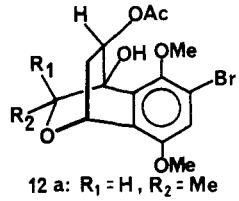
We postulated strong chelation of Ti(IV) to **5** by deprotonation and alkoxy exchange with $MeTi(OiPr)_3$ and then external delivery of the methyl nucleophile from the least hindered face (Figure 1). On treatment of **5** with methyltriisopropoxytitanium (3 mol equiv, THF, 25 °C, 16 h) the desired triol **6a** was produced as a single diastereoisomer, in 80% yield. This procedure is more selective than any MeMgBr additions we have attempted and readily gives complete conversion.

The third critical stage of the synthesis, oxidative cyclization to **11a**, was accomplished in two steps. First a crude benzylic bromination product was prepared (*N*-bromosuccinimide, cyclohexene oxide as acid scavanger, azoisobutyronitrile, sunlamp for 0.5 h at 10 °C in CCl_4), and then ring closure was induced by treatment with silver ion (silver perchlorate, THF, 0–20 °C over 0.5 h). Chromatography gave pure **11a** in 53% yield. The configuration of C-3 in **11a** was clear from the ^1H NMR spectrum, in which the C-3 methyl group appears as a doublet at δ 0.86, reflecting a strong upfield shift due to proximity to the face of the arene ring. In the epimeric series (e.g., **11b**) the C-3 methyl generally appears at δ 1.3. This is consistent with the data for the natural products, **1** and **2**.[1,2] In addition, in related studies, we prepared the isomers **12a** and **12b** by a similar sequence and



12 a: $R_1 = H, R_2 = Me$

b: $R_1 = Me, R_2 = H$

observed the parallel differences in the ^1H NMR spectral data. The structure of **12a** was confirmed by X-ray diffraction analysis.[14]

The intermediate **11a** is an obvious precursor of sarubicin A (**2**). The bromide substituent was first replaced by an acyl amide unit using the Pd(0)-catalyzed carbonylation procedure of Heck.[15] For our purposes ammonia would be the ideal nucleophilic trapping agent for the expected acylpalladium intermediate, but ammonia itself was not successful. A primary amine was chosen with a removable carbon substituent. Several candidates, such as benzylamine, performed well in the amido carbonylation, but we were less successful in cleaving the benzyl substituent.[16] The best solution is (2,4-dimethoxybenzyl)amine [with 10 mol % $(Ph_3P)_2PdCl_2$, Ph_3P, CO at 1.1 atm, 90 °C, 14 h] which produced **13** in 71% yield (60% after one recrystallization, mp 175–177 °C). Protection of the diol unit as the carbonate (*N*,*N*′-carbonyldiimidazole, methyl ethyl ketone, K_2CO_3, 105 °C) allowed oxidative removal of the 2,4-dimethoxybenzyl group [Ce(IV), CH_3CN, water, 0 °C, 0.5 h] and hydrolysis of the carbonate (0.5 M NaOH in 50% aqueous dioxan, 10 min, 25 °C) gave the key intermediate **3** in high purity, 77%. Recrystallization gave colorless plates (56% yield) with mp 207–209 °C. This compound has been converted to sarubicin A in one step (two operations),[4] and preparation of **3** provides a formal total synthesis of sarubicin A. The overall synthesis (Scheme II) is highly stereoselective and requires minimal use of protecting groups. We expect these procedures will make available useful quantities of intermediate **11a** for conversion to granaticin.

Acknowledgment. We are pleased to acknowledge support of this work through NIH Grant GM 31352.

Registry No. 1, 19879-06-2; **2**, 75533-14-1; **3**, 96866-91-0; (±)-**5** ($P_1 = P_2 = H$), 96866-92-1; (±)-**6a** ($R_1 = H$; $R_2 = Me$), 96866-93-2; (±)-**6b** ($R_1 = Me$; $R_2 = H$), 96866-94-3; **7**, 87338-27-0; (±)-**8** ($P_1 = t$-$BuMe_2Si$), 96866-96-5; (±)-*cis*-**9** ($P_1 = t$-$BuMe_2Si$; $P_2 = Me_3Si$), 96866-97-6; (±)-*trans*-**9** ($P_1 = t$-$BuMe_2Si$; $P_2 = Me_3Si$), 96866-98-7; (±)-**10** ($P_1 = t$-$BuMe_2Si$; $P_2 = Me_3Si$), 96867-00-4; **11a**, 96867-01-5; **13**, 96867-02-6; (±)-i, 96867-03-7; (±)-i·MeMGBr adduct (isomer 1), 96867-04-8; (±)-i·MeMgBr adduct (isomer 2), 96867-05-9; (±)-i·MeMgBr adduct (isomer 3), 96867-06-0; (±)-i·MeMgBr adduct (isomer 4), 96896-73-0; (±)-ii, 96867-07-1; (±)-iii, 96867-08-2; (±)-iv, 96947-22-7; 1-(*tert*-butyldimethylsiloxy)-6-bromo-5,8-dimethyl-3,4-dihydronaphthalene, 96866-95-4; (±)-*cis*-6-bromo-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1,2,3,4-tetrahydro-5,8-dimethoxy-1-[(trimethylsilyl)oxy]-1-(iminomethyl)naphthalene, 96866-99-8; (2,4-dimethoxybenzyl)amine, 20781-20-8.

Supplementary Material Available: Characterization data for **5**, **6a**, **8**, **9**, **11a**, **13**, and **3** (5 pages). Ordering information is given on any current masthead page.

(14) We are grateful for assistance from Professor Jon Clardy and the Cornell X-ray facility for these data.

(15) Heck, R. F.; Schoenberg, A. *J. Org. Chem.* **1974**, *39*, 3327.

(16) Attempts to remove the *N*-benzyl group by catalytic hydrogenation led to saturation of the aromatic ring in the benzyl group. See also ref 14 in: Williams, R. M.; Armstrong, R. W.; Dung, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 5748–5750.

Carbanion-Accelerated Vinylcyclopropane Rearrangement. Application in a General, Stereocontrolled Annulation Approach to Cyclopentene Derivatives

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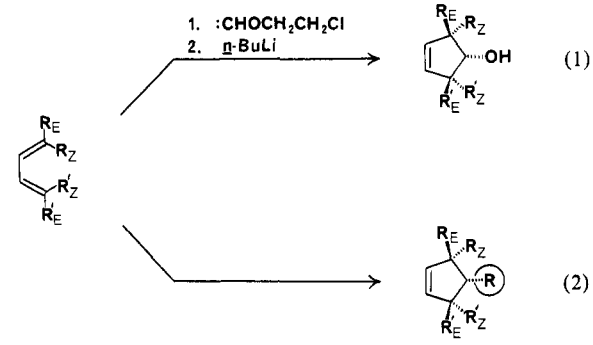
In the field of cyclopentanoid synthesis,[2] a problem of continuing interest is the development of a general method, analogous to the Diels–Alder reaction, for the conversion of conjugated dienes to cyclopentene derivatives. Toward this end, we have recently devised a highly stereoselective [4 + 1] annulation approach to substituted cyclopentenols.[3] As outlined in eq 1, this method



features an alkoxy-accelerated vinylcyclopropane rearrangement as a key step and results in the effective 1,4-addition of hydroxycarbene about the termini of a 1,3-diene. In this paper, we now report a second-generation version of our strategy, which extends this methodology to include the synthesis of cyclopentene derivatives bearing a variety of functionalized substituents in place of the hydroxyl group on the new five-membered ring (eq 2).

The pivotal step in our new annulation strategy is a *carbanion-accelerated vinylcyclopropane rearrangement*.[4] α-Sulfonyl carbanions have proved to be the most effective activating groups

(1) Fellow of the Alfred P. Sloan Foundation, 1981–1985.

(2) (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Paquette, L. A. *Ibid.* **1979**, *79*, 49.

(3) (a) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (b) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M. *J. Org. Chem.* **1980**, *45*, 1340.

(4) For previous examples of carbanion-accelerated pericyclic reactions, see: (a) Comber, R. N.; Swenton, J. S.; Wexler, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 5411. (b) Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. *Ibid.* **1981**, *103*, 1256. (c) Cooper, D.; Trippet, S. *J. Chem. Soc., Perkin Trans 1* **1981**, 2127. (d) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (e) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369. (f) Nemoto, H.; Suzuki, K.; Tsubuki, M.; Minemura, K.; Fukumoto, K.; Kametani, T.; Furuyama, H. *Tetrahedron* **1983**, *39*, 1123. (g) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (h) Blechert, S. *Tetrahedron Lett.* **1984**, *25*, 1547.

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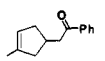
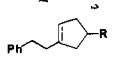
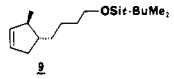
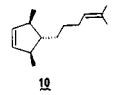
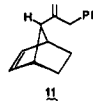
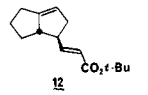
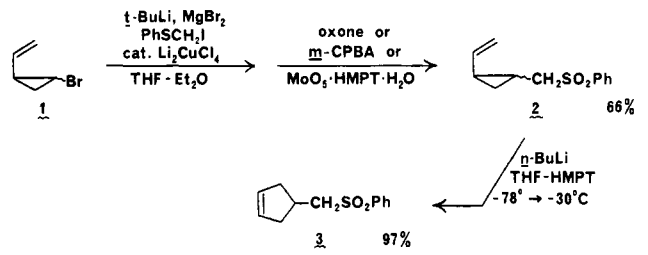
Table I. [4 + 1] Cyclopentene Annulations

entry	diene	bromocyclopropanation[a] % yield	phenylthiomethylation–oxidation overall yield[b]	rearrangement–trapping–desulfonylation: electrophile	product	overall yield[c]
1		*d*	66[e]	$PhCH_2Br$[f]	 4	77
2		*g*	74[e]	$PhCOSiMe_3$–LiBr[h]	 5	84
3		40	58,[e] 68[j]	*t*-BuOH[f] ethylene oxide[k] Me_3SiCH_2I[l]	 6, R = CH_3 7, R = $CH_2CH_2CH_2OH$ 8, R = $CH{=}CH_2$	77 75 88
4		*m*	60[n]	$Br(CH_2)_3OSi$-*t*-$BuMe_2$[f]	 9	73
5		35	56[n]	$Me_2C{=}CH(CH_2)_2I$[f]	 10	75[o]
6		71	53,[n] 74[j]	Me_3SiCH_2I, then *n*-BuLi, $PhCH_2Br$[l]	 11	77
7		19	45,[n] 70[j]	$BrCH_2CO_2$-*t*-Bu[p]	 12	46

[a] Monobromocyclopropanation was carried out using the method of Martel[6] unless otherwise indicated. [b] Overall yield for phenylthiomethylation and oxidation of unpurified sulfides. [c] Isolated yield for "one-flask" rearrangement, substitution, and desulfonylation. IR, ^1H NMR, ^{13}C NMR, and mass spectral data were fully consistent with the assigned structures. High-resolution mass spectra and/or elemental analyses were obtained for all new compounds. [d] Seyferth, D.; Yamasaki, H.; Alleston, D. L. *J. Org. Chem.* **1963**, *28*, 703. [e] Oxidation was accomplished using oxone (see ref 10). [f] In this case desulfonylation was effected by adding excess Li wire (2% Na) and *t*-BuOH and warming to 25 °C. [g] Singh, S.; Robertson, R. E. *Can. J. Chem.* **1976**, *54*, 1246. [h] Addition to the acylsilane produces a silyl enol ether: Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949. Hydrolysis was accomplished by adding aqueous KF. [i] Prepared from $PhCH_2CH_2CHO$ by (1) addition of $CH_2{=}CHMgBr$, (2) PCC oxidation, and (3) addition of $Ph_3P{=}CH_2$. [j] Oxidation was accomplished using $MoO_5{\cdot}HMPT{\cdot}H_2O$ (see ref 11b). [k] Desulfonylation was effected by adding 2.5% Na–Hg and MeOH. [l] Desulfonylation was achieved by adding *n*-Bu_4NF: Kocienski, P. J. *Tetrahedron Lett.* **1979**, 2649. [m] Singh, S.; Robertson, R. E. *Can. J. Chem.* **1977**, *55*, 2582. [n] Oxidation was accomplished using *m*-CPBA. [o] Obtained as a 27:1 mixture of **10** and the corresponding cis,trans isomer. [p] Desulfonylation was effected by adding DBU and warming to 25 °C.

for these reactions among the several carbanion derivatives examined thus far. For this initial investigation, the requisite 1-[(phenylsulfonyl)methyl]-2-vinylcyclopropanes were conveniently prepared via the phenylthiomethylation of vinylcyclopropyl Grignard reagents, followed by oxidation of the resulting sulfide derivatives.[5] Scheme I illustrates this new [4 + 1] annulation strategy as applied to 1,3-butadiene. First, the requisite 1-bromo-2-vinylcyclopropanes were prepared either using literature procedures, or via the reaction of a conjugated diene with :CHBr generated from CH_2Br_2 and NaHMDS according to the method of Martel.[6] Phenylthiomethylation[7] was then achieved most efficiently by the coupling of the Grignard derivatives with 1.1 equiv of iodomethyl phenyl sulfide[8] in the presence of 0.05 equiv of Li_2CuCl_4[9] in THF–Et_2O at −30 → 25 °C. Finally, chemoselective oxidation of the resulting sulfides was accomplished by using potassium hydrogen persulfate ("oxone") as previously described by Trost.[10,11]

Scheme I



Exposure of 1-[(phenylsulfonyl)methyl]-2-vinylcyclopropane (**2**) to 1.2 equiv of *n*-butyllithium in 5:1 THF–HMPT at −78 °C provided the corresponding lithium derivative, which rearranged smoothly upon warming to −30 °C to afford the desired cyclopentene **3** in 97% yield after purification.[12] The facility of this carbanion-accelerated process at low temperature stands in dramatic contrast to the 250–600 °C normally required to effect the conventional vinylcyclopropane rearrangement.[13] Also noteworthy is the fact that these carbanion-accelerated vinylcyclopropane rearrangements proceed considerably faster than the analogous reactions of vinylcyclopropanol salts previously investigated in our laboratory.[3]

(5) This route was selected in part since it simultaneously provided access to the corresponding α-sulfenyl and sulfinyl carbanion derivatives. Details will be described in the full report on this investigation.

(6) Martel, B.; Hiriat, J. M. *Synthesis* **1972**, 201.

(7) Mixtures of stereoisomeric (and in some cases regioisomeric) bromocyclopropanes were employed in this step without prior separation.

(8) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.

(9) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.

(10) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(11) In some cases oxidation was best achieved employing (a) 2.1 equiv of *m*-CPBA in CH_2Cl_2 at −78 to 25 °C or (b) $MoO_5{\cdot}HMPT{\cdot}H_2O$ as described by: Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469. Benneche, T.; Undheim, K. *Chem. Scr.* **1982**, *20*, 11.

(12) In some cases (Table I, entries 4–7) warming to 25 °C was necessary to complete the rearrangement of all isomeric (vinylcyclopropyl)methyl sulfones.

(13) Hudlicky, T.; Kutchan, T. M.; Naqui, S. M. *Org. React.* **1985**, *33*, 247.

The synthetic utility of this methodology is significantly enhanced by our discovery that the cyclopentenylmethyl sulfone anions generated in these rearrangements can be trapped in situ with a variety of organic electrophiles and that desulfonylation can then be conveniently achieved in the same flask under mild conditions. Table I summarizes our results. A number of useful substitution and addition reactions involving α-sulfonyl carbanions[14] can thus be exploited to prepare a wide variety of cyclopentenes bearing functionalized and branched appendages; the transformation of (vinylcyclopropyl)methyl sulfone to the cyclopentene derivative is effected as a single, efficient synthetic operation. Another notable feature of this annulation method is its stereoselectivity (Table I, entries 4–7). As in the case of our earlier [4 + 1] method, the predominant product of the overall annulation process can be viewed as resulting from the effective suprafacial exo cycloaddition of a substituted carbene to the conjugated diene (eq 2).[15]

In summary, we have developed an efficient [4 + 1] annulation strategy for the stereocontrolled synthesis of a wide variety of highly substituted and functionalized five-membered carbocycles. With the feasibility of the carbanion-accelerated vinylcyclopropane rearrangement now solidly established, we are currently investigating more direct, two-step variants of this [4 + 1] annulation strategy.

Acknowledgment. We thank the National Institutes of Health, Firmenich AG, and Eli Lilly and Co. for generous financial support.

(14) For reviews, see: (a) Durst, T. In "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; pp 171–213. (b) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019.

(15) However, our preliminary results suggest that the scope of this stereoselectivity may not prove as impressive as in the previous alkoxy series. Thus, rearrangement of the (vinylcyclopropyl)methyl sulfones derived from (*Z*)-1,3-pentadiene affords a mixture of both cis- and (mainly) trans-substituted cyclopentenes.

Insertion of Iridium into the C–H Bonds of Alkenes: The π-Complex Cannot Be an Intermediate

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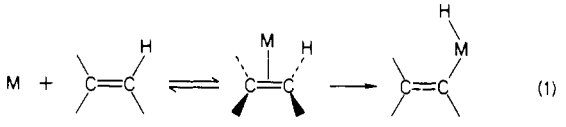
Despite their high bond energies[1], sp^2-hybridized (aromatic and vinyl) carbon–hydrogen bonds are more easily activated by transition metals than are the sp^3-hybridized C–H bonds in alkanes. It has been commonly assumed[2] that this is due at least partly to prior coordination of the metal to the π-electrons in the organic substrate (forming an η^2- or π-complex) followed by the oxidative addition step (eq 1).[3] We have now found that insertion

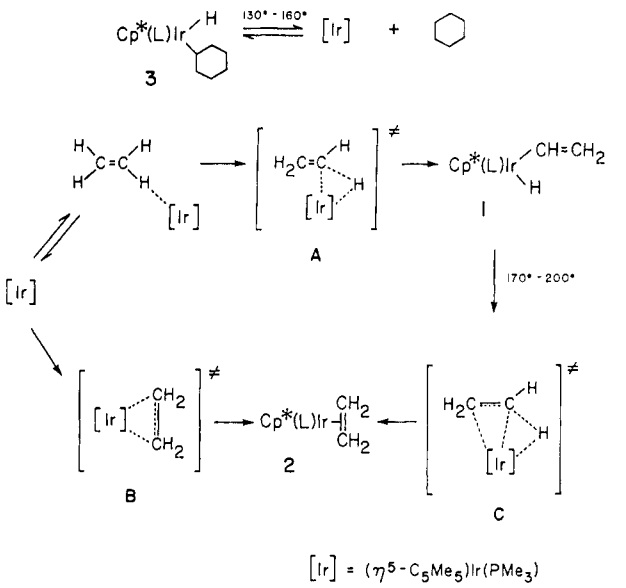


(1)

(1) Benson, S. W. "Thermochemical Kinetics"; Wiley: New York, 1968; p 309.

(2) (a) Parshall, G. W. *Acc. Chem. Res.* **1970**, *3*, 139. (b) Parshall, G. W. *Acc. Chem. Res.* **1975**, *8*, 113. (c) Parshall, G. W. "Homogeneous Catalysis"; Wiley: New York, 1980; Chapter 7. (d) Muetterties, E. L.; Bleeke, J. R. *Acc. Chem. Res.* **1979**, *12*, 324. (e) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1982**, *104*, 4240. (f) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650. (g) Chatt, J.; Davidson, J. M. *J. Chem. Soc.* **1965**, 843–855. (h) Parshall, G. W. *Catalysis* **1977**, *1*, 334. (i) Fryzuk, M. D.; Jones, T.; Einstein, F. W. D. *Organometallics* **1984**, *3*, 185. (j) Keister, J. B.; Shapley, J. R. *J. Organomet. Chem.* **1975**, *85*, C29. (k) Nubel, P. O.; Brown, T. L. *J. Am. Chem. Soc.* **1984**, *106*, 644–652.

Scheme I



of the iridium center in Cp*Ir(L) (Cp* = η^5-Me_5C_5; L = PMe_3) into the C–H bonds of ethylene occurs with concurrent, but *not* prior, formation of a π-complex. In addition, the chemistry of this system has allowed us to identify three distinct transition states having the formula $[Cp^*(L)Ir(C_2H_4)]$ and has provided the first X-ray structure of a mononuclear transition-metal hydrido vinyl complex.

Heating $Cp^*(L)Ir(C_6H_{11})(H)$ (**3**; cf. Scheme I)[4] in cyclohexane-d_{12} under 20 atm of $H_2C{=}CH_2$ at temperatures between 130 and 160 °C resulted in an essentially quantitative reductive elimination of cyclohexane,[5] leading to a solution containing 66% of the vinyl hydride **1** and 34% of the olefin complex **2**. Both products were prepared independently, **2** in a procedure based on Maitlis' preparation of the corresponding triphenylphosphine complex[6] and **1** by treatment of $Cp^*(L)IrCl_2$[7] with $H_2C{=}CH$-MgBr in THF at room temperature, followed by reduction with $NaBH_4$ in isopropyl alcohol. Chromatography of **1** at −80 °C followed by recrystallization yielded crystals suitable for an X-ray diffraction study. An ORTEP diagram of the molecular structure of **1** is illustrated in Figure 1; details of the structural study are included as supplementary information. To our knowledge this is the first structure determination of a mononuclear hydrido vinyl complex.

Significantly, the ratio of hydrido vinyl complex **1** to alkene complex **2** was invariant during the reaction of **3** with ethylene.[8]

(3) For the insertion of rhodium into arene C–H bonds, both kinetic and comparative inter- and intramolecular isotope effect studies (ref 2f; Jones, W. D., private communication) implicate η^2-arene complexes as true intermediates.

(4) (a) Janowicz, A. H.; Bergman, R. G. *J. Am. Chem. Soc.* **1983**, *105*, 3929. (b) Bergman, R. G. *Science (Washington, D.C.)* **1984**, *223*, 902.

(5) The reductive elimination is reversible, and cyclohexane-d_{12} is incorporated into the iridium complex as the reaction proceeds. However, conversion to **1** and **2** is complete at the end of the reaction. On thermolysis in mixed benzene/alkane solvents, hydridocyclohexyliridium complex **3** is converted cleanly and quantitatively to cyclohexane and the benzene C–H activation product $Cp^*(L)Ir(C_6H_5)(H)$. In studies parallel to those reported here (Buchanan, J. M.; Stryker, J. M.; Bergman, R. G., manuscript in preparation), we have demonstrated that this reaction proceeds by kinetics that are first order in **3** and zero order in benzene. The rates are inhibited at high concentration of added cyclohexane. These data are consistent with a mechanism involving reversible, rate-determining reductive elimination of cyclohexane to give Cp*IrL, followed by trapping of this intermediate by benzene in a subsequent fast step. We assume the same type of mechanism operates with ethylene in place of benzene as the trap.

(6) Moseley, K.; Kang, J. W.; Maitlis, P. M. *J. Chem. Soc. A* **1970**, 2875.

(7) Kang, J. W.; Moseley, K.; Maitlis, P. M. *J. Am. Chem. Soc.* **1969**, *91*, 5970.

(8) At 160 °C, upon extended thermolysis, a slow conversion of **1** to **2** occurs. If the reaction was stopped immediately after all $Cp^*(L)Ir(C_6H_{11})(H)$ was consumed, however, the amount of conversion of **1** to **2** was so small that it had no significant effect on the ratio.

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