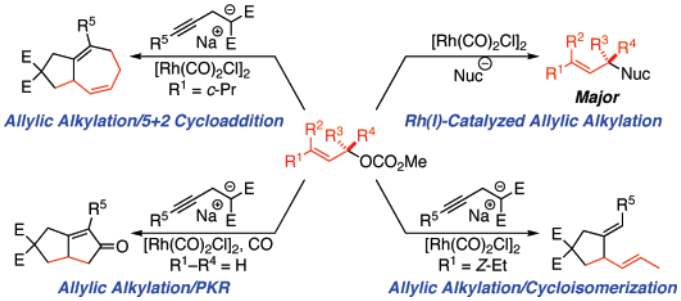

A novel regio- and stereoselective $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of unsymmetrical allylic carbonates was discovered. The regioselectivity of the reaction favors product ratios in which substitution occurs at the carbon bearing the leaving group. When an enantiomerically enriched carbonate (≥99% ee) was examined, the Rh(I)-catalyzed allylic alkylation proceeded stereoselectively to provide the alkylation product with retention of absolute stereochemistry (98% ee). To establish the scope of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation, a variety of carbon and heteroatom nucleophiles were examined and the results described. As an application of the Rh(I)-catalyzed allylic alkylation, a series of novel domino reactions have been developed that couple the unique regio- and stereoselective $[Rh(CO)_2Cl]_2$-catalyzed alkylation of allylic trifluoroacetates with an intramolecular Pauson−Khand annulation, a cycloisomerization, or a [5+2] cycloaddition. A unique aspect of the method described is the use of a *single* catalyst to effect sequential transformations in which the catalytic activity is moderated simply by controlling the reaction temperature. Implementation of such processes provides a rapid and efficient entry to a variety of bicyclic carbon skeletons from simple precursors.

Introduction

Transition metal-catalyzed allylic alkylations have had considerable impact on organic synthesis, and such transformations have been widely studied and applied since their discovery in the mid-1970's.[1] Indeed, such reactions are arguably some of the most versatile processes in organic chemistry as a wide range of allylic and nucleophilic reaction partners may be efficiently combined by using a variety of transition metal catalysts to form products in a highly regiospecific and stereospecific manner. The factors governing the regiochemical and stereochemical outcomes in transformations involving symmetrical and unsymmetrical allylic substrates have been explored extensively revealing a number of general trends. For example, palladium-catalyzed processes typically favor nucleophilic substitution at the sterically less hindered allylic terminus, irrespective of the structure of the starting materials (e.g., **1** or **2**), to yield substitution products **3**,[1a,2] whereas Ru,[3] Mo,[4] Rh,[5,6] Ir,[7,8] and W[9] preferentially deliver products **4** arising from substitution

(1) (a) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. (b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (c) Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Heidelberg, Germany, 1980. (d) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, UK, 1982; Vol. 8, pp 799. (e) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (f) Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 4, p 585. (g) Tsuji, J. *Palladium Reagents and Catalysts*: *Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995; p 1. (h) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (i) Trost, B. M.; Heumann, A. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 1, p 3. (j) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

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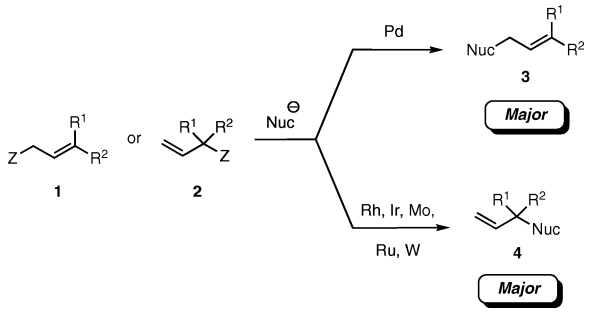
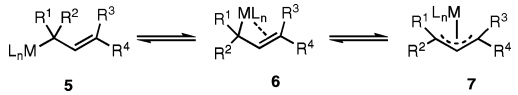
SCHEME 1



at the more substituted allylic terminus regardless of whether **1** or **2** is the starting material (Scheme 1).[1c,5,10]

Transition metal-catalyzed nucleophilic substitutions of allylic substrates are believed to proceed via metal-stabilized π-allyl intermediates. The structure of such intermediates can vary along the continuum between the η^1-allyl complex **5**, the enyl ($\sigma+\pi$)-complex **6**, and the η^3-allyl complex **7** depending upon the metal, its ligands, and the nature of the substituents R^1−R^4 (Scheme 2).[1h,5a] The regioselectivity of the ensuing nucleophilic

SCHEME 2

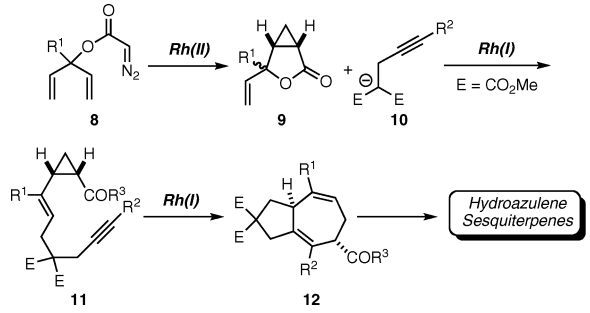


attack is therefore dictated by a combination of steric and electronic factors that vary with the intermediate complex and the nucleophile.[11] However, it is generally possible to selectively prepare either **3** or **4** through a judicious selection of catalyst and allylic substrate **1** or **2**. However, examination of the prior art reveals that no *single* catalyst enables allylic substitution at the carbon atom bearing the leaving group, such that the starting material structure may map directly onto the structure of the major product, a situation that might prove advantageous in certain circumstances. It was thus with some excitement that we recently discovered [Rh(CO)$_2$Cl]$_2$ catalyzes the allylic alkylation of unsymmetrical allylic substrates with excellent regio- and stereoselectivity to provide products arising from substitution at the carbon atom bearing the leaving group, irrespective of the structure of the starting carbonate. Herein we report the details of these findings, together with their application to the design of novel cascade reactions.[12]

Results and Discussion

Background to the Discovery. In the context of developing concise strategies for the syntheses of hydroazulene sesquiterpenes, we were intrigued by the observation that the cyclopropanations of divinyl diazoesters **8** to provide lactones **9**[13] and the [5+2] cycloadditions of enynes of the general structure **11** to yield bicyclo[5.3.0]decanes **12**[14] were both rhodium-catalyzed processes (Scheme 3). It occurred to us that if the allylic alkylation of **9** with malonate **10** could also be rhodium-catalyzed, a novel cascade of reactions might be devised that would rapidly transform structurally simple diallylic diazoesters into complex hydroazulenes. Although Evans had previously shown that allylic substitutions could in fact be promoted by a modified Wilkinson's catalyst, the major products of such transformations resulted from nucleophilic attack at the *more* substituted terminus of the allylic moiety.[6b] Literature precedent thus argued persuasively that the regiochemical outcome of an allylic alkylation involving **9** and **10** would be opposite of that which we required. However, if a rhodium(I) catalyst were capable of catalyzing the conversion of **9** to **11**, the possibility of inducing a subsequent intramolecular [5+2] cycloaddition in situ was simply too attractive to ignore. Initial experiments were thus conducted to assess the viability of this novel approach to hydroazulenes.

SCHEME 3



Inasmuch as our primary interest was to gain access to cyclopropyl enynes related to **11**, we conducted preliminary experiments in which the vinyl cyclopropyl lactone **13** was treated with the substituted malonate anion **14** in the presence of RhCl(PPh$_3$)$_3$/P(OMe)$_3$ (eq 1).[6b] However, these initial efforts failed to yield any alkylation product, even after extended

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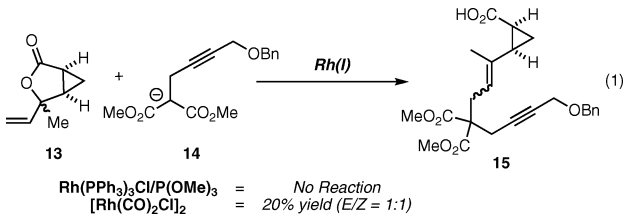
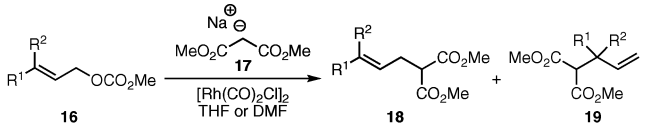


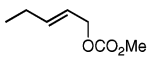
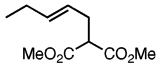
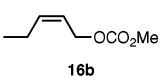
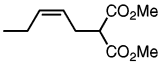
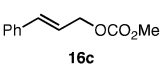
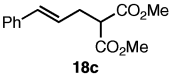
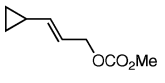
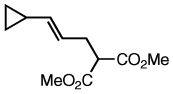
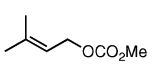
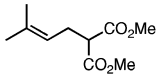
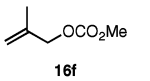
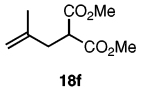
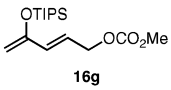
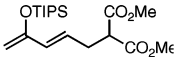
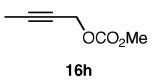
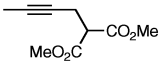
reaction times and elevated temperatures. Because the dimeric rhodium(I) catalyst $[Rh(CO)_2Cl]_2$ was known to catalyze the intramolecular [5+2] cycloadditions of cyclopropyl enynes,[14a] we queried if perchance it might also induce allylic alkylations. To address this question, a preliminary experiment was conducted in which **13** and **14** were combined in the presence of $[Rh(CO)_2Cl]_2$ to afford an *E*/*Z*-mixture (1:1) of **15** as the only isolable product, albeit in 20% yield. This was an exciting and important discovery that demonstrated the heretofore unknown ability of $[Rh(CO)_2Cl]_2$ to catalyze allylic alkylations. Equally intriguing was the observation that this reaction of an unsymmetrical substrate proceeded with a regioselectivity *opposite* that anticipated based upon considering examples found in the literature.[4] This fortuitous result prompted us to explore the scope of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations with more traditional substrates such as allylic acetates and carbonates.

Reactions of Unsubstituted Malonates. In an initial series of experiments, we examined the reactions of unsymmetrical primary allylic carbonates **16a**−**h** as well as secondary and tertiary allylic carbonates **20a**−**l** with sodiodimethyl malonate (**17**) (Tables 1 and 2). Dimethyl malonate was chosen as the nucleophilic partner in these preliminary experiments due to its ready availability and ease of handling. However, a variety of other nucleophiles proved to be viable partners in the substitution reaction vida infra. We never observed bis-alkylation products, a common and undesired byproduct in non-transition metal-catalyzed S_N2 reactions involving dimethyl malonate. The corresponding allylic acetates were also found to be reactive toward alkylation in the presence of $[Rh(CO)_2Cl]_2$. However, compared to the corresponding allylic carbonates, the allylic acetates required longer reaction times and provided the substitution products in slightly diminished yields. In our initial studies, we thus employed a methyl carbonate as the leaving group to examine regio- and stereochemical trends in $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions.

Before embarking on an extensive examination of the scope and limitations of $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations, the various reaction parameters were optimized for the reaction of **16a** with the sodium salt of dimethyl malonate (**17**). This reaction was highly regioselective, providing a mixture of the alkylation products **18a** and **19a** in a 97:3 ratio. We first conducted experiments to ascertain what solvent(s) would be preferred and found that the allylic alkylation of **16a** with **17** proceeded in good yields when DMF, THF, MeCN, or Et_2O was used as solvent. However, the reactions in DMF and THF were much faster (1−2 h at room temperature) than those in MeCN and Et_2O (∼12 h at room temperature); reactions in MeCN and Et_2O were also less efficient, proceeding in 10−15% lower yields. Reactions proceeded readily at concentrations ranging from 0.01 to 0.1 M, and were generally performed at 0.1 M. Initial alkylations were conducted with 10 mol % of the $[Rh(CO)_2Cl]_2$ dimer, but we found that lowering the catalyst loading to 5 mol % did not adversely affect the efficiency of the reaction, although the reaction was slightly slower, requiring an additional 30−45 min to completely consume **16a**. When the catalyst loading was decreased to 1−2 mol %, yields of alkylated product dropped to less than 20%. Although the reactions proceeded with equal quantities of allylic substrate and nucleophile, we found that the use of 2.5 equiv of dimethyl malonate and 2.0 equiv of NaH as base was generally a good starting point for further optimizations.

TABLE 1. $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Unsymmetrical Primary Carbonates[a]

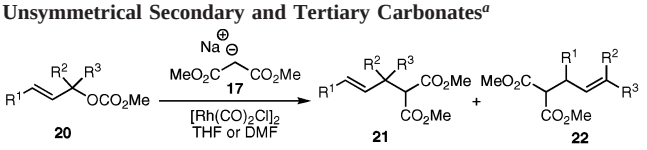


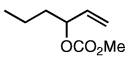
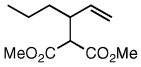
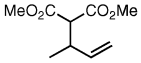
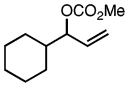
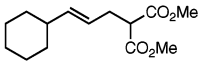
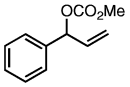
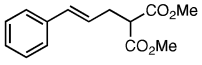
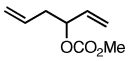
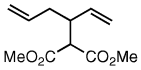
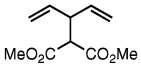
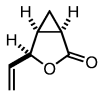
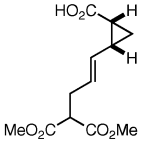
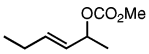
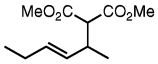
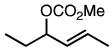
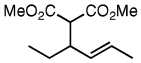
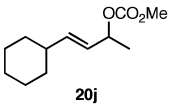
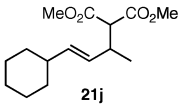
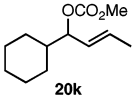
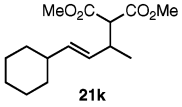
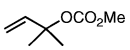
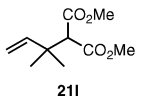
Entry	Substrate	Major Product	Yield (%)[b]	18:19[c]
1[d]	 16a	 18a	84	97:3
2[e]	 16b	 18b	86	99:1 (97:3)[h]
3[e]	 16c	 18c	93	90:10
4[e]	 16d	 18d	84	89:11
5[f]	 16e	 18e	75	92:8
6[g]	 16f	 18f	71	–
7[g]	 16g	 18g	94	97:3
8[e]	 16h	 18h	52	99:1

[a] Conditions: 5 mol % of $[Rh(CO)_2Cl]_2$, 2.5 equiv of $CH_2(CO_2Me)_2$, 2.0 equiv of NaH, 0.1 M in carbonate. [b] Isolated yields. [c] Ratios determined by GLC. [d] THF, rt. [e] THF, 0 °C. [f] DMF, −20 °C. [g] DMF, rt. [h] Ratio of *cis*/*trans* isomers.

Having established the essential parameters for the reaction, we conducted a series of studies to explore the scope and regioselectivity of the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations of different allylic substrates, and these results are summarized in Table 1. The reactions were typically performed by treating the allylic substrate (1.0 equiv; 0.1 M) with dimethyl malonate (2.5 equiv) and NaH (2. 0 equiv) in the presence of 5 mol % of $[Rh(CO)_2Cl]_2$ in THF. However, if the reaction was sluggish or proceeded with modest selectivity, DMF was used as the solvent. The temperature was varied so that the reactions were completed in a reasonable period of time.

TABLE 2. [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Alkylation of Unsymmetrical Secondary and Tertiary Carbonates[a]



Entry	Substrate	Major Product	Yield (%)[b]	21:22[c]
1[d]	 **20a**	 **21a**	80	60:40
2[e]	 **20b**	 **21b**	75	80:20 (59:41)[d]
3[d]	 **20c**	 **21c**	97	79:21
4[d]	 **20d**	 **21d**	93	80:20 (50:50)[e]
5[f]	 **20e**	 **21e**	89	91:9
6[f,h]	 **20f**	 **21f**	74	96:4
7[d]	 **20g**	 **21g**	93	100:0
8[g]	 **20h**	 **21h**	88	96:4 (76:24)[d]
9[e]	 **20i**	 **21i**	73	69:31 (45:55)[d]
10[f]	 **20j**	 **21j**	94	93:7
11[g]	 **20k**	 **21k**	94	93:7
12[g]	 **20l**	 **21l**	80	94:6

[a] Conditions: 5 mol % of [Rh(CO)$_2$Cl]$_2$, 2.5 equiv of CH$_2$(CO$_2$Me)$_2$, 2.0 equiv of NaH, 0.1 M in carbonate. [b] Isolated yields. [c] Ratios determined by GLC. [d] THF, rt. [e] DMF, −20 °C. [f] THF, 0 °C. [g] DMF, 0 °C. [h] The corresponding carbonate was unstable.

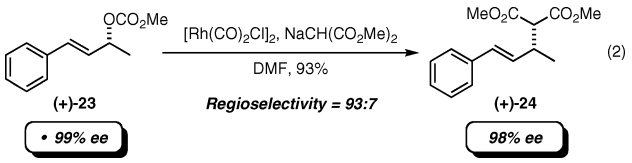
Examination of the entries in Table 1 reveals a number of important findings. Perhaps most striking is that primary allylic carbonates having di- and trisubstituted carbon−carbon double bonds provided linear alkylation products with generally >9:1 regioselectivity, even when the other terminus of the allylic moiety is benzylic (entry 3). This mode of reactivity resembles that normally observed with palladium catalysts,[1j] not rhodium,[5,6] iridium,[7,8] molybdenum,[4] or ruthenium[3] catalysts, although there are isolated reports of similar regioselectivities for some rhodium[5a] and iridium[8] catalysts. Indeed, that **16e** (Entry 5) underwent *any* alkylation is noteworthy because 2,3,3-trisubstituted allylic carbonates are inert to the modified Wilkinson's catalyst reported by Evans and typically require forcing conditions when other transition metal catalysts are used.[5a,15] The observation that the *Z*-carbonate **16b** (entry 2) underwent alkylation with little carbon−carbon double bond isomerization is noteworthy because extensive *Z*/*E* isomerization of *Z*-allylic substrates normally occurs when other transition metal catalysts are used, although there are some exceptions involving iridium,[8,10b,16] palladium,[17] and tungsten[18] catalysts. The temperature and solvent played critical roles in maintaining the *Z*-double bond geometry. For example, the *Z*/*E*-ratio fell to 86:13 when the reaction was conducted in THF at room temperature instead of 0 °C. If the reaction was run in DMF at temperatures even as low as −20 °C, the *E*-isomer was obtained as the major product (>60:40). Finally, the presence of conjugated enol ethers did not adversely affect the regiochemistry or efficiency of the reaction (entry 7), and propargylic carbonates underwent substitution to give substituted alkynes that were not contaminated with allenic products commonly observed in palladium-catalyzed substitutions (entry 8).[19]

Secondary and tertiary allylic carbonates were found to be excellent substrates in [Rh(CO)$_2$Cl]$_2$-catalyzed allylic alkylations, but substitution patterns influenced the regioselectivity of the reaction to a greater extent than observed with primary allylic carbonates (Table 2). For example, reactions of carbonates and carboxylates derived from linear allylic carbinols tended to give products resulting from substitution at the secondary carbon atom bearing the leaving group, although the preference was sometimes modest (entries 1, 2, 5, 6, 8, and 9). Conversely, when the substituent attached to one terminus of the allylic moiety was branched, carbon−carbon bond formation occurred preferentially at the sterically less congested terminus (entries 3, 4, 7, 10, and 11). Comparing the results of entries 9 and 11 suggests that branching on the carbon atom *attached* to the allyl moiety may be a more important controlling factor than branching on a carbon atom contained *within* the allylic array. Further support for this hypothesis is found in entry 12. Namely, alkylation of the tertiary allylic carbonate **20l** occurred at the carbon atom bearing the leaving group even though a quaternary center was generated in the process. In those cases examined, changing solvent from THF to DMF and lowering the reaction temperature sometimes led to modest increases in the observed regioselectivity favoring alkylation of the carbon atom bearing

(15) (a) Takahashi, T.; Nemoto, H.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2005. (b) Trost, B. M.; Lautens, M.; Chan, C.; Jebaratnam, J.; Mueller, T. *J. Am. Chem. Soc.* **1991**, *113*, 636.
(16) Takeuchi, R. *Polyhedron* **2000**, *19*, 557.
(17) (a) Huntzinger, M. W.; Oehlschlager, A. C. *J. Org. Chem.* **1991**, *56*, 2918. (b) Sjogren, M. P. T.; Hansson, S.; Akermark, B. *Organometallics* **1994**, *13*, 1963. (c) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802.
(18) Frisell, H.; Akermark, B. *Organometallics* **1995**, *14*, 561.
(19) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006.

the leaving group (entries 2, 4, 8, and 9). Interestingly, alkylations of substrates bearing additional double bonds are highly regioselective (entries 5 and 6), even when the alternate mode of reaction would generate a conjugated product. Such selectivity is not without precedent as it has been observed that pendant olefins can direct the regiochemistry of transition metal-catalyzed allylic alkylation reactions, presumably via a weak coordination of the carbon−carbon double bond to the metal.[20]

Stereochemistry of $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Substitutions. To determine the stereochemical outcome of $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions with malonate nucleophiles, enantioenriched allylic carbonate (+)-**23** was synthesized in ≥99% ee in three steps from cinnamaldehyde via Sharpless kinetic resolution of the intermediate allylic alcohol.[21] When allylic carbonate (+)-**23** was treated with the sodium salt of dimethyl malonate in the presence of $[Rh(CO)_2Cl]_2$, malonate (+)-**24** was obtained in 93% yield and 98% ee (regioselectivity = 93:7) (eq 2). On the basis of this experiment, $[Rh(CO)_2Cl]_2$ appears to catalyze substitutions of secondary allylic carbonates with net retention of configuration as has been observed with Pd,[1g,h,j] Ru,[3c] Mo,[22] Rh,[5a] and Ir[10b] catalysts.

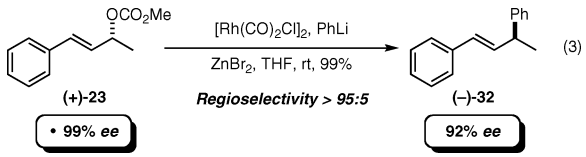


(2)

Reactions of Substituted Malonates. In accord with our plan of developing approaches toward hydroazulene sesquiterpenes and other cyclic ring systems, we initiated a brief survey of $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations in which substituted malonates were employed as nucleophiles. These studies, which are summarized in Table 3, were focused on the homopropargyl malonates **25a** (R^5 = 2-butyn-1-yl) and **25b** (R^5 = propynyl) because the 1,6-enynes that would be formed as products were known to be substrates for a variety of transition metal-catalyzed reactions, including Pauson−Khand annulations,[23] cycloisomerizations,[24] and ring-closing metatheses.[25] Additionally, malonate **25c** (R^5 = *n*-Bu) was employed to examine what effect an alkyl chain lacking a coordinating alkyne moiety would have on the alkylation. The yields in these reactions were generally excellent, again providing the substitution product arising from nucleophilic substitution at the carbon atom bearing the carbonate group with excellent regioselectively. This regiochemical trend persisted even in cases when two adjacent quaternary carbon centers were generated (entries 8 and 10). It is again noteworthy that the substitution reaction of the *Z*-carbonate **16b** (entry 2) with **25a** proceeded regioselectively to furnish enyne **26b** with minimal olefin isomerization. Inasmuch as rhodium(I) catalysts are known to interact in a nonproductive fashion with terminal acetylenes,[26] it is significant that reactions involving **25b** are efficient.

Other Carbon Nucleophiles. The anions derived from β-ketoesters and α-sulfonyl esters such as **28** and **29** were also found to be competent nucleophiles in the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation (Table 4). The regiochemical trends in these reactions parallel those with malonate nucleophiles in which the predominant product arises from substitution at the carbon bearing the leaving group, even when contiguous quaternary centers are formed (entry 3).

We were also intrigued by the possibility that $[Rh(CO)_2Cl]_2$ might catalyze allylic substitutions of *unstabilized* carbon nucleophiles. This inquiry was inspired in part by Evans, who reported that allylic hexafluoroisopropyl carbonates underwent regio- and stereoselective alkylation upon treatment with aryl zinc reagents in the presence of $TpRh(C_2H_4)_2$, LiBr, and dibenzylidene acetone.[27] We were thus pleased to find that when enantioenriched methyl carbonate (+)-**23** (≥99% ee) was simply treated with a premixed solution of PhLi and $ZnBr_2$ in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %), the arylated product (−)-**32** was obtained in 99% yield (eq 3). Notably, the reaction



(3)

proceeded with >95:5 regioselectivity without significant loss of enantiopurity (92% ee). Comparison of the optical rotation of (−)-**32** with the literature data showed that the reaction proceeded with an overall net *inversion* of absolute configuration, an outcome consistent with nucleophilic attack of the aryl zinc reagent on the allyl metal center followed by reductive elimination.[28]

Allylic Alkylations of Oxygen and Nitrogen Nucleophiles. Transition metal-catalyzed allylic etherifications and aminations are well-known although the former are less commonly encountered in target directed synthesis.[7,29] The regioselectivities of these reactions vary with the nature of the transition metal complex, but the general trends are similar to those observed with carbon nucleophiles.[30] For example, palladium-catalyzed reactions of alcohol and amine nucleophiles tend to give products arising from substitution at the less sterically hindered allylic terminus,[30b] although this selectivity can be reversed when C_2-symmetric ligands are used to yield products in enantioselective processes.[30d] Rhodium and iridium catalysts typically

(20) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 9174.
(21) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981.
(22) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469. (b) Dvorak, D.; Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1995**, *117*, 6130. (c) Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 702.
(23) (a) Jeong, N.; Lee, S.; Sung, B. K. *Organometallics* **1998**, *17*, 3642. (b) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (c) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771. (d) Park, K. H.; Son, S. U.; Chung, Y. K. *Tetrahedron Lett.* **2003**, *44*, 2827. (e) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.
(24) (a) Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490. (b) Kobayashi, T.; Koga, Y.; Narasaka, K. *J. Organomet. Chem.* **2001**, *624*, 73. (c) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601.
(25) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.
(26) Wender, P. A.; Sperandio, D. *J. Org. Chem.* **1998**, *63*, 4164.
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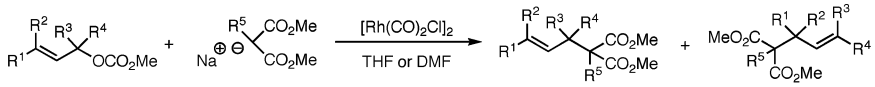
(28) (a) Matsushita, H.; Negishi, E.-i. *J. Chem. Soc., Chem. Commun.* **1982**, 160. (b) Fiaud, J. C.; Legros, J. Y. *J. Org. Chem.* **1987**, *52*, 1907.
(29) (a) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303. (b) Negishi, E.-i. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley: New York, 2002; Vol. 2, p 1845.
(30) (a) Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964. (b) Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, *50*, 3558. (c) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474. (d) Trost, B. M.; McEachern, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 12702. (e) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1998**, *29*, 2931.

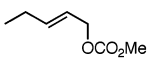
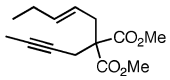
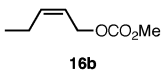
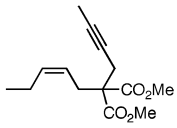
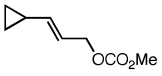
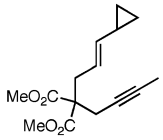
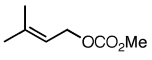
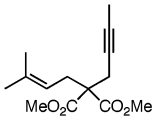
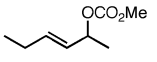
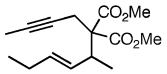
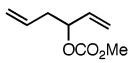
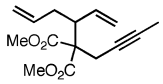
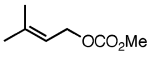
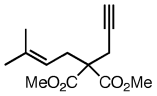
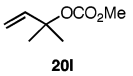
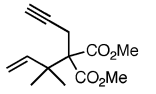
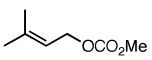
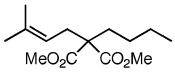
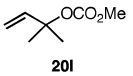
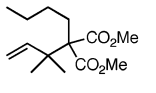
TABLE 3. Regioselectivity in the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Alkylation of Unsymmetrical Allylic Carbonates Utilizing α-Substituted Malonate Nucleophiles[a]



16: R^3, R^4 = H
20: R^2 = H

25a: R^5 = CH$_2$C≡CMe
25b: R^5 = CH$_2$C≡CH
25c: R^5 = *n*-Bu

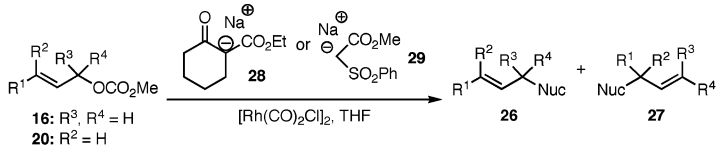
26 **27**

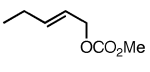
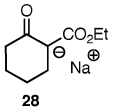
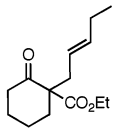
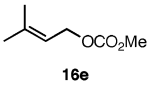
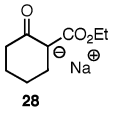
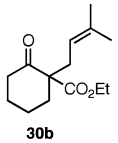
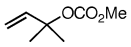
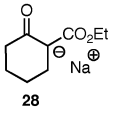
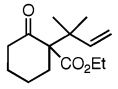
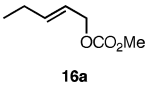
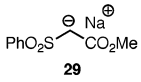
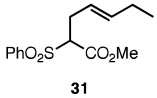
Entry	Substrate	Nucleophile	Major Product	Yield (%)[b]	**26:27**[c]
1[d]	 **16a**	**25a**	 **26a**	95	94:6
2[e]	 **16b**	**25a**	 **26b**	98	100:0 (88:12)[g]
3[d]	 **16d**	**25a**	 **26c**	98	>95:5
4[f]	 **16e**	**25a**	 **26d**	85	99:1
5[f]	 **20h**	**25a**	 **26e**	88	93:7
6	 **20e**	**25a**	 **26f**	74	67:33
7[f]	 **16e**	**25b**	 **26g**	70	99:1
8[f]	 **20l**	**25b**	 **26h**	98	88:12
9[f]	 **16e**	**25c**	 **26i**	88	95:5
10[f]	 **20l**	**25c**	 **26j**	62	93:7

[a] Conditions: 10 mol % of [Rh(CO)$_2$Cl]$_2$, 1.5 equiv of malonate **24**, 1.4 equiv of NaH, 0.1 M in carbonate. [b] Isolated yields. [c] Ratios determined by GLC or ^{1}H NMR (400 MHz). [d] THF, rt. [e] THF, −20 °C. [f] DMF, −20 °C. [g] Ratio of *cis/trans* isomers.

lead to the formation of the more highly substituted alkylation products.[31] There is no transition metal catalyst that reliably promotes allylic substitutions with oxygen or nitrogen nucleophiles so that the structure of the product maps directly onto the starting material. It was thus a logical extension of our studies of carbon nucleophiles to determine the regioselectivity of [Rh(CO)$_2$Cl]$_2$-catalyzed alkylations of selected oxygen and nitrogen nucleophiles (Table 5).

TABLE 4. Regioselectivity in the $[Rh(CO)_2Cl]_2$-Catalyzed Allylic Alkylation of Unsymmetrical Allylic Carbonates Utilizing Other Enolates[a]



Entry	Substrate	Nucleophile	Major Product	Yield (%)[b]	26:27[c]
1	 **16a**	 **28**	 **30a**	98	95:5
2	 **16e**	 **28**	 **30b**	86	99:1
3	 **20l**	 **28**	 **30c**	74	90:10
4	 **16a**	 **29**	 **31**	75	99:1

[a] Conditions: 10 mol % of $[Rh(CO)_2Cl]_2$, 1.5 equiv of nucleophile, 1.4 equiv of NaH, 0.1 M in carbonate, THF, rt. [b] Isolated yields. [c] Ratios determined by GLC.

Phenols have been found to be excellent coupling partners in transition metal-catalyzed etherifications.[32] Consequently, we first examined the $[Rh(CO)_2Cl]_2$-catalyzed reaction of carbonate **16a** with the phenoxide ion generated from **33** by deprotonation with LiHMDS or Et_2Zn,[33] but little of the desired ether was formed. Following the lead of Evans[31b,c] and Hartwig,[31d] we discovered that copper(I) phenoxides were excellent nucleophiles, and *O*-allylated phenols were obtained in good to excellent yields and regioselectivities when primary and secondary disubstituted *E*-allylic carbonates were employed as substrates (Table 5, entries 1−3). On the other hand, the more highly substituted carbonates such as **16e** and **20l** were less reactive with no appreciable product formation observed after 24 h at room temperature. We also found that $[Rh(CO)_2Cl]_2$-catalyzed substitutions of primary allenic substrates as illustrated by the efficient and regioselective coupling of carbonate **16i** with phenoxide **33** (entry 4). Although only exploratory experiments were conducted, we were unable to induce allylations of lithium or copper alkoxides derived from secondary alcohols.

Inasmuch as allylic amines are important synthetic intermediates, we then queried whether $[Rh(CO)_2Cl]_2$ would catalyze alkylations of sulfonamide salts or secondary amines. Gratifyingly, we discovered that **16a** underwent facile reaction with the lithium salts **33c** and **33d** with good regioselectivity (entries 5 and 6). In preliminary experiments the corresponding reactions of the secondary carbonate **20h** with the salts of secondary sulfonamides were found to be low yielding. Initial attempts to induce the $[Rh(CO)_2Cl]_2$-catalyzed allylation of secondary amines were unsuccessful, and the starting allylic carbonates were recovered in near-quantitative yield. In thinking about what modifications to the procedure we might explore, we were inspired to examine the use of iodide ion as an additive based upon reports of Lautens,[34,3535] who has proposed that exchanging the bridging chloride ion of $[Rh(CO)_2Cl]_2$ with an iodide ion generates a more stable Rh(I)−I complex that is less prone to react with an amine nucleophile to give an unreactive complex. In this event, we discovered that allylic aminations with pyrrolidine and methylbenzylamine as nucleophiles proceeded readily and efficiently at room temperature in the presence of tetrabutylammonium iodide (TBAI) (20 mol %) (entries 7−10). The regioselectivity of the process was invariably excellent, but dependent upon the nature of the starting allylic substrate. Namely, the preferred product generally arose from nucleophilic substitution at the carbon bearing the carbonate moiety (entries 6−8); however, amination of the dimethallyl substrate **16e** proceeded with the opposite regioselectivity (entry 10). The allenic carbonate **16i** also proved to be an excellent coupling partner for allylic aminations, giving a nearly quantitative yield of **34j** with excellent regioselectivity (entry 11). The application

(31) (a) Takeuchi, R.; Ue, N.; Tanabe, K.; Yamashita, K.; Shiga, N. *J. Am. Chem. Soc.* **2001**, *123*, 9525. (b) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882. (c) Evans, P. A.; Leahy, D. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4788. (d) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794.

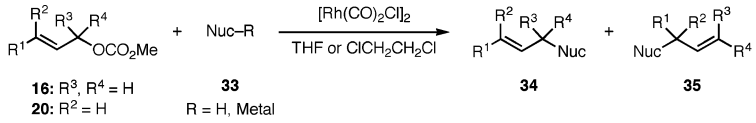
(32) Takacs, J. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: New York, 1995; Vol. 12, p 814.

(33) Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369.

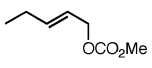
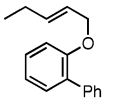
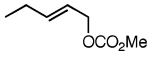
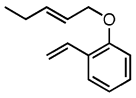
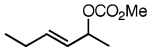
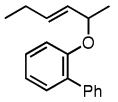
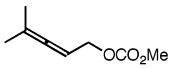
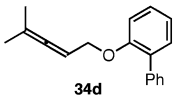
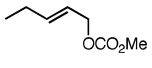
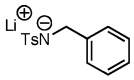
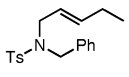
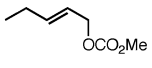
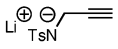
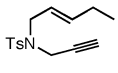
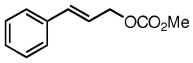
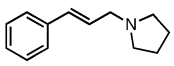
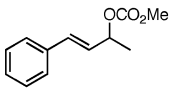
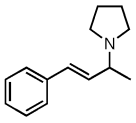
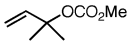
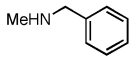
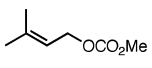
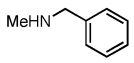
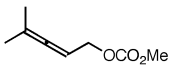
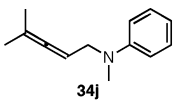
(34) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884.

(35) (a) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755. (b) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

TABLE 5. Regioselectivity in the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Alkylation of Oxygen and Nitrogen Nucleophiles with Unsymmetrical Allylic Carbonates[a]

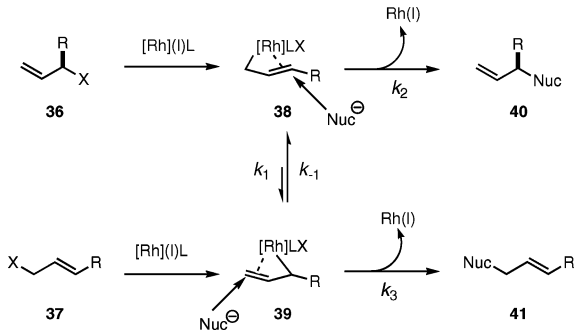


16: R^3, R^4 = H; **20:** R^2 = H — **33** R = H, Metal — **34** — **35**

Entry	Substrate	Nucleophile	Major Product	Yield (%)[b]	**34:35**[c]
1[d]	 **16a**	 **33a**	 **34a**	84	92:8
2[d]	 **16a**	 **33b**	 **34b**	77	>95:5
3[d]	 **20h**	 **33a**	 **34c**	87	71:29
4[d]	 **16i**	 **33a**	 **34d**	75	>95:5
5[e]	 **16a**	 **33c**	 **34e**	78	90:10
6[e]	 **16a**	 **33d**	 **34f**	42	88:12
7[f]	 **16c**	 **33e**	 **34g**	96	>95:5
8[f]	 **(±)-23**	 **33e**	 **34h**	99	>95:5
9[f]	 **20l**	 **33f**	 **34i**	89	>95:5
10[f]	 **16e**	 **33f**	 **34i**	85	>95:5
11[f]	 **16i**	 **33g**	 **34j**	99	>95:5

[a] Conditions: 10 mol % of [Rh(CO)$_2$Cl]$_2$, 2.0 equiv of nucleophile, 0.1 M in carbonate. [b] Isolated yields. [c] Ratios determined by GLC. [d] LiHMDS (1.0 M in THF), CuI, THF, rt. [e] LiHMDS (1.0 M in THF), THF, rt. [f] TBAI (20 mol %), DCE, rt.

SCHEME 4



of this Rh(I)-catalyzed allylic amination reaction could find utility in the synthesis of complex alkaloid natural products, and we are currently exploring several such applications, the results of which will be reported in due course.

Mechanistic Considerations. These investigations show that $[Rh(CO)_2Cl]_2$-catalyzed alkylations of carbon-, oxygen-, and nitrogen-based nucleophiles with unsymmetrical allylic substrates are unique. No other transition metal catalyst has been reported to catalyze these reactions regioselectively to give products arising predominantly from new bond formation at the allylic carbon atom bearing the leaving group, irrespective of the structure of the allylic starting material. The structure of the starting material thus maps directly onto that of the product in the majority of $[Rh(CO)_2Cl]_2$-catalyzed alkylations we have studied. This phenomenon may be regarded as a type of "memory effect", but it is distinctly different from the classical examples involving palladium-catalyzed allylic alkylations of enantioenriched and racemic secondary allylic substrates having the *same* number of substituents on the allyl moiety.[36] Of course, the observed regiochemical trend in these $[Rh(CO)_2Cl]_2$-catalyzed allylations is not *completely* independent of allylic substitution as steric effects do seem to play a role in certain situations, especially in the case of secondary substrates. In this context, it is noteworthy that Evans has observed a similar memory effect in several symmetrically substituted systems involving carbon-based nucleophiles using a $RhCl(PPh_3)_3$/$P(OPh)_3$ complex.[5a]

Mechanistic studies must be conducted to understand the origin of the regioselectivity in $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylations and why it differs from analogous reactions promoted by other transition metal catalysts. However, one can set forth some general hypotheses if one accepts the mechanism proposed by Evans for allylic alkylations catalyzed by modified Wilkinson's catalysts (Scheme 4) as being applicable to our results.[5a] Oxidative additions of a rhodium(I) complex to simple allylic substrates of the general types **36** and **37** are thus envisioned to generate the corresponding enyl ($\sigma+\pi$) intermediates **38** and **39** that then undergo nucleophilic attack to generate the observed products **40** and **41**, respectively. Inasmuch as Evans found that the branched isomers **40** were generally found to be the favored products irrespective of the substitution of the allylic substrate, he proposed that the equilibrium between **38** and **39** favored the former.

Accepting the general mechanistic features outlined in Scheme 4, it follows that if equilibration of the enyl intermediates **38** and **39** is slow relative to nucleophilic attack, then the structure of the preferred product will correlate more closely with the substitution pattern in the starting material. The relative stabilities of enyl intermediates **38** and **39**, the rates of their equilibration (k_1 and k_{-1}), and the relative rates of nucleophilic attack on these complexes (k_2 and k_3) will be dictated by a combination of steric and electronic effects. Although predicting how the interplay of these factors influences the regioselectivity of the allylic alkylation is a complex matter, a few observations may be made. The modified Wilkinson's catalysts used by Evans have phosphite ligands that are more electron donating than the CO ligands in the $[Rh(CO)_2Cl]_2$ complex, so the metal center in the latter complex is more electron deficient.[37] Since we find that $[Rh(CO)_2Cl]_2$-catalyzed reactions preferentially furnish products in which the nucleophile becomes bonded to the allylic carbon atom bearing the leaving group, increasing the Lewis acidity of rhodium appears to result in slower equilibration of the enyl intermediates **38** and **39** and/or an increased rate of nucleophilic attack on these complexes. Supporting this hypothesis, Evans has observed that allylic alkylations using Wilkinson's catalyst modified by triphenylphosphite, which is *less* electron-donating than trimethylphosphite, also tend to give products in which substitution occurs at the carbon atom bearing the leaving group.[5a]

Although we find that *modest* steric factors do not play a significant role in influencing the regiochemistry of nucleophilic attack on rhodium enyl ($\sigma+\pi$) intermediates such as **38** and **39**, steric effects are not inconsequential. For example, substitution reactions of the allylic substrates **20c**, **20d**, and **20k** did not proceed preferentially to provide the expected regioisomer as the major product (Table 2, entries 3, 4, and 11). In these cases, it appears that branching on the carbon atoms attached to the π-allyl fragment influences the site of nucleophilic attack. The presence of unbranched alkyl groups on the allylic moiety does not appear to have as large an effect on regioselectivity (Table 2, entries 8 and 9). On the other hand, the degree of substitution on the three carbon atoms comprising the π-allyl moiety does not seem to impart any steric influence on the regioselectivity of the alkylation reaction (Table 2, entry 12). The differential effects of substituents on the allylic starting material is consistent with nucleophilic attack onto the π-allyl metal complex at an oblique angle, but this proposal must be considered speculative in the absence of additional information.

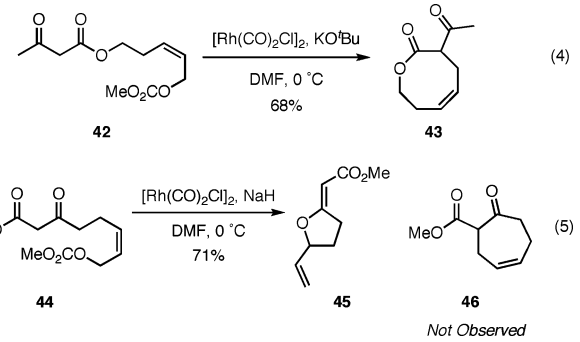
Synthetic Applications. We have thus demonstrated that $[Rh(CO)_2Cl]_2$ has an uncommon propensity to catalyze allylic substitutions at the carbon atom bearing the leaving group on a variety of structurally different substrates. The question that naturally arises is whether this regioselectivity can be exploited in synthesis. We are currently pursuing this query on a number of fronts, and some preliminary results will be presented herein.

The observation that allylic substitutions of *Z*-alkenes proceeded with retention of double bond geometry suggested that $[Rh(CO)_2Cl]_2$ might be used to catalyze cyclizations to give medium and large rings containing *Z*-olefins. That $[Rh(CO)_2Cl]_2$ might be especially well-suited to such constructions was based upon the fact that most metal-stabilized π-allyl species exist preferentially as *anti* complexes that lead to *E*-olefins. Inasmuch as the synthesis of eight-membered rings via transition metal-catalyzed allylic alkylations is particularly demanding,[38] we first examined whether eight-membered lactones might be formed. In the event, stirring the salt of the β-ketoester **42** with

(36) (a) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1981**, *22*, 1399. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (c) Poli, G.; Scolastico, C. *Chemtracts*: *Org. Chem.* **1999**, *12*, 837. (d) Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Starý, I.; Langer, V.; Spoor, P.; Vinader, V.; Kocovský, P. *Chem. Eur. J.* **2006**, *12*, 6910.

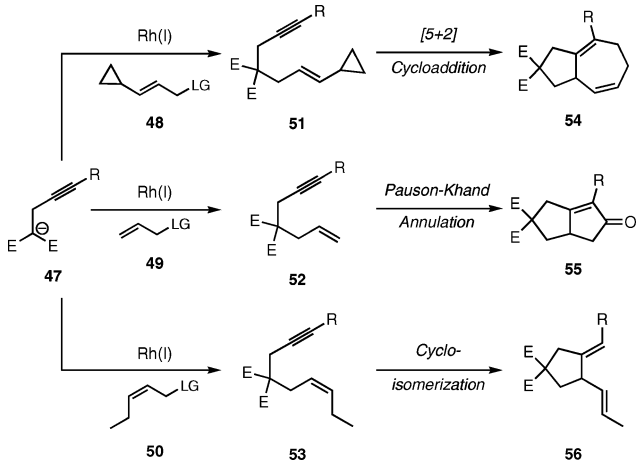
(37) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 2953.

$[Rh(CO)_2Cl]_2$ in DMF at 0 °C provided lactone **43** in 68% yield (eq 4) with none of the corresponding six-membered lactone being observed. Although a palladium-catalyzed cyclization of a β-sulfonyl ester to give an eight-membered lactone is known,[38a] the formation of **43** represents to our knowledge the first example of a transition metal-catalyzed allylic alkylation of a β-ketoester to give an eight-membered lactone. When this same reaction was conducted with $Pd(PPh_3)_4$ as catalyst, a mixture (60:40) of eight- and six-membered lactones was obtained. In a related experiment directed toward constructing a carbocyclic seven-membered ring, we discovered that the [Rh-$(CO)_2Cl]_2$-catalyzed cyclization of **44** in DMF at room temperature gave exclusively the *O*-alkylation product **45** in 71% yield (eq 5); none of the desired carbocycle **46** was obtained.

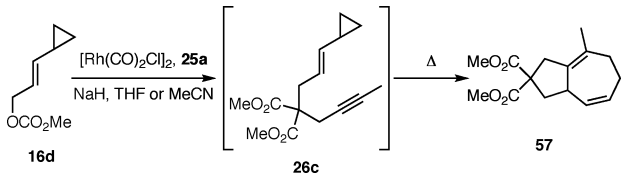


Novel [Rh(CO)$_2$Cl]$_2$-Catalyzed Cascade Reactions. The development of methods that transform relatively simple starting materials into structurally complex intermediates with high efficiency and atom economy is one of the major goals of contemporary synthetic organic chemistry. In the context of transition metal-catalyzed reactions, one tactic to achieve this objective is to design one-pot, multistep sequences wherein the product of the first serves as the starting material for the second, and where *each* transformation is catalyzed by the *same* transition metal.[39] Hence, the discovery and development of multifunctional catalysts that can be utilized to promote mechanistically discrete cascade or domino reactions has emerged as a worthy endeavor.[12b] It was well-known that [Rh-$(CO)_2Cl]_2$ and other rhodium(I) complexes catalyze cyclizations of 1,6-enynes via [5+2] cycloadditions,[40] Pauson−Khand annulations (PKR),[23b,d,24b] and cycloisomerizations.[41,24a,b] It occurred to us that we might couple the $[Rh(CO)_2Cl]_2$-catalyzed allylic alkylation of an α-alkynyl substituted malonate with such cyclizations to enable the rapid formation of complex molecular architectures from simple starting materials according to the basic plan adumbrated in Scheme 5. Indeed, other sequential reaction processes in which an allylic substitution serves as the initial construction have been reported.[42]

SCHEME 5



SCHEME 6



One of the initial driving forces that led us to explore [Rh-$(CO)_2Cl]_2$-catalyzed allylic alkylations was the desire to develop new and concise strategies for the synthesis of hydroazulenes as outlined in Scheme 3.[43] Toward this objective, initial studies were focused upon an allylic alkylation/[5+2] cycloaddition cascade involving carbonate **16d** and malonate **25a** to yield **26c** as the first step en route to cycloadduct **57** (Scheme 6). Although the first step occurred smoothly, we were unable to induce the [5+2] cycloaddition in the same pot. A variety of solvents and temperatures were examined to no avail.

We then queried whether the methyl carbonate anion formed as a product in the first step of the reaction might somehow inhibit the [5+2] cycloaddition of **26c**. Consistent with this hypothesis, we discovered that when the acetate derivative of **16d** was employed as the alkylating agent we were able to isolate **57**, albeit in poor yield. Because we had previously found that allylic acetates reacted more sluggishly than their carbonate we switched to trifluoroacetate **58**, which proved to be an excellent substrate for the cascade reaction. Accordingly, treatment of **58** with 1.5 equiv of malonate **25a** in the presence of $[Rh(CO)_2Cl]_2$ (5 mol %) at room temperature gave intermediate cyclopropyl 1,6-enyne **26c** that underwent facile [5+2] cycloaddition to give **57** by simply elevating the bath temperature to 80 °C (eq 6). Similarly, subjecting allylic trifluoroacetates **59** and **61** to the same conditions provided cycloadducts **60** and **62**, respectively, in excellent overall yields (eqs 7 and 8). The diastereoselectivity and regiochemical trends observed in these [5+2] cycloadditions are in accord with precedent established by Wender.[14a]

Seeking to expand the breadth of $[Rh(CO)_2Cl]_2$-catalyzed cascade reactions, we explored the feasibility of a process commencing with an allylic alkylation and terminating with a Pauson−Khand reaction. If successful, this reaction would provide a facile entry to bicyclic cyclopentenones. We examined

(38) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173. (c) Trost, B. M.; Vos, B. A.; Brzezowski, C. M.; Martina, D. P. *Tetrahedron Lett.* **1992**, *33*, 717.

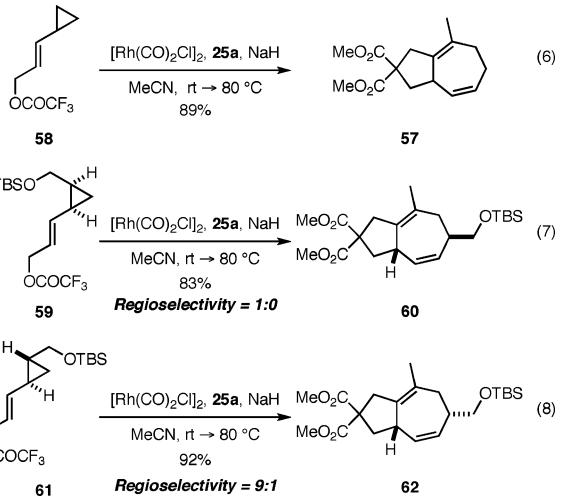
(39) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134.

(40) (a) Wender, P. A.; Husfeld, C. O.; Langkopf, E.; Love, J. A.; Pleuss, N. *Tetrahedron* **1998**, *54*, 7203. (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Scanio, M. J. C. *Org. Lett.* **2000**, *2*, 1609. (c) Trost, B. M.; Shen, H. C. *Org. Lett.* **2000**, *2*, 2523.

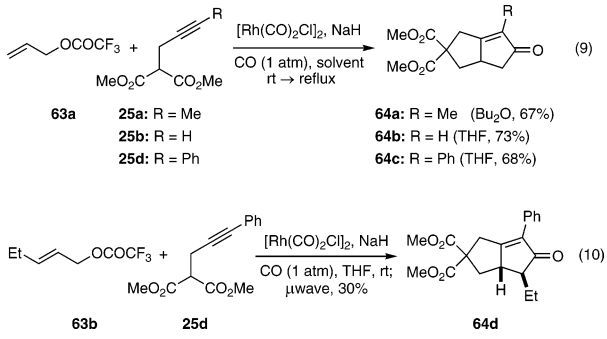
(41) (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215.

(42) (a) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (b) Yamamoto, Y.; Nakagai, Y.-i.; Itoh, K. *Chem. Eur. J.* **2004**, *10*, 231.

(43) (a) Ashfeld, B. L.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4535. (b) Ashfeld, B. L.; Martin, S. F. *Tetrahedron* **2006**, *62*, 10497.

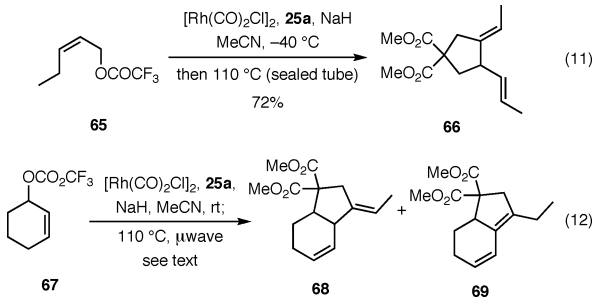


this sequence by reacting allyl trifluoroacetate **63** with 1.3 equiv of malonates **25a**, **25b**, and **25d** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol %) and a CO atmosphere. Gratifyingly, the 1,6-enyne intermediates formed after the allylic alkylation underwent cyclization upon heating to furnish bicyclic enones **64a**−**c** in good overall yields (eq 9). Additionally, we found that the subsequent [2+2+1] cycloaddition could be effected through microwave heating. Treatment of allylic trifluoroacetate **63b** with the malonate **25d** in the presence of $[Rh(CO)_2Cl]_2$ under an atmosphere of CO followed by microwave heating yielded cyclopentenone **64d** in moderate yield (eq 10). These transformations represent an attractive complement to a related tandem Rh(I)-catalyzed allylic alkylation/Pauson−Khand annulation protocol reported by Evans that led to bicyclo[3.3.0]octenones having a different substitution pattern.[42a]



While conducting exploratory experiments toward developing this cascade of allylic alkylation and Pauson−Khand reactions, we discovered that $[Rh(CO)_2Cl]_2$ catalyzed the isomerization of 1,6-enynes to yield vinyl alkylidene cyclopentanes. This was an interesting result as *neutral* Rh(I) species have not been utilized effectively as enyne cycloisomerization catalysts. On the other hand, *cationic* Rh(I) complexes are known to catalyze the cycloisomerization of a variety of 1,6-enynes,[24a,c] but most such examples involve *Z*-enynes. Indeed, we are aware of only one example of the Rh(I)-catalyzed cycloisomerization of an *E*-enyne, and in this case two products were obtained in approximately equal amounts.[24c]

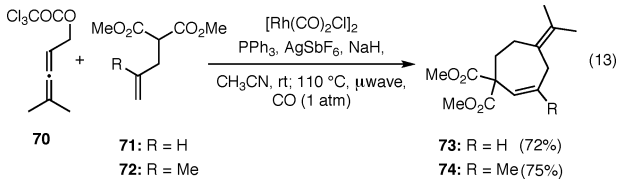
Having discovered that the $[Rh(CO)_2Cl]_2$-catalyzed allylic substitutions of *Z*-substrates proceeds with little *Z*/*E*-isomerization, it occurred to us that a novel cascade process involving an allylic alkylation followed by a cycloisomerization might be orchestrated. We were thus gratified to discover that reaction of the allylic trifluoroacetate **65** with malonate **25a** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol %) gave the expected 1,6-enyne (*Z*/*E* > 95:5), and when the reaction mixture was simply heated to 110 °C (bath temperature) in a sealed tube, the diene **66** was isolated in 72% yield (eq 11). The corresponding allylic methyl carbonate **15b** was not a suitable substrate for this one-pot allylic alkylation/cycloisomerization tandem sequence. It was necessary to use an excess of **65** (2.5 equiv), rather than an excess of the malonate as required in other domino sequences, to ensure reasonable yields in the overall reaction.



Although we found that the cyclic allylic trifluoroacetate **67** could be converted to **68** in a similar cascade sequence (eq 12), this reaction proved to be rather capricious, despite extensive efforts to optimize the process. The initial allylic alkylation failed with allylic carbonates and acetates, and was sluggish even with the highly reactive trifluoroacetate as a leaving group. Not only is the allylic alkylation step problematic, but the high temperature and reaction times required to effect cycloisomerization facilitate double bond isomerization, leading to inseparable mixtures of olefinic isomers. Isomerization could be minimized by the use of microwave heating, often yielding **68** as the major isomer, but the conjugated isomer **69** was always present. Although yields of **68** as high as 65% were sometimes achieved, the most reproducible yields were in the range of 40−45%.

Inspired by the work of Ito and Brummond,[44] we then queried whether the scope of $[Rh(CO)_2Cl]_2$-catalyzed cascade allylic alkylations and carbocyclizations might be extended to allenic substrates. In preliminary experiments, we found that allenic trifluoroacetates were difficult to handle, and allenic acetates were unreactive toward the initial alkylation. Although allenic carbonates underwent the initial $[Rh(CO)_2Cl]_2$-catalyzed substitution, the resultant products could not be induced to undergo cycloisomerization in the same operation. Considering our prior experiences with the use of carbonate leaving groups in domino sequences, this was not a surprising result. Ultimately, allenic trichloroacetates were found to be suitable reaction partners for the alkylation step. Toward implementing the cascade sequence, allenic trichloroacetate **70** was treated with 1.5 equiv of malonate **71** in the presence of $[Rh(CO)_2Cl]_2$ (10 mol %), but the subsequent cycloisomerization of the intermediate allenyl olefin to give **73** was not successful (eq 13).We reasoned that the cycloisomerization might be facilitated by pre-generating an open coordination site on the metal center,[24a] and after some experimentation we found that addition of PPh_3 and $AgSbF_6$ *prior* to the alkylation step led to the formation of **73** in a moderate 55% yield. Ito and co-workers have reported that the

(44) (a) Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161. (b) Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395.



70 **71:** R = H **72:** R = Me **73:** R = H (72%) **74:** R = Me (75%)

efficiencies of allen−ene cycloisomerizations were improved when the reaction was performed under an atmosphere of carbon monoxide.[44b] To our delight, when the argon atmosphere was exchanged with carbon monoxide following completion of the allenic alkylation step, the yield of the overall process improved to 72%. Extension of these optimized conditions to the reaction of **70** with the anion of malonate **72** led to the production of **74** in 75% yield.

Conclusions

In summary, we have discovered that the commercially available rhodium(I) species [Rh(CO)$_2$Cl]$_2$ may be used to catalyze the facile and highly regioselective allylic alkylation of unsymmetrical substrates. Among transition metal-catalyzed allylic substitution reactions, these processes are unique in the sense that absent significant steric effects the major products arise from substitution at the allylic carbon atom bearing the leaving group, irrespective of the structure of the allylic starting material. These reactions also proceed with a high level of stereoselectivity in which enantioenriched starting materials provide the substitution products with minimal loss of enantiomeric excess. Additionally, the carbon−carbon double bond geometry of primary *Z*-allylic substrates is maintained, a rare mode of selectivity in the realm of transition metal-catalyzed allylic alkylations. In addition to the unusual regioselectivity in [Rh(CO)$_2$Cl]$_2$-catalyzed alkylations, there are several other noteworthy features attending its use. The reactions may be easily conducted without exercising stringent precautions to exclude oxygen, and the mild conditions under which the reaction is typically performed make it useful for thermally sensitive substrates. The procedure is operationally simple because additives or other ligands are not required for allylic alkylations.

Because [Rh(CO)$_2$Cl]$_2$ is known to catalyze other transformations, a number of synthetic applications may be envisaged in which allylic alkylations are combined with other transformations, resulting in an atom economical cascade process to rapidly assemble complex structures from relatively simple starting materials. This concept was illustrated by development of the first cascade sequences involving allylic alkylation/[5+2] cycloaddition and allylic alkylation/cycloisomerization. The method was also applicable to a cascade allylic alkylation/Pauson−Khand annulation that nicely complements existing procedures. The ability to exploit multifunctional catalysts to promote two or more sequential reactions in a single operation has significant potential for the rapid preparation of structurally complex targets. Studies to explore these and other [Rh(CO)$_2$Cl]$_2$-catalyzed cascade reactions are in progress and will be reported in due course.

Experimental Section

General Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Alkylation with Stabilized Carbon Nucleophiles. Allylic substrate (**16**, **20**, or **23**) (1.0 mmol) was added to a solution of [Rh(CO)$_2$Cl]$_2$ (5 mol %) in THF or DMF (see text) (5 mL), and the solution was stirred for 10 min at the indicated temperature (see text). In a separate flask the pronucleophile (**17**, **25**, **28**, or **29**) (1.5 mmol) was added to a slurry of NaH (60% w/w in mineral oil, 1.4 mmol) in THF (5 mL) at room temperature, and the mixture was stirred for 20 min. The resulting sodium enolate was added via syringe to the solution of allylic substrate and [Rh(CO)$_2$Cl]$_2$ at the indicated temperature (see text). The mixture was sealed in a screw cap vial under an atmosphere of argon, and stirring was continued until the starting carbonate was consumed (as indicated by TLC analysis). The reaction was then filtered through a short plug of silica gel eluting with Et$_2$O (50 mL), and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et$_2$O (5:1 or 10:1) to furnish a mixture of **18/19**, **21/22**, (+)-**23**, or **26/27**. The mixture was then analyzed by either GLC or ^{1}H NMR (400 MHz) (see text) to determine the designated ratio of regioisomers.

***trans*-2-Pent-2-enylmalonic Acid Dimethyl Ester (18a).** Malonate **18a** was obtained in 84% yield (0.34 mmol scale) after 2 h in THF at room temperature as a clear, colorless oil after chromatography (pentane/Et$_2$O = 5:1) in a 98:2 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 5.56 (dddt, J = 15.2, 6.8, 5.2, 1.6 Hz, 1 H), 5.34 (dddt, J = 15.2, 7.2, 5.2, 1.6 Hz, 1 H), 3.73 (s, 3 H), 3.41 (t, J = 7.6 Hz, 1 H), 2.58 (app dt, J = 8.0, 1.2 Hz, 2 H), 2.02−1.95 (m, 2 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.2, 135.5, 123.9, 52.4, 52.0, 31.9, 25.6, 13.8; IR (CDCl$_3$) 2955, 1731, 1436, 1272, 1232, 1158 cm^{-1}; mass spectrum (CI) *m*/*z* 201.1117 [C$_{10}$H$_{17}$O$_4$ (M + 1) requires 201.1127] 201 (base), 169.

***cis*-2-Pent-2-enylmalonic Acid Dimethyl Ester (18b).** Malonate **18b** was obtained in 86% yield (0.34 mmol scale) after 12 h in THF at 0 °C as a clear, colorless oil after chromatography (pentane/Et$_2$O = 5:1) in a 99:1 regioisomeric ratio and 97:3 cis/trans ratio: ^{1}H NMR (400 MHz) δ 5.58 (dddt, J = 10.4, 8.8, 7.2, 1.2 Hz, 1 H), 5.25 (dddt, J = 10.8, 9.2, 7.6, 2.0 Hz, 1 H), 3.73 (s, 6 H), 3.39 (t, J = 7.2 Hz, 1 H), 2.67−2.63 (m, 2 H), 2.11−2.03 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 169.2, 134.8, 123.6, 52.5, 51.8, 26.7, 20.6, 14.2; IR (CDCl$_3$) 2956, 2258, 1732, 1437, 1240, 1158 cm^{-1}; mass spectrum (CI) *m*/*z* 201.1124 [C$_{10}$H$_{17}$O$_4$ (M + 1) requires 201.1127] 201 (base), 169.

General Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Alkylation with Phenolic Nucleophiles. A 1.0 M solution of LiHMDS (0.66 mL, 0.66 mmol) was added to a slurry of phenol **33** (0.69 mmol) and CuI (132 mg, 0.69 mmol) in THF (1.5 mL) at room temperature. The mixture was stirred at room temperature for 30 min. In a separate flask, [Rh(CO)$_2$Cl]$_2$ (13 mg, 0.034 mmol) was dissolved in THF (2 mL), stirred for 5 min at room temperature, then transferred via syringe to the flask containing phenoxide. Allylic carbonate **16** or **20** (0.34 mmol) was then added to the mixture, and the reaction was stirred at room temperature for 24 h. The mixture was filtered through a short plug of SiO$_2$ eluting with Et$_2$O (50 mL). The eluent was concentrated under reduced pressure, and the crude residue was purified by flash chromatography eluting with pentane/Et$_2$O (5:1) to provide aryl ether **34**.

2-Phenyl-1-[(*E*)-pent-2-enyloxy]benzene (34a). Ether **34a** was obtained in 84% yield (0.34 mmol scale) in THF after 24 h at room temperature as a clear, brown oil after chromatography (pentane/Et$_2$O = 5:1) in a ≥95:5 regioisomeric ratio: ^{1}H NMR (500 MHz) δ 7.57−7.54 (comp, 2 H), 7.41−7.37 (comp, 2 H), 7.34−7.28 (comp, 3 H), 7.06−6.96 (comp, 2 H), 5.78 (dtt, J = 15.4, 7.8, 1.4 Hz, 1 H), 5.60 (dtt, J = 15.4, 5.6, 1.6 Hz, 1 H), 4.48 (ddt, J = 5.6, 2.5, 1.6 Hz, 2 H), 2.08−2.02 (m, 2 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 155.7, 138.6, 137.8, 136.1, 130.9, 129.6, 127.9, 126.8, 124.0, 121.0, 113.4, 69.4, 25.3, 13.3; IR (CHCl$_3$) 2964, 1596, 1480, 1434, 1255, 1216, 912, 846 cm^{-1}; mass spectrum (CI) *m*/*z* 239.1426 [C$_{17}$H$_{19}$O$_1$ (M + 1) requires 239.1436] 243, 239, 199, 171 (base).

1-Pent-2-enyloxy-2-vinylbenzene (34b). Ether **34b** was obtained in 77% yield (0.25 mmol scale) in THF after 24 h at room temperature as a clear, colorless oil after chromatography (hexane)

in a ≥95:5 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 7.48 (dd, J = 7.2, 1.6 Hz, 1 H), 7.20 (dt, J = 8.4, 1.6 Hz, 1 H), 7.09 (dd, J = 17.6, 11.2 Hz, 1 H), 6.92 (t, J = 7.6 Hz, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 5.89 (dt, J = 15.2, 6.4, Hz, 1 H), 5.74 (dd, J = 17.6, 1.6 Hz, 1 H), 5.71 (m, 1 H), 5.24 (dd, J = 11.6, 2.0 Hz, 1 H), 4.49 (dd, J = 6.0, 1.2 Hz, 2 H), 2.11 (app p, J = 6.4 Hz, 2 H), 1.03 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz) δ 155.9, 136.6, 131.7, 128.7, 127.0, 126.4, 123.9, 120.6, 114.2, 112.4, 69.2, 25.3, 13.2; IR ($CHCl_3$) 3033, 2967, 2934, 2874, 1625, 1597, 1485, 1452, 1239, 1107, 1003, 969 cm^{-1}; mass spectrum (CI) m/z 189.1278 [$C_{17}H_{19}O_1$ (M + 1) requires 189.1279] 189 (base), 122, 107.

General Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Amination of Unsymmetrical Allylic Carbonates with Sulfonamides. [Rh(CO)$_2$Cl]$_2$ (5 mol %) was dissolved in dry, degassed THF (5 mL), the allylic substrate **16** (1.0 mmol) was added, and the solution was stirred for 30 min at room temperature. In a separate flask, a 1.0 M solution of LiHMDS in THF (2.0 mmol) was added to a solution of sulfonamide **33** (2.5 mmol) in THF (5 mL) and the mixture was stirred for 20 min at room temperature. The resulting amide was added via syringe to the solution of allylic substrate and [Rh(CO)$_2$Cl]$_2$ at room temperature. The mixture was then sealed in a screw cap vial under argon and stirred for 2 h at room temperature. The resulting dark brown solution was filtered through a short plug of silica gel eluting with Et$_2$O (50 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et$_2$O to provide the amination products in the specified ratios.

(*E*)-*N*-Benzyl-4-methyl-*N*-(pent-2-enyl)benzenamine (34e). Sulfonamide **34e** was obtained in 71% yield (0.34 mmol scale) after 24 h at room temperature as a clear, colorless oil after chromatography (pentane/Et$_2$O = 5:1) in a 82:18 regioisomeric ratio: ^{1}H NMR (500 MHz) δ 7.73 (d, J = 6.8 Hz, 2 H), 7.57−7.54 (comp, 7 H), 5.42 (dddt, J = 12.4, 6.4, 5.6, 1.6 Hz, 1 H), 5.06 (dddt, J = 12.4, 6.8, 5.6, 1.2 Hz, 1 H), 4.32 (s, 2 H), 3.69 (br d, J = 5.6 Hz, 2 H), 2.44 (s, 3 H), 1.91−1.86 (m, 2 H), 0.84 (t, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 143.1, 137.7, 137.6, 136.3, 129.6, 128.4, 128.4, 127.2, 122.0, 50.0, 48.9, 25.1, 21.5, 13.1; mass spectrum (CI) m/z 330.1531 [$C_{19}H_{24}NO_2S$ (M + 1) requires 330.1528] 330 (base), 274.

(*E*)-4-Methyl-*N*-(pent-2-enyl)-*N*-(prop-2-ynyl)benzeneamine (34f). Sulfonamide **34f** was obtained in 42% yield (0.14 mmol scale) after 2 h at room temperature as a clear, colorless oil after chromatography (pentane/Et$_2$O = 5:1) in a 82:12 regioisomeric ratio. Spectral data are consistent with those reported in the literature.[45]

General Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Allylic Amination of Unsymmetrical Allylic Carbonates with Secondary Amines. Pyrrolidine (36 mg, 0.50 mmol) was added to a solution of **23** (52 mg, 0.25 mmol), TBAI (19 mg, 0.050 mmol), and [Rh(CO)$_2$Cl]$_2$ (10 mg, 0.025 mmol) in dichloroethane (1 mL). The reaction was stirred for 12 h at room temperature. The reaction was concentrated under reduced pressure, and hexane (1 mL) was added. The heterogeneous mixture was filtered through Celite washing with hexane, and the combined filtrate and washings were concentrated under reduced pressure. The residue was purified by flash chromatography by using silica deactivated with 10% Et$_3$N eluting with the indicated solvent.

1-(1-Methyl-3-phenylallyl)pyrrolidine (34h). Amine **34h** was obtained in 99% yield (0.25 mmol scale) as a yellow oil after chromatography (hexanes/EtOAc = 1:1) in ≥95:5 regioisomeric ratio: ^{1}H NMR (400 MHz) δ 7.40−7.00 (comp, 5 H), 6.45 (d, J = 15.6 Hz, 1 H), 6.22 (dd, J = 15.6, 7.0 Hz, 1 H), 2.88 (dt, J = 14.8, 6.4 Hz, 1 H), 2.56 (comp, 4 H), 1.77 (comp, 4 H), 1.27 (d, J = 7.0, 3 H); ^{13}C NMR (100 MHz) δ 137.2, 134.0, 129.6, 128.5, 127.2, 126.2, 63.1, 52.2, 23.3, 21.0; IR (neat) 2967, 2780, 1494, 1446, 1310, 1167, 965, 748, 692; MS (CI) m/z 202.1586 [$C_{14}H_{20}N_1$ (M + 1) requires 202.1596] 202 (base), 186, 159, 131.

Benzyl-1,1-dimethylallylmethylamine (34i). Amine **34i** was obtained in 89% yield (0.25 mmol scale) as a yellow oil after chromatography (hexanes/EtOAc = 9:1) in ≥95:5 regioisomeric ratio: ^{1}H NMR (300 MHz) δ 7.60−7.20 (comp, 5 H), 6.03 (dd, J = 17.7, 10.8 Hz, 1 H), 5.13 (dd, J = 17.7, 1.5 Hz, 1 H), 5.09 (dd, J = 10.5, 1.5 Hz, 1 H), 3.52 (s, 2 H), 2.14 (s, 3 H), 1.25 (s, 6H); ^{13}C NMR (75 MHz) δ 147.0, 141.3, 128.5, 128.1, 126.5, 112.0, 58.6, 55.7, 34.5, 22.8; IR (neat) 2973, 2842, 2794, 1494, 1453, 1411, 1355, 1181, 1001, 914, 696; mass spectrum (CI) m/z 190.1591 [$C_{13}H_{20}N_1$ (M + 1) requires 190.1596] 190 (base), 122.

Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Tandem Allylic Alkylation/[5+2] Cycloaddition of Allylic Trifluoroacetates 58, 59, and 61. The allylic trifluoroacetate **58**, **59**, or **61** (0.1 mmol) was added to a solution of [Rh(CO)$_2$Cl]$_2$ (5 mol %) in degassed MeCN (0.5 mL), and the solution was stirred for 10 min at room temperature. In a separate flask, malonate **25a** (1.5 mmol) was added to a slurry of NaH (1.4 mmol, 60% w/w in mineral oil) in degassed MeCN (0.5 mL) at room temperature, and this mixture was stirred for 20 min. The resulting sodium enolate was then added via syringe to the solution of the allylic trifluoroacetate and [Rh(CO)$_2$Cl]$_2$ at room temperature. The mixture was sealed in a screw cap vial under an atmosphere of argon, and stirring was continued at room temperature until the starting material was consumed (6−8 h, as indicated by TLC analysis). The reaction was then heated to 80 °C (bath temperature) and stirring was continued until intermediate enyne was consumed (as indicated by TLC analysis). The reaction was then filtered through a short plug of silica gel eluting with Et$_2$O (50 mL), and the combined filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with pentane/Et$_2$O (5:1 or 10:1) to furnish **57**, **60**, or **62** that gave spectral characteristics consistent with those reported in the literature.[14a]

Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Tandem Allylic Alkylation/Pauson−Khand Annulation of 63. Malonate **25a**, **25b**, or **25d** (0.26 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 0.22 mmol) in dry, degassed THF (1 mL) and the reaction was stirred for 15 min at room temperature. The solvent was removed under reduced pressure, and the resulting yellow oil was azeotroped with toluene (2 × 3 mL) under reduced pressure. The residue was dissolved in THF (1 mL) and transferred via syringe to a solution of **63** (0.2 mmol) and [Rh(CO)$_2$Cl]$_2$ (10 mol %) in THF (1 mL). The reaction was stirred at room temperature for 1 h, and then the solution was heated under reflux until the starting material was consumed (12−24 h) (as indicated by TLC analysis). The solvent was removed under reduced pressure and the residue was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to furnish **64a**−**c** that gave spectral characteristics consistent with those reported in the literature.[46]

Procedure for the [Rh(CO)$_2$Cl]$_2$-Catalyzed Tandem Allylic Alkylation/Cycloisomerization of Allylic Trifluoroacetate 65 To Furnish (3*E*)-Dimethyl 3-Ethylidene-4-((*E*)-prop-1-enyl)cyclopentane-1,1-dicarboxylate (66). 65 (169 mg, 0.67 mmol) was added to a solution of [Rh(CO)$_2$Cl]$_2$ (10 mol %) in degassed MeCN (0.75 mL), and the solution was stirred for 10 min at −40 °C. In a separate flask, **25a** (50 mg, 0.27 mmol) was added to a slurry of NaH (16 mg, 0.41 mmol, 60% dispersion in mineral oil) in MeCN (2.0 mL) at room temperature, and the mixture was stirred for 30 min. The resulting solution of sodium enolate was then added via syringe to the solution of **65** and [Rh(CO)$_2$Cl]$_2$ at −40 °C. The reaction mixture was stirred for 6 h at −40 °C, whereupon it was transferred to a screw cap vial that was sealed and heated at 110 °C (bath temperature) until the intermediate enyne **26b** was consumed (30 min). The reaction mixture was diluted with H$_2$O (2 mL) and Et$_2$O (2 mL), and the layers were separated. The aqueous phase was extracted with Et$_2$O (5 × 2 mL), and the combined

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organic fractions were dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash chromatography eluting with pentane/Et_2O (5:1) to furnish 49 mg (72%) of **66** as a pale yellow oil: ^{1}H NMR (500 MHz) δ 5.50−5.41 (app ddq, J = 15.7, 6.4, 0.6 Hz, 1 H), 5.52−5.22 (comp, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.04−2.98 (comp, 2 H), 2.85−2.80 (m, 1 H), 2.52−2.48 (ddd, J = 12.9, 7.4, 1.8 Hz, 1 H), 1.92−1.87 (dd, J = 12.9, 11.6 Hz, 1 H), 1.69−1.67 (dd, J = 6.4, 1.6 Hz, 3 H), 1.61−1.55 (comp, 3 H); ^{13}C NMR (500 MHz) δ 172.5, 172.4, 141.4, 132.3, 126.8, 117.5, 58.5, 52.8, 52.7, 46.8, 40.9, 36.8, 17.9, 14.6; mass spectrum (CI) m/z 252.1361 [$C_{14}H_{20}O_4$ requires 252.1362] 253 (base), 252, 221, 193, 192.

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Supporting Information Available: Specific experimental procedures, spectral characterization, and copies of ^{1}H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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