Variable Regiochemistry in the Stoichiometric and Catalytic Hydroamination of Alkynes by Imidozirconium Complexes Caused by an Unusual Dependence of the Rate Law on Alkyne Structure and Temperature

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Abstract: We have investigated the regiochemistry of the stoichiometric and catalytic hydroamination of disubstituted alkynes by imidozirconium complexes. The addition of alkynes to $Cp_2Zr{=}NR$ occurred regioselectively to give metallacycles **2**, with the larger alkyne substituent R_L located α to the metal center. Hydrolysis of the metallacycles then gave enamines and their tautomeric imines which were the net result of anti-Markovnikov addition to the alkyne. The size of the R group on the imido ligand and the size of the alkyne were influential in determining the degree of regioselectivity. By utilizing $Cp_2(THF)Zr{=}NR$ to generate $Cp_2Zr{=}NR$ at room temperature and $Cp_2Zr(R')(NHR)$ to generate $Cp_2Zr{=}NR$ at high temperature, it was determined that the thermodynamic and kinetic regioselectivities were nearly identical for dialkylacetylenes. In contrast, for 1-phenylpropyne, the thermodynamic regioselectivity was found to be greater than the kinetic regioselectivity. The regioselectivity was found to be invariant from −6 to 45 °C in the addition of both 4-methyl-2-pentyne and 2-hexyne to $Cp_2(THF)Zr{=}NAr$. However, a significant erosion of regioselectivity was observed when 2-hexyne and 4-methyl-2-pentyne were catalytically hydroaminated by $Cp_2Zr(NHAr)_2$ at 120 °C. A kinetic study of the catalytic reaction suggested that the reason for this erosion was that the protonation step in the catalytic cycle (k_3[amine]) was slower than the cycloreversion of the stereoisomeric metallacycles to alkyne and $Cp_2Zr{=}NAr$ (k_{-2}) (the step that leads to regioequilibration). Because the protonation is selective for the metallacycle in which the smaller substituent is located at the position adjacent to the metal center, it counters the regioselectivity of the cycloaddition. This was an unexpected result because (1) an earlier study showed that k_3[amine] was larger than k_{-2} for the addition of diphenylacetylene to $Cp_2Zr{=}NR$ at both 25 °C and the catalytic reaction temperature (95 °C in this case) and (2) in the present work, it was demonstrated that k_3[amine] was also larger than k_{-2} for dialkylacetylenes at 25 °C. It was concluded that the relative magnitudes of the rate constants k_3 (protonation) and k_{-2} (reversion) must vary with temperature more dramatically in the dialkylacetylene + $Cp_2Zr{=}NR$ reaction than in the diarylacetylene + $Cp_2Zr{=}NR$ reaction. This was confirmed by direct competition experiments carried out at 25, 60, and 100 °C. We believe that the cycloreversion step k_{-2} is characterized by both a larger $\Delta H^{\ddagger}$ and a larger $\Delta S^{\ddagger}$ than protonation because the former is a unimolecular and the latter a bimolecular reaction.

Introduction

The addition of N–H bonds across double and triple bonds in unsaturated organic molecules (hydroamination) is a potentially valuable synthetic reaction. However, general, high-yield methods for carrying out this transformation are not yet available.[1-12] One possible approach to the development of hydroamination reactions is to explore the possibility of finding general cycloaddition reactions in which unsaturated organic molecules react with metal–nitrogen multiple bonds.[13] This would lead to metallacycles that might undergo cleavage in acid to give overall hydroamination products. Although the cycloaddition of alkenes and alkynes to metal carbene complexes is well-known,[14,15] it is virtually unknown when a heteroatom is multiply bonded to a metal center[16-19] although it has often been invoked as a mechanistic step in several transformations.[20,21]

In one example of such a process, we recently carried out a study of the reactions of intermediates of general formula

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(2) For a review of additions of amines to alkenes, see: Gasc, M. B.; Latties, A.; Perie, J. J. *Tetrahedron* **1983**, *339*, 703.
(3) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1.
(4) Chekulaeva, I. A.; Kondrat'eva, L. V. *Russ. Chem. Rev. (Engl. Transl.)* **1965**, *34*, 669.
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(6) Hudrlik, P. F.; Hudrlik, A. *J. Org. Chem.* **1973**, *38*, 4254.
(7) Barluenga, J.; Azar, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2732.
(8) Barluenga, J.; Azar, F. *Synthesis* **1975**, 704.
(9) For an example of transition metal catalyzed intermolecular alkene hydroamination, see: Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.
(10) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.
(11) Tamaru, Y.; Hofo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994.
(12) Gagné, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.
(13) For a recent intramolecular example of such a reaction, see: McGrane, P. L.; Jensen, J.; Livinghouse, T. *J. Am. Chem. Soc.* **1992**, *114*, 5459.
(14) (a) Ivin, K. J. *Olefin Metathesis*; Academic Press: London, 1983. (b) Nugent, W. A.; Mayer, J. M. *Metal-Ligand Multiple Bonds*; John Wiley & Sons: New York, 1988.
(15) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.
(16) We have previously reported the addition of alkynes to $Cp^*_2Zr{=}O$ and $Cp^*_2Zr{=}S$: Carney, M. J.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 6426.
(17) The addition of dimethyl acetylenedicarboxylate to $Cp^*Ir{=}N\text{-}t\text{-}Bu$ to give an η^4-pyrrole complex is probably initiated by a 2+2 cycloaddition: Glueck, D. S.; Wu, J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1991**, *113*, 2041.
(18) It is likely that an oxametallacycle is an intermediate in the trimethylphosphine-induced alkyne cycloaddition of Cp^*ReO_3 to provide a metallapyran: de Boer, E. J. M.; de With, J.; Orpen, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 8271.
(19) The dissociation of a tantalum oxametallacycle to provide a tantalum oxo complex and an alkene has been observed: Whinnery, L. L.; Henling, L. M.; Bercaw, J. E. *J. Am. Chem. Soc.* **1991**, *113*, 7575.
(20) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
(21) Jorgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483.

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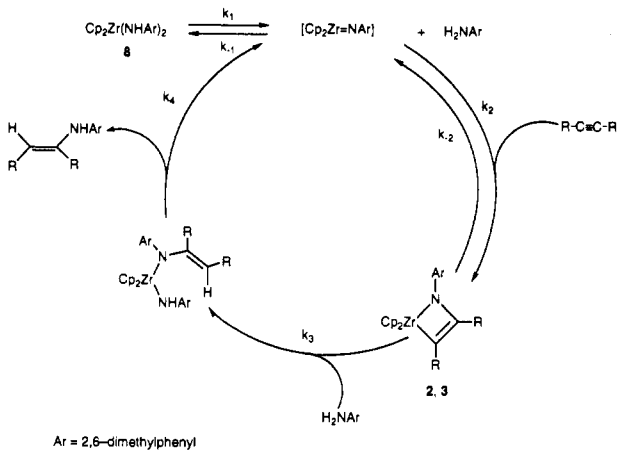
Scheme I



$Cp_2Zr{=}NR$, which react readily with alkynes to form azametallacyclobutenes.[22] The reactive intermediates $Cp_2Zr{=}NR$ can be generated by thermolysis of $Cp_2Zr(R)(NHR)$ or $Cp_2Zr(NHR)_2$ complexes or by dissociation of weakly-bound ligands L from $Cp_2(L)Zr{=}NR$ complexes. The enamide fragment can be removed from the metal center by protonation, leading initially to enamine products resulting from overall hydroamination of the alkyne. When the amine RNH_2 serves as the protonating agent, $Cp_2Zr{=}NR$ is regenerated, resulting in a catalytic cycle for conversion of alkynes to enamines or imines (Scheme I).[1]

The catalytic hydroamination is relatively slow and is limited to disubstituted alkynes, so in its present form, the reaction is not yet generally useful in organic synthesis. However, as one of the few early transition metal processes capable of inducing catalytic transformations of organic compounds, it seemed worthy of mechanistic study. Our earlier paper reported an examination of this reaction with symmetrical disubstituted alkynes, along with a kinetic and mechanistic study that provided support for the mechanism summarized in Scheme I.[1] Here we report an extension of this work to unsymmetrical alkynes, which provides an opportunity to examine the regiochemistry of the addition. We find that under stoichiometric conditions the regioselectivity is relatively high, leading to anti-Markovnikov addition across the alkyne triple bond. However, the regioselectivity of the catalytic process is quite dependent on reaction conditions, and this led us to carry out a detailed study of its mechanism, in hopes that such information would help us to understand this phenomenon and ultimately be of use in improving the practicality of the system. We report the results of the study in this paper.

Results

Regiochemistry of Stoichiometric Reactions of $Cp_2Zr{=}NR$ Generated from $Cp_2(THF)Zr{=}NR$ at 25 °C with Unsymmetrical Alkynes. The mildest way to generate $Cp_2Zr{=}NR$ is to utilize the THF-trapped imido complexes $Cp_2(THF)Zr{=}NR$ (**1**; cf. Scheme II). These complexes lose THF rapidly and reversibly at 25 °C, leading to the formation of azametallacyclobutenes in the presence of alkynes. As reported earlier, the metallacycles undergo thermal reversion to $Cp_2Zr{=}NR$ and alkyne at elevated temperatures, but at room temperature, this reaction is very slow,[1] providing support for the supposition that the use of $Cp_2(THF)Zr{=}NR$ as a precursor leads to the kinetic ratio of metallacycle regioisomers. Reaction of **1** with 1-phenylpropyne led predominantly to the formation of the royal blue product of anti-Markovnikov addition, metallacycle **2** (R_L = Ph, R_S = Me). Hydrolysis of the crude reaction mixture provided phenylacetone and propiophenone in a 4.7:1 ratio by GC and GCMS. The reaction of **1** with 2-hexyne and 4-methyl-2-pentyne also gave reasonable stereoselectivity. In these cases, the NMR spectra of the metallacycle mixtures were too complicated to assign regioselectivities reliably, and so they were again determined by hydrolysis of metallacycles to the corresponding ketones (Table I). These results show that the kinetically favored metallacycles are those in which the larger alkyne substituent is located α to the zirconium center. We also examined the regioselectivity of the reaction of the monomeric imido complex **1** with unsymmetrical dialkylacetylenes at various temperatures (Table I). Between –6 and 46 °C, the product ratio was independent of temperature within the experimental error of our product ratio determinations.

Addition of 4,4-dimethyl-2-pentyne to **1** proceeded with similar (but more highly selective) regiochemistry, providing azametallacyclobutene **2** (R_L = *t*-Bu, R_S = Me) in >98% NMR yield (70% isolated yield) with no trace of the other regioisomer **3**. In contrast to hydrolyses of the other metallacycles, however, hydrolysis of the crude reaction mixture in this case did not lead to the ketone 4,4-dimethyl-2-pentanone or 2,2-dimethyl-3-pentanone but instead regenerated 4,4-dimethyl-2-pentyne. Similar results were obtained by GC analysis of the organic phase obtained from the reaction of trifluoroacetic acid with **2** (R_L = *t*-Bu, R_S = Me) in hexanes at –40 °C followed by addition of H_2O. Accordingly, the regiochemistry of this reaction was determined by analysis of the NMR spectrum of **2** in a 2D NOESY experiment.

Regiochemistry of Stoichiometric Reactions of $Cp_2Zr{=}NR$ Generated from Thermolysis of $Cp_2Zr(NHR)(R)$. We next investigated the regiochemistry of reactions in which $Cp_2Zr{=}NR$ was generated by thermolysis. When a solution containing 3.78 equiv of the unsymmetrical alkyne 1-phenylpropyne and the alkyl amido complex $Cp_2Zr(NHR)(CH_2CH_2C(CH_3))$ (**4b**, R = 2,6-dimethylphenyl) in benzene was heated to 120 °C for 1 day, the blue metallacycle **2** (R_L = Ph, R_S = Me) was formed. Hydrolysis of the crude reaction mixture provided exclusively phenylacetone by GC and GCMS. Thus this reaction again shows anti-Markovnikov regioselectivity. More extensive regiochemisty data were collected utilizing the alkyl amido complexes **5**–**7** (see Table I) as starting materials and the unsymmetrical alkynes 2-hexyne and 4-methyl-2-pentyne as substrates. The crude mixture of regioisomeric metallacycles generated in each of these experiments was subjected to hydrolysis and analyzed by GC and GCMS. The absolute yield of ketones formed by thermolysis of **4a** with 2-hexyne was determined to be 72–78% (see Experimental Section for details).

The results from thermolysis of alkyl amido complex **4a** with 2-hexyne and 4-methyl-2-pentyne can be compared directly with those obtained at lower temperature using THF complex **1**. It is clear that the observed regioselectivity is very similar despite the fact that the metallacycles undergo reversible cleavage to $Cp_2Zr{=}NAr$ and alkyne at these temperatures.[1] We conclude that, in this case, the kinetic and thermodynamic isomeric metallacycle product ratios are nearly identical. However, in the case of 1-phenylpropyne, the kinetic and thermodynamic product ratios are different. The thermodynamically controlled reaction is more stereoselective, giving exclusively anti-Markovnikov addition. Reaction of the alkyl amido complex **4a** with 4,4-dimethyl-2-pentyne at 85 °C did not lead to metallacycles but instead gave intractable products.

Regiochemistry of Hydroaminations Catalyzed by $Cp_2Zr{=}NR$. As reported earlier,[1] bis(amido)zirconocene complexes, such as **8**, catalyze conversion of the corresponding amine and internal alkynes, such as diphenylacetylene and 2-butyne, to enamines (Scheme III). The enamine made catalytically with $Cp_2Zr(NHAr)_2$ (**8**) from diphenylacetylene (**E-10**, R_L = Ph, R_S = Ph) and 2,6-dimethylaniline was isolated and characterized by X-ray diffraction.[1] 1-Phenylpropyne, 2-hexyne, and 4-methyl-2-pentyne also undergo this reaction. With 1-phenylpropyne or 2-butyne,

(22) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729.

Scheme II

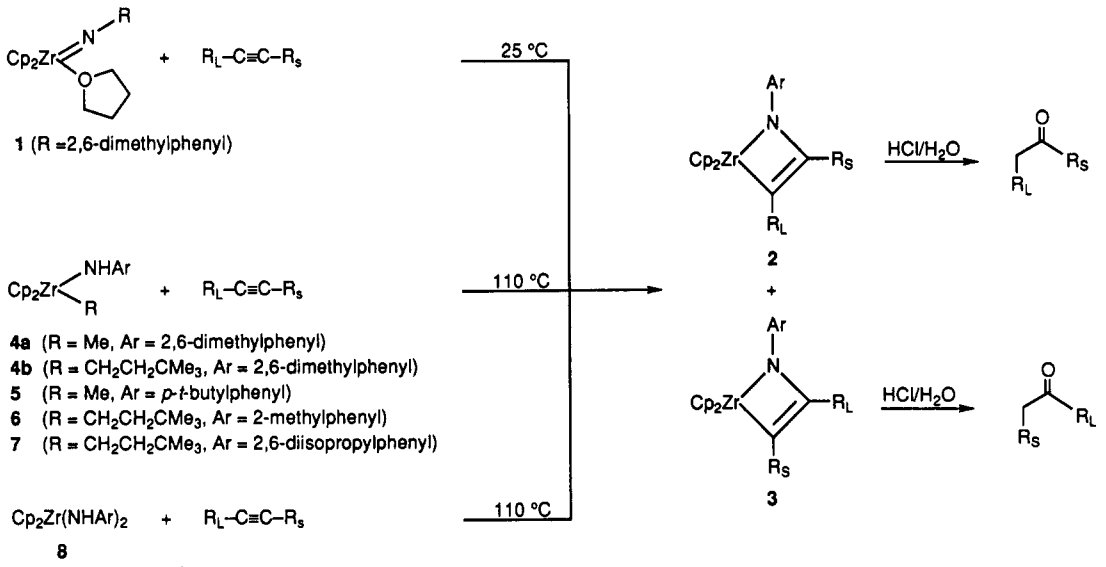
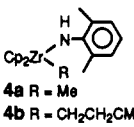
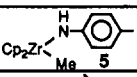
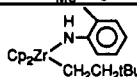
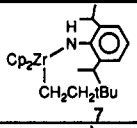
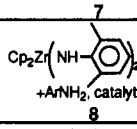


Table I. Ketones Formed on Reaction of Alkynes with Hydroaminating Reagents

		Ph–C≡C–CH_3		CH_3–C≡C–*n*-Pr		CH_3C≡C–*i*-Pr	
Reagent	T(°C)						
$Cp_2(THF)Zr$=NR	46	–	–	85	15	88	13
1 R=2,6-dimethylphenyl	22	18	82	86	14	90	10
	-6	–	–	86	14	91	9
 **4a** R = Me **4b** R = $CH_2CH_2CMe_3$	110	<1[a]	>99	82[b]	18	93[b]	7
 **5**	110	–	–	69	31	–	–
 **6**	110	–	–	68	32	–	–
 **7**	110	–	–	95	5	98	2
 +$ArNH_2$, catalytic **8**	110	18[c]	82	65	35	54	46

[a] 4b was used for this reaction. [b] 4a was used for this reaction. [c] Reaction performed at 120 °C.

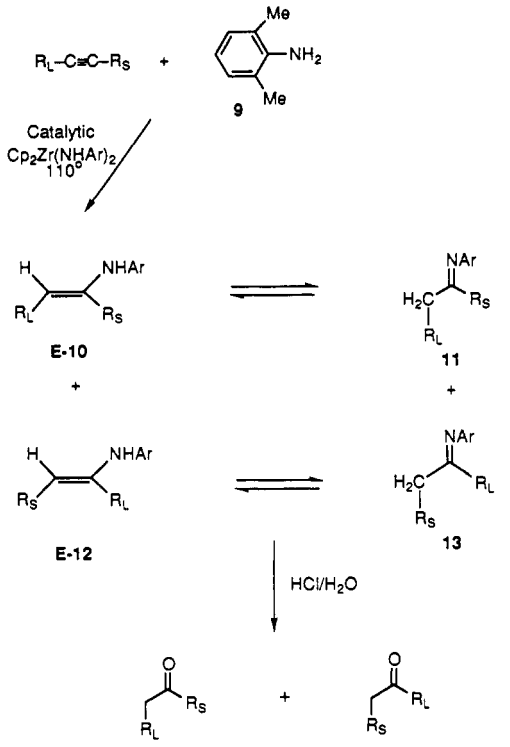
the enamine products **E-10** (R_L = Ph, R_S = Me) and **E-10** (R_L = R_S = Me) can be observed by ^1H NMR but tautomerize to the isomeric imines under the reaction conditions, as illustrated in Scheme III. When the unsymmetrical alkynes 2-hexyne and 4-methyl-2-pentyne were subjected to the catalytic hydroamination conditions with **8**, the (presumably initially formed) enamines rearranged more rapidly than they were formed, and imines were the only detectable products.

As shown in Table I, the catalytic hydroamination of 1-phenylpropyne leads to the formation of enamines **E-10** and **E-12** (R_L = Ph, R_S = Me) in a ratio of 82:18. This result suggests that the selectivity of the catalytic cycle is kinetically controlled. However, *catalyzed hydroamination of unsymmetrical alkyl-substituted alkynes using bis(amide) 8 showed substantial erosion of regioselectivity compared to that observed in the corresponding stoichiometric reactions.* Thus, the ratio of 2-hexanone to 3-hexanone formed from 2-hexyne was determined to be 69:31 (compared with 82:18 for the stoichiometric reaction using **1**) while the ratio of 4-methyl-2-pentanone to 2-methyl-3-pentanone formed from 4-methyl-2-pentyne was 54:46 (compared with 90:10 using **1**). This decrease in regioselectivity is surprising in view of the high regioselectivity observed in *both* the kinetically and thermodynamically controlled stoichiometric reactions discussed above and the high regioselectivity observed in both the stoichiometric and catalytic reactions carried out with 1-phenylpropyne.

Discussion of Regioselectivity Results

Regiochemistry of Stoichiometric Alkyne Addition to Cp_2Zr=NR. Two sets of conclusions can be drawn from inspection of the results of stoichiometric hydroamination. First, the kinetic and thermodynamic selectivities are different for dialkylacetylenes and 1-phenylpropyne. In the case of 1-phenylpropyne, the thermodynamically controlled reaction provides only phenylacetone after hydrolysis while the kinetically controlled reaction gives both regioisomers. Due to the moderate size of the

Scheme III



phenyl group compared with the alkyl groups discussed above, it seems likely that an electronic component (perhaps the stabilization of partial negative charge at the α-carbon by delocalization into the ring) supplements the α-directing steric effect for the thermodynamic product. For some reason, these effects are attenuated in the transition states leading to the two products, making them somewhat closer in energy.

In the case of the dialkylacetylenes, the ratios of isomeric ketones obtained upon hydrolysis of the products formed in the higher- and lower-temperature stoichiometric reactions are almost identical (Table I). Under the high-temperature conditions required for formation of $Cp_2Zr{=}NAr$ from $Cp_2Zr(NHR)(R')$, metallacycle formation is reversible.[1] However, at the low temperatures employed in reaction of the $Cp_2Zr(NAr)(THF)$ with alkynes, metallacycle formation is not reversible. As noted above, this forces us to conclude that the thermodynamic and kinetic ratios of metallacycle products formed from $Cp_2Zr{=}NAr$ are essentially the same. This appears to be a clear case of "product-development" control; that is, the energetic factors that control the relative stability of the azametallacycle products are present to almost the same extent in the transition states leading to these products as in the metallacycles themselves.

Second, in the hydroamination of dialkylacetylenes by thermolysis of the alkyl amides **4**–**7**, it is apparent that increasing the size of either the *N*-aryl group or the α-substituent on the alkyne increases the regioselectivity of metallacycle formation. Typically, the larger group on the unsymmetrical alkyne is located α to the metal in the product metallacycles. Although both the *N*-alkyl group and the Cp_2Zr moiety are sterically very demanding, the $Zr{-}C_\alpha$ distance in **2** ($R_L = R_S$ = Ph) of 2.21 Å is considerably longer than the $N{-}C_\beta$ distance of 1.43 Å. We believe this factor is responsible for determining the regiochemistry of the cycloaddition of unsymmetrical dialkylacetylenes. Changing the *N*-aryl group from 4-*tert*-butylphenyl to 2-methylphenyl results in no change in the regioselectivity toward 2-hexyne within experimental error, and so the ortho-methyl group can apparently rotate out of the way and does not influence the product ratio. However, changing the *N*-aryl group to 2,6-dimethylphenyl increases the percentage of 2-hexanone to 82% in the hydrolysis products. Increasing the steric bulk of the *N*-aryl ligand to 2,6-diisopropylphenyl further increases the fraction of 2-hexanone in the hydrolysis products to 95%. A similar trend was observed with the reaction of the alkyl amides **4a** and **7** with 4-methyl-2-pentyne.

Table II provides data that allow a comparison of the regioselectivity of the zirconium reaction with that observed using various hydroborating reagents.[23] The imidozirconium hydroamination demonstrates slightly greater selectivity, but the reaction is more limited—it cannot be extended to alkenes, and the Zr reagents are not compatible with organic carbonyls (although ethers do not pose a problem). In addition, hydroboration is more tolerant of remote functional groups and requires milder conditions.

Differences in Regiochemistry between the Stoichiometric Cycloaddition and Catalytic Enamine-Forming Reactions for Dialkylacetylenes. The most perplexing aspect of the regiochemistry experiments summarized under Results is the erosion of regioselectivity in the catalytic reaction involving dialkylacetylenes. This is especially surprising because it cannot be accounted for by assuming a change from kinetic to thermodynamic control in the cycloaddition step of the reaction—the direct stoichiometric studies show that the kinetic and thermodynamic azametallacycle product ratios are very similar.

In order to understand this result, we need to first summarize the results of kinetic studies carried out earlier that led us to propose the mechanism for the catalytic hydroamination shown in Scheme I.[1] We examined the catalytic formation of enamine **E-10** ($R_S = R_L$ = Ph) from the aryl-substituted alkyne diphenylacetylene and 2,6-dimethylaniline at 95 °C using the bis(amide) **8** as the catalyst. These studies were consistent with the rate law shown in eq 2. In the presence of excess alkyne (>10 equiv), the rate of disappearance of amine showed an inverse first-order dependence on [amine] (eqs 3 and 4). Measuring k_{obs} using different excess amounts of alkyne demonstrated that the reaction was first order in [alkyne]. Steady-state analysis of the mechanism in Scheme I leads to the rate law in eq 1. This reduces to the experimentally observed rate law in eq 2 if one assumes that the k_3[amine] step is faster than the k_{-2} step; that is, that protonation of the metallacycle occurs more rapidly than reversion of the metallacycle to alkyne and $Cp_2Zr{=}NR$. This situation can be summarized most clearly with reference to the free energy diagram in Figure 1.

$$\frac{d[\text{enamine}]}{dt} = \frac{-d[\text{amine}]}{dt} = \frac{k_1k_2k_3[\text{alkyne}][Cp_2Zr(NHAr)_2]}{k_{-1}(k_{-2} + k_3[\text{amine}])} \quad (1)$$

$$\frac{-d[\text{amine}]}{dt} = \frac{k_1k_2[\text{alkyne}][Cp_2Zr(NHAr)_2]}{k_{-1}[\text{amine}]} \quad (2)$$

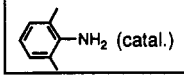
$$\frac{-d[\text{amine}]}{dt} = k_{obs}\left[\frac{1}{[\text{amine}]}\right] \quad (3)$$

$$\frac{1}{2}\left[[\text{amine}]_o^2 - [\text{amine}]^2\right] = k_{obs}t \quad (4)$$

In addition to the kinetic results, we obtained supporting evidence for the k_3[amine] $\gg k_{-2}$ assumption by studying directly the reaction between metallacycle **2** ($R_L = R_S$ = Ph) and 2,6-dimethylaniline. We found that treatment of isolated metallacycle **2** with 2,6-dimethylaniline rapidly gave enamide amide **14** at room temperature (Scheme IV), and reaction of **14** with a second equivalent of the aniline gave enamine **E-10** and regenerated $Cp_2Zr(NHAr)_2$. Exchange of alkyne fragments in the metallacycle, on the other hand, required several days at 45 °C. This conclusion was confirmed by carrying out competition experiments

(23) Brown, H. C.; Campbell, J. B. *Aldrichimica Acta* **1981**, *14*, 3.

Table II. Comparison of Internal Alkyne Hydroboration[a] and Zirconium Hydroamination Regioselectivities

	Ph–C≡C–CH_3		CH_3–C≡C–*n*-Pr		CH_3–C≡C–*i*-Pr	
Reagent						
Diborane	–	–	60	40	75	25
Thexylborane	–	–	61	39	81	19
Disiamylborane	19	81	61	39	93	7
Dicyclohexylborane	29	71	67	33	92	8
$HBBr_2$•SMe_2	64	36	75	25	96	4
9•BBN	65	35	78	22	96	4
$Cp_2Zr(R)(NHAr)$ heat (stoich.)	<1	>99	82	18	93	7
$Cp_2Zr(NHAr)_2$ +  (NH_2 (catal.)	18	82	65	35	54	46

[a]Determined by oxidation of the alkenylboranes to the corresponding carbonyl compounds; cf. Brown, H.C.; Campbell, J.B. *Aldrichimia Acta* **1981**, *14*, 3

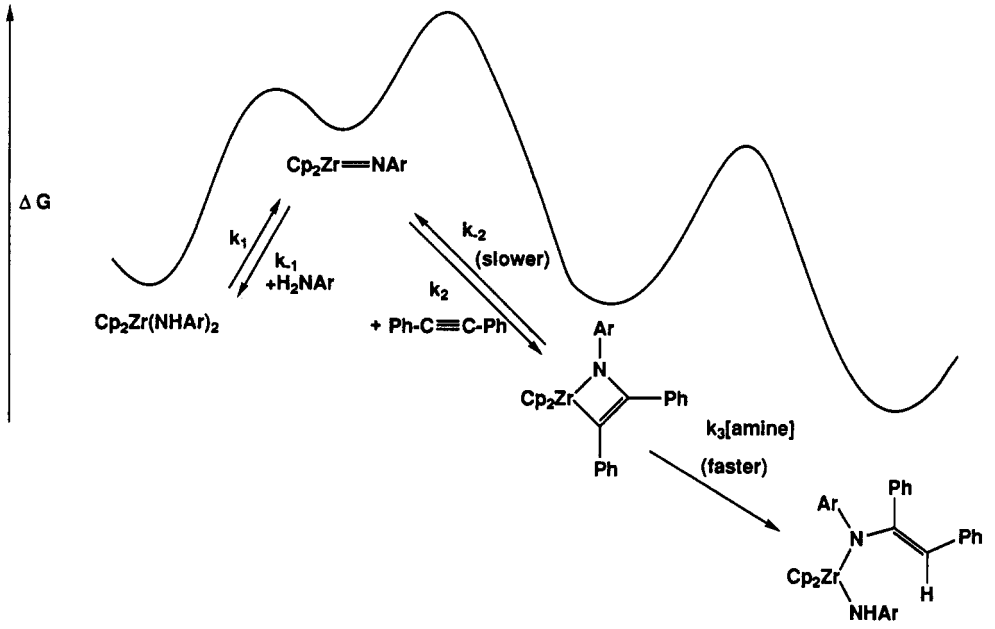


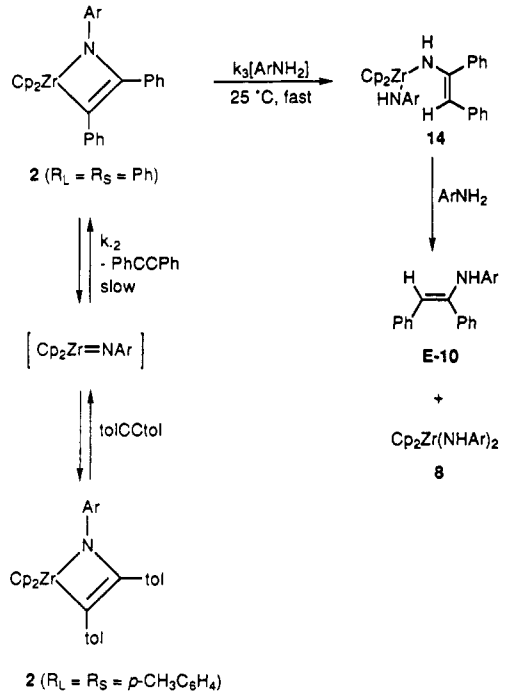
Figure 1. Free energy diagram for the catalytic reaction with diphenylacetylene.

in which the metallacycles formed from both diaryl- and dialkylacetylenes were treated with arylamines at room temperature and then the products subjected to hydrolysis and analysis by gas chromatography. At room temperature, complete conversion to ketones was observed, contaminated with no traces of alkynes.

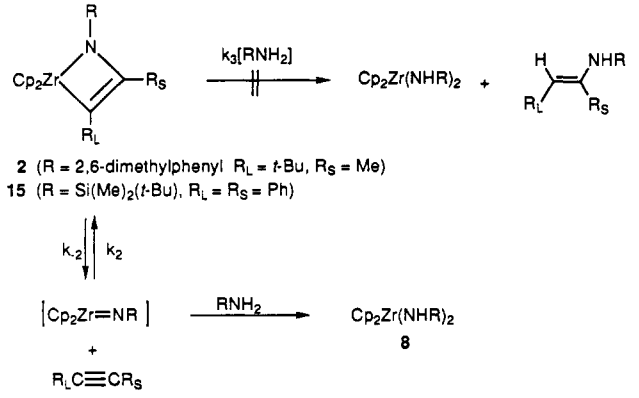
However, we observed that the k_3[amine] $\gg k_{-2}$ assumption was sensitive to the nature of the alkyne and amine used. For example, upon addition of 2,6-dimethylaniline to **2** (R_L = *t*-Bu, R_S = Me), a metallacycle in which a *tert*-butyl group is located at the position α to the metal center (Scheme V), the solution slowly changed color from purple to yellow over 45 min. Monitoring the resulting mixture by ^{1}H NMR spectrometry showed that *no* protonation of the metallacycle had occurred. Instead, reversion to 4,4-dimethyl-2-pentyne and Cp_2Zr=NAr had taken place, followed by rapid trapping of the imido complex by amine to give $Cp_2Zr(NHAr)_2$. We previously found that addition of (*tert*-butyldimethylsilyl)amine to metallacycle **15** resulted in no protonation presumably because of the large size of the amide (Scheme V). Thus, sufficient steric hindrance at the α-position substantially retards the rate of protonation and increases the propensity for cycloreversion of the metallacycle, completely inverting the relative magnitudes of retrocyclization (k_{-2}) and protonation (k_3[amine]). However, it is clear from the direct protonation and exchange studies summarized above that, at room temperature and normal amine concentrations, k_3[amine] for metallacycles fomed from simple, relatively unhindered amines and diaryl- and dialkylacetylenes is larger than k_{-2}.

What, then, is responsible for the erosion in regioselectivity observed during the catalytic hydroamination of dialkylacetylenes? Because the ratio of ketone products reflects neither the kinetic nor the thermodynamic ratio of metallacycles and k_3[amine] is larger than k_{-2} at room temperature, we are forced to conclude that these rate constants become comparable, or their relative magnitudes even invert, for the dialkylacetylenes (but not for the diarylacetylenes) as the temperature is raised near and above 140 °C. When this change in relative rate takes place, the reaction is represented by the free energy diagram illustrated in Figure 2 rather than in Figure 1. Here, interconversion of the metallacycles occurs rapidly under the reaction conditions, but more significantly, *the transition states for protonation lie at higher free energy than those for cycloaddition.* In the limiting case, interconversion of the metallacycles becomes substantially more rapid than protonation. In this so-called "Curtin–Hammett" situation,[24-26] the ratio of protonated products is determined only

Scheme IV



Scheme V



by the relative free energies of the transition states leading to these products and does not correspond to the ratio of regioisomeric metallacycles present in solution.

Kinetics of Dialkylacetylene Hydroamination. The above hypothesis, that the rate law for the catalytic system changes in going from diaryl- to dialkylacetylene hydroamination, is testable. First, the kinetic behavior of the catalytic dialkylacetylene hydroamination should be different from that of the diarylacetylene hydroamination. If the assumption that $k_{-2} \gg k_3$[amine] is applied to the general rate law in eq 1, the resulting reduced rate law now predicts no dependence, rather than an inverse dependence, on [amine] (eqs 5 and 6). We therefore decided to

$$\frac{-\,d[\text{amine}]}{dt} = \frac{k_1 k_2 [\text{alkyne}][Cp_2Zr(NHAr)_2]}{k_{-1}} = k_{obs} \qquad (5)$$

$$[\text{amine}]_o - [\text{amine}] = k_{obs} t \qquad (6)$$

determine the rate law of the reaction of $Cp_2Zr{=}NR$ (R = 2,6-dimethylphenyl) with 2-hexyne. Kinetic studies were carried out at 140 °C in benzene-d_6 solution employing conditions and techniques essentially identical to those used to measure the rates of hydroamination of diphenylacetylene described earlier.[1] This included running the reactions in the presence of excess alkyne and following the disappearance of amine by ^{1}H NMR spectrometry. As noted above, this technique had earlier revealed that the diphenylacetylene reaction followed inverse first-order kinetics in [amine]. As predicted in eqs 5 and 6, Figure 3 shows that, for the dialkylacetylene, a plot of the absolute concentration of amine vs time is linear; i.e., the reaction exhibits *pseudo-zero-order* dependence in [amine]. To be certain of this result, plots of [amine]^2/2 and of ln [amine] vs time were also made (Figures 4 and 5). These show definite curvature relative to the zero-order plot. Pseudo-zero-order rate constants for the disappearance of amine were then measured at several different concentrations of alkyne and catalyst, and the data are recorded in Table III. Plotting these data (Figures 6 and 7) demonstrates that, parallel to that of the diphenylacetylene reaction, the rate law is first order in catalyst and alkyne concentrations and allows calculation of the derived rate constant ratio $(k_1k_2k_3)/(k_{-1}k_{-2})$, which is also presented in Table III.

A second consequence of the inverted k_3[amine]$/k_{-2}$ hypothesis is that the temperature dependence of this ratio ought to be directly measurable for the diaryl- and dialkylacetylene systems. To determine this, we treated the metallacycles formed from dialkylacetylenes and **1** with excess 2,6-dimethylaniline and measured the ratio of ketones to liberated alkyne produced over a range of temperatures (Scheme VI). We confirmed in a second experiment that the reaction of $Cp_2(THF)Zr{=}NAr$ was faster with amine than with alkyne. This assured us that the alkyne liberated in the k_{-2} step did not react again with $Cp_2Zr{=}NAr$ (k_2) and result in an inaccurate alkyne concentration being observed (Scheme VII). We found (as noted above) no alkyne at room temperature in the reaction of the metallacycles with amine, and in the case of diphenylacetylene, only small amounts at 95 °C (ketone/alkyne = 1000) and 120 °C (ketone/alkyne = 250). However, there is a much more dramatic temperature dependence on the ratio of products formed from the dialkylmetallacycles. In contrast to the fact that no alkyne is formed on protonation/hydrolysis of metallacycles **2** and **3** (R_L = *i*-Pr, R_S = Me) at room temperature, at 60 °C the ratio changes to ketone/alkyne = 31, and at 100 °C it becomes 3.3. This confirms the assumption made above that the k_3[amine]$/k_{-2}$ ratio is high for both diaryl- and dialkylacetylenes at room temperature but drops much more dramatically for the latter than for the former system as the temperature rises. This is the reason for the erosion in regioselectivity in the catalytic hydroamination of dialkylacetylenes and for the different reduced rate laws observed in the two systems.

Final Discussion and Conclusions

The combined results of the earlier paper[1] and this one provide an unusually detailed picture of the mechanism of the imidozirconocene-catalyzed alkyne hydroamination reaction. In this paper we have demonstrated that the regioselectivity of stoichiometric hydroamination is high for both aryl- and alkylacetylenes but undergoes a surprising erosion in the catalytic reaction. Our earlier results demonstrated that hydroamination of diphenylacetylene proceeds with kinetics that are consistent with the general rate law written in eq 1, assuming that protonation (k_3[amine]) is faster than cycloreversion of the metallacycle to $Cp_2Zr{=}NAr$ and alkyne (k_{-2}). When the alkyne is changed to 4-methyl-2-pentyne, we believe that the same mechanism (and therefore the same general rate law written in eq 1) holds. However, the observed dependence on [amine] changes from inverse to zero order. The most economical way to rationalize this is to assume that in the dialkylacetylene hydroamination the relative magnitudes of k_3 and k_{-2} are indeed reversed at the temperatures needed to run the catalytic reaction and k_3[amine]

(24) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.
(25) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 151–152.
(26) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111.

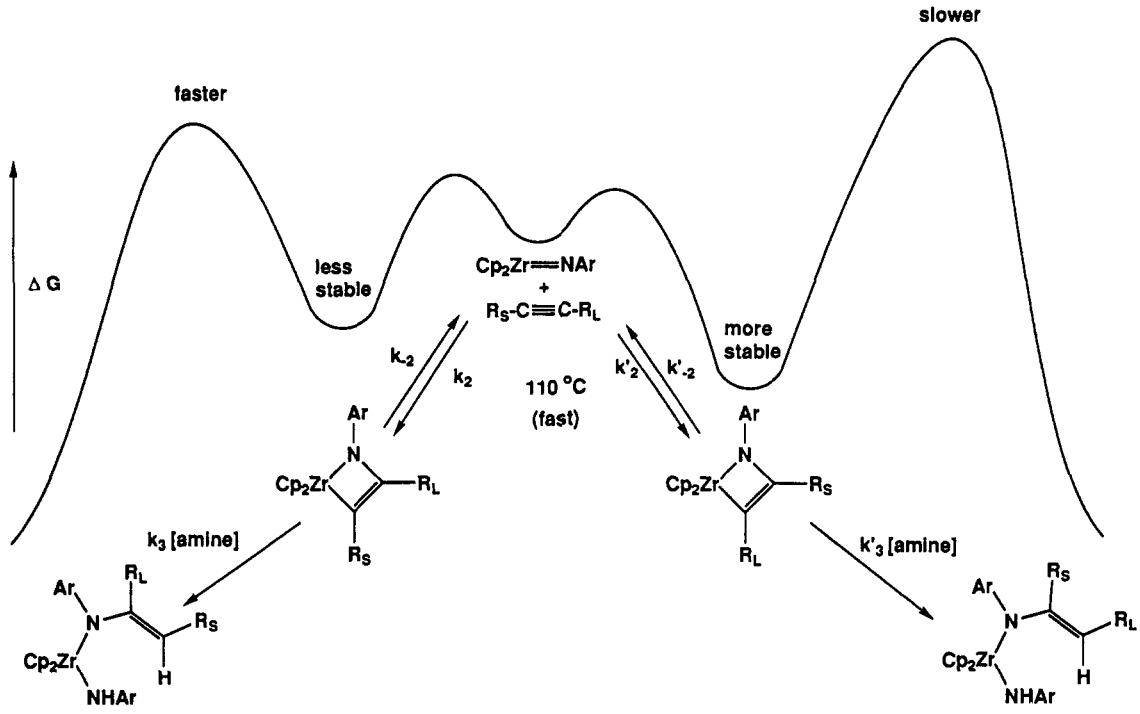


Figure 2. Free energy diagram for the catalytic reaction with 4-methyl-2-pentyne.

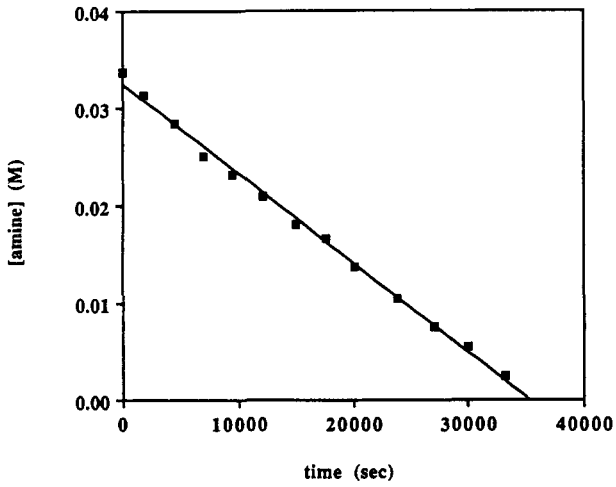


Figure 3. Plot of the concentration of amine vs time for kinetic run 1. See Table III for an estimate of error in the kinetic data.

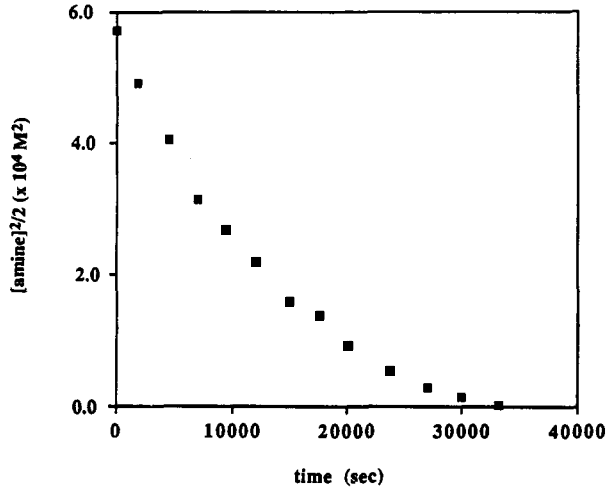


Figure 4. Plot of $[amine]^2/2$ vs time for kinetic run 1.

$\ll k_{-2}$ for this system. This serves to rationalize the erosion in regioselectivity for the dialkylacetylenes because the change in rate law requires a change in the product ratio-determining step from metallacycle formation to (now presumably slower) protonation. When protonation controls the reaction, a larger proportion of rapidly equilibrating metallacycles is funneled off to the enamine formed by protonation of the metallacycle that has the less hindered α-carbon atom, as shown in Figure 2.

We believe that this change in relative rates is due to compensating differences in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for metallacycle protonation and cycloreversion. Cycloreversion of the metallacycle is unimolecular and is thus expected to have a positive $\Delta S^{\ddagger}$. As a bimolecular process, the k_2 step should have a negative $\Delta S^{\ddagger}$. Since the rates and therefore the $\Delta G^{\ddagger}$ values for the two processes are similar at temperatures near 100 °C, $\Delta H^{\ddagger}$ for the reversion must be larger than $\Delta H^{\ddagger}$ for protonation. This means that the temperature dependence of k_{-2} is steeper (i.e., the rate of unimolecular reaction increases more rapidly with temperature) and a significant difference in rate at 25 °C is transformed into competitive velocities at 110 °C, as illustrated in Figure 8. Unfortunately, our data were not precise enough to get an accurate estimate of $\Delta\Delta H^{\ddagger}$ or $\Delta\Delta S^{\ddagger}$. For the diarylacetylene case, the activation parameters for protonation and retrocyclization differ in a similar way. However, the difference in rates is apparently sufficiently great at room temperature that the crossover point, where the rates become similar, is not yet reached at the temperature needed to carry out the catalytic reaction.

The selectivity of the catalytic cycle involving 1-phenylpropyne at 120 °C is the same as that of the kinetically controlled metallacycle formation. This could be because $k_3[amine] \gg k_{-2}$ as in the diphenylacetylene reactions and the regioselectivity is therefore under kinetic control. However, this same selectivity could be seen if $k_{-2} \gg k_3[amine]$ and the protonation caused an erosion of the thermodynamic product selectivity.

This work and that in the previous paper[1] demonstrate that early transition metal–nitrogen multiple bonds can undergo cycloaddition reactions with carbon–carbon triple bonds and that these processes can be used as the basis for catalytic organic functionalization reactions. It further establishes that the regiochemistry need not be determined by either the kinetically or thermodynamically controlled mixture of metallacycle regioisomers but by a complex interplay of metallacycle-formation, retrocycloaddition, and protonation rates. We hope that this

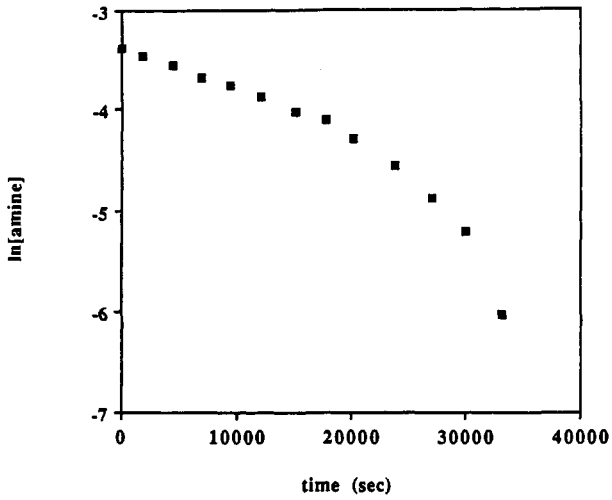


Figure 5. Plot of ln [amine] vs time for kinetic run 1.

Table III. Initial Concentrations and Rate Constants for the Catalytic Hydroamination of 4-Methyl-2-pentyne in the Presence of 2,6-Dimethylaniline and $Cp_2Zr(NHAr)_2$ Catalyst[a]

expt	$[amine]_0$ (M)	10^3[cat] (M)	[alkyne] (M)	k_{obs} (M^{-1} s^{-1})	$10^4 k_1k_2k_3/k_{-1}k_{-2}$[b] ($M^{-1}$ s^{-1})
1	0.0338	4.05	0.337	9.20×10^{-7}	6.74
2	0.0311	5.80	0.479	2.22×10^{-6}	7.99
3	0.0322	5.79	0.661	2.88×10^{-6}	7.52
4	0.0319	6.11	0.813	3.95×10^{-6}	7.95
5	0.0349	1.16	0.347	2.85×10^{-6}	7.00
6	0.0317	2.82	0.317	6.48×10^{-6}	7.25
7	0.0329	9.51	0.330	2.40×10^{-6}	7.65

[a] Standard deviation of k_{obs} for experiment 1 was calculated to be 0.2×10^{-7} M^{-1} s^{-1}. [b] Average value of $k_1k_2k_3/k_{-1}k_{-2}$ is $(7.4 \pm 0.5) \times 10^{-4}$ M^{-1} s^{-1}.

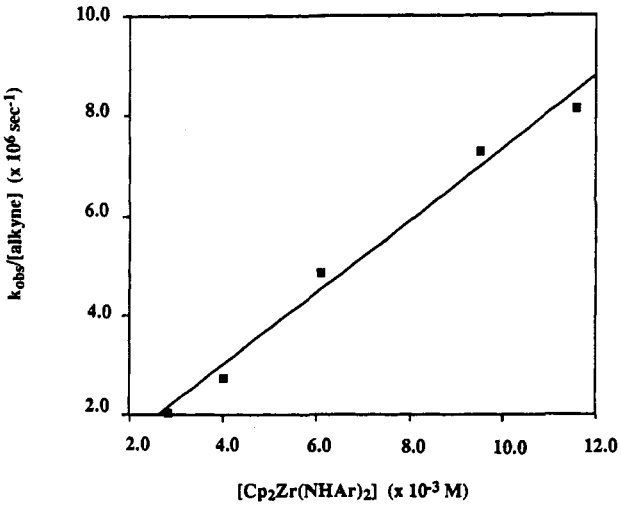


Figure 6. Plot of k_{obs}/[alkyne] vs the concentration of catalyst.

study will lead to methods for better regiochemical control of M=NR cycloadditions, as well as to systems in which oxygen as well as nitrogen can be transferred and both alkenes and alkynes can be used as substrates.

Experimental Section

General Procedures. Unless otherwise noted, all manipulations were carried out under an inert atmosphere in a Vacuum Atmospheres 553-2 drybox with attached M6-40-1H Dritrain or by using standard Schlenk or vacuum line techniques. Degassed solutions were frozen to −196 °C, evacuated under high vacuum, and thawed. This sequence was repeated three times in each case. Glass reaction vessels fitted with ground glass joints and Teflon stopcocks are referred to as bombs.

^1H NMR spectra were obtained on either the 250-, 300-, 400-, or 500-MHz Fourier transform spectrometer at the University of California, Berkeley (UCB), NMR facility. The 250- and 300-MHz instruments were constructed by Mr. Rudi Nunlist and interfaced with either a Nicolet 1180 or 1280 computer. The 400- and 500-MHz instruments were commercial Bruker AM series spectrometers. ^1H NMR spectra were recorded relative to residual protiated solvent. $^{13}C\{^1H\}$ NMR spectra were obtained at either 75.4 or 100.6 MHz on the 300- or 400-MHz instrument, respectively, and chemical shifts were recorded relative to the solvent resonance. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane, and all coupling constants are reported in hertz.

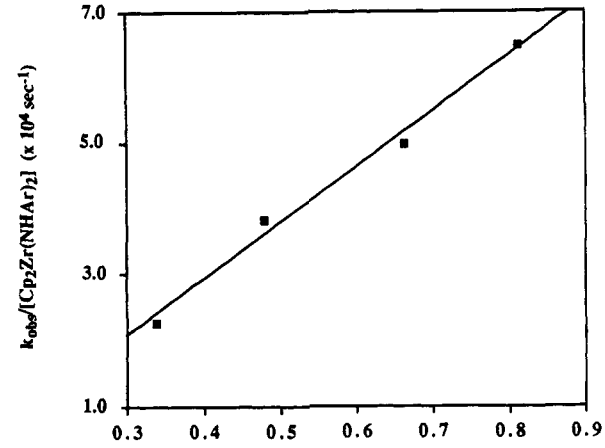
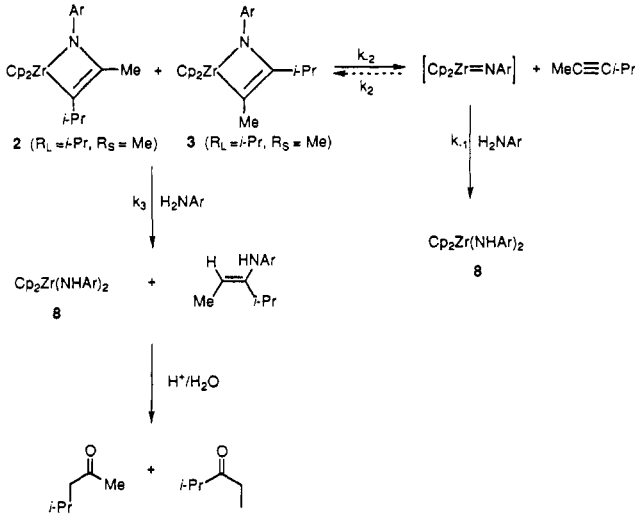
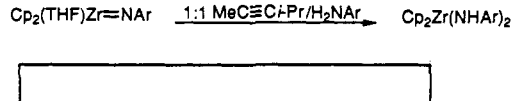


Figure 7. Plot of k_{obs}/[catalyst] vs the concentration of alkyne.

Scheme VI



Scheme VII



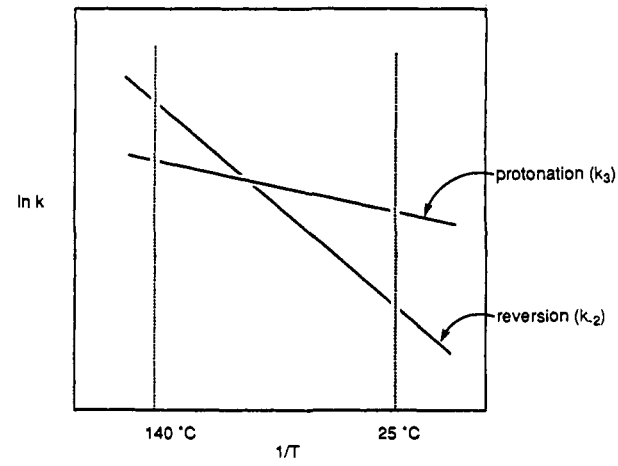


Figure 8. Arrhenius plot of protonation (k_3) and reversion (k_{-2}).

IR spectra were obtained on a Nicolet 510 FT-IR spectrometer. Mass spectroscopic (MS) analyses were obtained at the UCB mass spectrometry facility on AEI MS-12 and Kratos MS-50 mass spectrometers. Elemental analyses were obtained from the UCB Microanalytical Laboratory.

Selected NMR tubes were prepared using Wilmad 505-PP and 504-PP tubes attached via Cajon adapters directly to Kontes vacuum stopcocks and degassed using freeze–pump–thaw cycles before flame-sealing.[27] Known-volume-bulb vacuum transfers were accomplished with an MKS baratron attached to a high-vacuum line.

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without further purification. 2,6-Dimethylaniline, 4-*tert*-butylaniline, and 2-methylaniline (Aldrich) were dried over sodium and distilled under vacuum. 2-Hexyne and 4-methyl-2-pentyne were vacuum-transferred from sodium.

Pentane and hexanes (UV grade, alkene free) were distilled from sodium benzophenone ketyl/tetraglyme under nitrogen. Benzene, toluene, ether, and THF were distilled from sodium benzophenone ketyl under nitrogen. Deuterated solvents for use in NMR experiments were dried as their protiated analogues but were vacuum-transferred from the drying agent. $Cp_2Zr(Me)(Cl)$[22,28] and $Cp_2Zr(CH_2CH_2CMe_3)(Cl)$[29,30] were prepared by literature methods. Compounds **1**, **4b**, **5**, **8**,[31] **2** (R_L = R_S = Ph), **4a**, and **E-10** (R_L = R_S = Ph)[1] are reported elsewhere.

$C_{27}H_{27}NZr$ (2, R_L = Ph, R_S = Me). The bis(amide) $Cp_2Zr(NH(2,6\text{-dimethylphenyl}))_2$ (448 mg, 9.70×10^{-4} mol) and 1-phenylpropyne (458 mg, 3.95×10^{-3} mol, 4.1 equiv) were dissolved in 10 mL of benzene, and the mixture was transferred to a glass bomb. The solution was degassed and heated at 110 °C for 20 h, during which time the color changed from yellow to royal blue. The volatile materials were removed under reduced pressure, the remaining oil was taken up in 10 mL of hexanes, and the mixture was cooled to −30 °C. Dark blue crystals of the metallacycle were recovered by filtration to yield 350 mg (7.66×10^{-4} mol, 79%) of **2** (R_L = Ph, R_S = Me). IR (C_6H_6): 1589 (w), 1521, 1435, 1417, 1293, 1275, 1229, 1102, 1071, 850, 800, 765 cm^{-1}. ^1H NMR (C_6D_6): δ 7.38 (t, J = 7.15 Hz, 2 H), 7.12 (m, 5 H), 6.91 (t, J = 7.37 Hz, 1 H), 5.78 (s, 10 H), 2.14 (s, 6 H), 1.75 (s, 3 H). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 177.10, 150.90, 148.49, 130.93, 129.41, 128.38, 128.18, 123.68, 123.52, 121.23, 111.95, 20.77, 15.35. MS (EI): m/e 455 (M^+), 115 (base). UV–vis: λ_{max} = 310 nm (ϵ 5.5×10^3), 334 nm (ϵ 4.7×10^3). Anal. Calcd for $C_{27}H_{27}NZr$: C, 71.00; H, 5.96; N, 3.01. Found: C, 71.18; H, 6.02; N, 3.15.

$C_{24}H_{29}NZr$ (2, R_L = *i*-Pr, R_S = Me). The bis(amide) **8** (200 mg, 4.33×10^{-4} mol) and 4-methyl-2-pentyne (178 mg, 2.17×10^{-3} mol, 5.0 equiv) were dissolved in 10 mL of toluene, and the solution was transferred to a glass bomb. The solution was degassed and heated to 120 °C for 18 h, after which the volatile materials were removed under reduced pressure, leaving a purple oil. The oil was dissolved in 3 mL of toluene, and the mixture was layered with 3 mL of hexanes. The solution was then cooled to −30 °C, and the dark purple crystals that appeared were isolated by filtration to provide 145 mg (3.43×10^{-4} mol, 79%) of metallacycle **2** (R_L = *i*-Pr, R_S = Me). IR (C_6H_6): 1590, 1466, 1459, 1437, 1432, 1415, 1291, 1270, 1237, 1192, 1107, 1014, 812, 795, 762, 516, 499, 469, 455 cm^{-1}. ^1H NMR (C_6D_6): δ 7.09 (d, J = 7.37 Hz, 2 H), 6.88 (t, J = 6.88 Hz, 1 H), 5.78 (s, 10 H), 3.08 (m, J = 6.66 Hz, 1 H), 2.15 (s, 6 H), 1.53 (s, 3 H), 1.15 (d, J = 6.66 Hz, 6 H). $^{13}C\{^1H\}$ NMR (THF-d_8): δ 189.27, 151.26, 129.84, 129.35, 120.44, 116.97, 110.06, 33.86, 25.40, 20.82, 15.22. Anal. Calcd for $C_{24}H_{29}NZr$: C, 68.19; H, 6.91; N, 3.31. Found: C, 68.01; H, 6.93; N, 3.13.

$C_{25}H_{31}NZr$ (2, R_L = *t*-Bu, R_S = Me). To a stirred solution containing the imido complex $Cp_2Zr(N(2,6\text{-}Me_2C_6H_3))(THF)$ (**1**) (56.8 mg, 1.38×10^{-4} mol) in 7 mL of C_6H_6 was added 4,4-dimethyl-2-pentyle (59.2 mg, 6.17×10^{-4} mol, 4.5 equiv) at 25 °C. Upon addition of the alkyne, the solution began to darken and turned purple within 5 min. The reaction mixture was stirred for 1 h, and the volatile materials were removed under reduced pressure, leaving a purple solid. The solid was dissolved in 3 mL of toluene, the solution was layered with 1 mL of pentane, and the mixture was cooled to −30 °C. The purple crystals that formed under these conditions were isolated by decanting the solvent to provide 42.4 mg (9.71×10^{-5} mol, 70%) of **2** (R_L = *t*-Bu, R_S = Me). The yield of **2** (R_L = *t*-Bu, R_S = Me) was also determined by ^1H NMR spectrometry as follows. An NMR tube was charged with $Cp_2Zr(N(2,6\text{-}Me_2C_6H_3))(THF)$ (7.5 mg, 1.81×10^{-5} mol), *p*-dimethoxybenzene (2.5 mg, 1.81×10^{-5} mol), and 0.6 mL of C_6D_6. Two single-pulse ^1H NMR spectra were acquired in which the resonance due to the cyclopentadienyl ligands was integrated against the methyl resonance of the *p*-dimethoxybenzene. 4,4-Dimethyl-2-pentyne (6.5 mg, 6.76×10^{-5} mol, 3.7 equiv) was added to the NMR tube at 25 °C, and the color of the solution changed from orange to purple. After 20 min, another set of ^1H NMR spectra were obtained as described above. Averaging the integrated areas, it was determined that the reaction proceeded in >98% yield. IR (THF): 3104, 3085, 3067, 1814, 1587, 1490, 1317, 1271, 789, 760, 733. ^1H NMR (C_6D_6): δ 7.09 (d, J = 7.43 Hz, 2 H), 6.88 (t, J = 7.42 Hz, 1 H), 5.80 (s, 10 H), 2.15 (s, 6 H), 1.62 (s 3 H), 2.16 (s, 9 H). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 187.63, 151.41, 130.08, 129.37, 120.48, 116.97, 110.20, 37.06, 32.76, 20.99, 16.81. Anal. Calcd for $C_{25}H_{31}NZr$: C, 68.75; H, 7.15; N, 3.21. Found: C, 68.34; H, 6.95; N, 3.15.

$Cp_2Zr(NH(2\text{-}MeC_6H_4))(CH_2CH_2CMe_3)$ (6). 2-Methylaniline (135.8 mg, 1.27×10^{-3} mol) was dissolved in 10 mL of THF at 25 °C, and 0.55 mL of 2.3 M *n*-BuLi in hexanes (1.27×10^{-3} mol) was added via syringe. The solution was stirred for 5 min, and $Cp_2Zr(CH_2CH_2CMe_3)(Cl)$ (394 mg, 1.15×10^{-3} mol) was added to the stirred solution of the lithium amide. The mixture was stirred for 7 h, after which the volatile materials were removed under vacuum. The remaining yellow solid was extracted into 10 mL of toluene, and the solution was filtered. The filtrate was concentrated to 3 mL and layered with hexanes, and the mixture was cooled to −30 °C. Under these conditions, large yellow blocklike crystals appeared; these were isolated by decanting the solvent and washing with hexanes to provide 377 mg (9.13×10^{-3} mol, 79%) of the alkyl amide **6**. IR (C_6H_6): 3353 (w), 2949 (s), 2888 (s), 2861, 1439, 1255, 775, 720, 620, 610 cm^{-1}. ^1H NMR (C_6D_6): δ 7.17 (t, J = 6.40 Hz, 1 H), 7.09 (d, J = 7.17 Hz, 1 H), 6.99 (d, J = 7.71 Hz, 1 H), 6.87 (td, J = 7.29, 0.92 Hz, 1 H), 6.27 (s, 1 H), 5.65 (s, 10 H), 1.89 (s, 3 H), 1.56 (m, 2 H), 1.07 (s, 9 H), 0.94 (m, 2 H). $^{13}C\{^1H\}$ NMR (C_6D_6): δ 155.23, 129.64, 127.05, 124.99, 122.60, 120.57, 109.76, 48.60, 35.67, 32.98, 22.66, 18.57. Anal. Calcd for $C_{23}H_{31}NZr$: C, 66.93; H, 7.57; N, 3.39. Found: C, 67.12; H, 7.61; N, 3.34.

$Cp_2Zr(NH(2,6\text{-}i\text{-}Pr_2C_6H_3))(CH_2CH_2CMe_3)$ (7). To a solution of 10 mL of THF containing 2,6-diisopropylaniline (311 mg, 1.76×10^{-3} mol) was added 0.76 mL of 2.3 M *n*-BuLi in hexanes (1.76×10^{-3} mol). The solution was stirred for 5 min, and $Cp_2Zr(CH_2CH_2CMe_3)(Cl)$ (547 mg, 1.60×10^{-3} mol) was added as a solid. After 4 h at 25 °C, the volatile materials were removed under vacuum, and the remaining solid was extracted with 10 mL of pentane. The extract was filtered to remove LiCl, and the filtrate was concentrated to 2 mL under reduced pressure. Cooling this solution to −40 °C resulted in the formation of crystals, which were isolated by decanting the solvent to provide 372 mg (7.71×10^{-4} mol, 48%). IR (C_6H_6): 3310 (w), 2958, 2899, 2888, 2863, 1433, 1321, 1241, 1194, 993, 672, 577 cm^{-1}. ^1H NMR (THF-d_8): δ 7.01 (d, J = 7.59 Hz, 2 H), 6.91 (t, J = 7.59 Hz, 1 H), 5.99 (s, 1 H), 5.90 (s, 10 H), 3.33 (septet, J = 6.89 Hz, 2 H), 1.49 (m, 2 H), 1.16 (d, J = 6.89 Hz, 12 H), 0.89 (s, 9 H), 0.71 (m, 2 H). $^{13}C\{^1H\}$ NMR (THF-d_8): δ 157.80, 128.03, 127.35, 115.06, 53.34, 38.45, 33.74, 33.96, 32.85, 28.23 (the resonance for the ipso carbon of the isopropylphenyl group could not be found in THF-d_8 or C_6D_6). Anal. Calcd for $C_{28}H_{41}NZr$: C, 69.65; H, 8.56; N, 2.90. Found: C, 69.73; H, 8.62; N, 2.83.

Procedure for Experiments 1–7 of Table IV. Reaction of 4–7 with 2-Hexyne and 4-Methyl-2-pentyne. An NMR tube was charged with $Cp_2Zr(R')(NHR)$ (**4–7**), alkyne, and 0.7 mL of C_6D_6. The solution was degassed and the NMR tube flame-sealed and heated to 110 °C for 20 h, at which time all the starting material had been consumed as judged by ^1H NMR spectrometry. Under an inert atmosphere, the NMR tube was opened, and the volatile materials were removed under vacuum, leaving a purple solid. This solid was dissolved in 1 mL of diethyl ether, and in air, 0.5 mL of 5% HCl was immediately added; the solution was then shaken until both layers were clear. The ether layer was removed by pipet and analyzed by GC and GCMS. Two peaks were detected which were identical in retention time and mass spectral fragmentation patterns to authentic samples of the ketones. The ratios of ketones was determined by integration of the GC trace corrected for differences in response factors by calibration of the GC integrator using a cyclohexanone standard.

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Table IV. Experimental Data for Stoichiometric Generation of Azametallacyclobutenes and Catalytic Enamine Formation[a]

expt	temp (°C)	imido complex precursor	amt (mg)	amt (mol × 10^{-5})	alkyne	amt (mg)	amt (mol × 10^{-5})	equiv
1	110	**4a**	15.5	4.37	2-hexyne	16.5	20.1	4.6
2	110	**5**	25.7	6.68	2-hexyne	26.0	31.6	4.7
3	110	**6**	27.2	6.59	2-hexyne	25.3	30.8	4.7
4	110	**7**	36.0	7.46	2-hexyne	32.8	39.9	5.4
5	110	**4a**	19.5	5.47	4-methyl-2-pentyne	19.6	23.9	4.4
6	110	**7**	20.8	4.31	4-methyl-2-pentyne	25.1	30.6	7.1
7	110	**4a**	13.0	3.56	1-phenylpropyne	21.5	18.5	5.2
8[b]	110	**8**	10.8	2.34	2-hexyne	12.0	14.6	6.24
9[b]	110	**8**	13.4	2.90	4-methyl-2-pentyne	8.9	10.8	3.7
10	−6	**1**	11.9	2.88	2-hexyne	14.2	17.8	6.2
11	22	**1**	11.9	2.88	2-hexyne	14.2	17.8	6.2
12	47	**1**	11.2	2.71	2-hexyne	14.2	17.8	6.6
13	−6	**1**	11.9	2.88	4-methyl-2-pentyne	14.2	17.8	6.2
14	22	**1**	11.9	2.88	4-methyl-2-pentyne	14.2	17.8	6.2
15	47	**1**	11.7	2.84	4-methyl-2-pentyne	14.2	17.8	6.3
16[c]	110	**1**	16.6	4.65	2-hexyne	18.3	22.3	4.8
17[d]	110	**1**	16.6	4.65	2-hexyne	18.3	22.3	4.8
18[e]	110	**1**	16.6	4.65	2-hexyne	18.3	22.3	4.8
19[f]	22	**1**	13.3	3.23	1-phenylpropyne	22.2	19.1	5.9
20[g]	120	**4b**	21.4	5.04	1-phenylpropyne	22.1	19.1	3.8
21[b]	120	**8**	11.9	2.58	1-phenylpropyne	13.4	11.6	4.5

[a] Regiochemistries were determined by hydrolysis and are listed in Table I except those for experiments 16–18. [b] Experiments 8, 9, and 21 were run under catalytic conditions with excess amine. The quantities of 2,6-dimethylaniline were as follows: experiment 8, 26.4 mg, 21.5 × 10^{-5} mol, 9.3 equiv; experiment 9, 29.2 mg, 24.1 × 10^{-5} mol, 8.3 equiv; experiment 21, 30.2 mg, 25.0 × 10^{-5} mol, 9.7 equiv. [c] The absolute yield was determined to be 75%; the ratio of 2-hexanone to 3-hexanone was 86:14. [d] The absolute yield was determined to be 78%; the ratio of 2-hexanone to 3-hexanone was 88:12. [e] The absolute yield was determined to be 72%; the ratio of 2-hexanone to 3-hexanone was 87:13. [f] The absolute yield was determined to be 88%. [g] The absolute yield was determined to be 97%.

Procedure for Experiments 8 and 9 of Table IV. Effect of Added Amine on the Regiochemistry of Alkyne Cycloaddition to $Cp_2Zr{=}NAr$ (Ar = 2,6-Dimethylphenyl). An NMR tube was charged with the bis(amide) **8**, alkyne, and 0.6 mL of C_6D_6. The solution was degassed, and the NMR tube was flame-sealed and heated to 110 °C for 8 days, at which time just over half of the alkyne had been consumed as judged by ^{1}H NMR spectrometry. The reaction mixtures were worked up, and the regiochemistry was determined in the manner outlined above.

Procedure for Experiments 10–15 of Table IV. Effect of Temperature on the Regiochemistry of Alkyne Cycloaddition to $Cp_2Zr{=}NAr$ (Ar = 2,6-Dimethylphenyl). An NMR tube was charged with **1** and 0.7 mL of toluene and fitted with a rubber septum. In the cases where the reactions were performed at −6 °C (experiments 10 and 13) and 47 °C (experiments 12 and 15), the NMR tubes were allowed to equilibrate for 15 min in a temperature-controlled circulating bath by submerging all but about 2 cm of the tube in the bath. At this point, 20 μL of alkyne (under N_2) was injected via syringe through the septum and the NMR tube septum wrapped with paraffin. Upon injection, the solution began to turn purple, characteristic of metallacycle formation. Reactions run at −6 °C were gently agitated periodically over the course of 2 h without removing the reaction mixture from the cold bath. No noticeable changes in color were observed after 15 min. For additions performed at 47 °C, the mixtures were allowed to react for 15 min and gently shaken periodically over the course of the reactions. For additions carried out at room temperature (22 °C) (experiments 11, 14, and 16), the mixtures were also allowed to react for 15 min. All reaction mixtures were worked up and analyzed as described above.

Procedure for Experiments 16–18 of Table IV. Determination of Absolute Yields of Ketones in the Cycloaddition/Hydrolysis of $Cp_2Zr{=}NAr$ (Ar = 2,6-Dimethylphenyl) with 2-Hexyne. Under an N_2 atmosphere, a vial was charged with the alkyl amide **4** (49.7 mg, 1.39 × 10^{-4} mol), 2-hexyne (55.0 mg, 6.70 × 10^{-4} mol), and 2 mL of C_6D_6. The solution was divided equally into three portions and each was put into an NMR tube. The solutions were degassed, and the NMR tubes were flame-sealed and heated to 110 °C for 20 h, after which time the starting material had been consumed as judged by ^{1}H NMR spectrometry. Under an inert atmosphere, the NMR tubes were opened and the volatile materials removed under vacuum, leaving purple solids. The solids were each dissolved in 1 mL of diethyl ether, and in air, 1 mL of 5% HCl was immediately added; the solutions were then shaken until both layers were clear. To each of the solutions was added 6.0 μL of cyclohexanone as an internal GC standard. The samples were analyzed by GC, integrating the ketones against the cyclohexanone internal standard. In this manner, the absolute yields of 2-hexanone and 3-hexanone were determined to be 72–78%, as stated in the footnotes to Table IV. These experiments also demonstrated that isomer ratio measurements were reproducible to ±1% (absolute).

Procedure for Experiment 19 of Table IV. Regiochemistry of the Addition of 1-Phenylpropyne to 1. A vial was charged with **1** (13.3 mg, 2.23 × 10^{-5} mol) and 0.5 mL of toluene. 1-Phenylpropyne (22.2 mg, 1.91 × 10^{-4} mol, 5.9 equiv) was added to the solution in 0.2 mL of toluene. The solution immediately turned dark blue. After 5 min, the solvent was removed under reduced pressure. The solid was dissolved in 1 mL of diethyl ether, and in air, 1 mL of 10% CF_3COOH and 5.0 μL of mesitylene (3.59 × 10^{-5} mol) were added. The mixture was allowed to stir for 2 h, and then 1 μL was analyzed by GC. The yield was 88.4% as determined by integration against the internal standard.

Procedure for Experiment 20 of Table IV. Regiochemistry of the Addition of 1-Phenylpropyne to 4b. An NMR tube was charged with **4b** (21.4 mg, 5.04 × 10^{-5} mol), 1-phenylpropyne (22.1 mg, 1.91 × 10^{-4} mol, 3.8 equiv), and 0.6 mL of C_6D_6. The solution was degassed and heated at 120 °C for 2 days, at which time the reaction was complete as shown by ^{1}H NMR spectrometry. Under an inert atmosphere, the NMR tube was opened, and the volatile materials were removed under reduced pressure. The blue solid was dissolved in 1 mL of diethyl ether, and in air, 1 mL of 10% CF_3COOH and 5 μL of mesitylene (3.59 × 10^{-5} mol) were added. The mixture was stirred for 3 h, and then a 1-μL sample was injected onto the GC column. The yield was determined to be 97.1% by integration against the mesitylene internal standard.

Procedure for Experiment 21 of Table IV. Regiochemistry of the Addition of 1-Phenylpropyne in the Catalytic Reaction. An NMR tube was charged with **8** (11.9 mg, 2.58 × 10^{-5} mol), 1-phenylpropyne (13.4 mg, 1.16 × 10^{-4} mol, 4.5 equiv), and 2,6-dimethylaniline (30.2 mg, 2.50 × 10^{-4} mol, 9.7 equiv). The solution was degassed and heated at 120 °C for 2 days, at which time the reaction was complete as shown by ^{1}H NMR spectrometry. Under an inert atmosphere, the NMR tube was opened, and the volatile materials were removed under reduced pressure. The yellow solid was dissolved in 5 mL of ether, and 1 mL of this solution was brought out of the drybox. To this portion were added 1 mL of 10% CF_3COOH and 5 μL of mesitylene (3.59 × 10^{-5} mol). The mixture was stirred for 2 h, and then a 1-μL sample was injected onto the GC column. The yield was determined to be 86.1% by integration against the mesitylene internal standard.

Hydrolysis of 2 (R_L = t-Bu, R_S = Me). The crude metallacycle **2** (R_L = t-Bu, R_S = Me), prepared as described above, was subjected to high vacuum to remove the volatile materials, including excess 4,4-dimethyl-2-pentyne. To the remaining purple solid were added 1 mL of ether and, in air, 1 mL of 5% HCl. The solution turned yellow and then clear in

under 1 min upon addition of the acid solution. The ether layer was analyzed by GC, which indicated that neither of the expected ketones were present; 4,4-dimethyl-2-pentyne was identified as the only organic product.

Similar results were obtained upon addition of CF_3COOH to **2** (R_L = *t*-Bu, R_S = Me) in hexanes at −40 °C followed by an H_2O workup and GC analysis. The regiochemistry of **2** (R_L = *t*-Bu, R_S = Me) was determined by a 2D-NOESY experiment.

Reaction of 2 (R_L = *t*-Bu, R_S = Me) with 2,6-Dimethylaniline. An NMR tube was charged with metallacycle **2** (R_L = *t*-Bu, R_S = Me) (8.4 mg, 1.18×10^{-5} mol), *p*-dimethoxybenzene internal standard (2.5 mg, 1.81×10^{-5} mol), and 0.6 mL of C_6D_6. Two single-pulse ^1H NMR spectra were acquired in which the resonance due to the cyclopentadienyl ligands was integrated against the methyl resonance of the *p*-dimethoxybenzene. 2,6-Dimethylaniline (7.8 mg, 6.44×10^{-5} mol, 5.5 equiv) was added to the NMR tube at 25 °C, and the color of the solution changed from purple to yellow over a 30-min period. After 40 min, another set of ^1H NMR spectra were obtained as described above. By averaging the integrated areas, it was determined that bis(amide) **1** was produced in 79% and 4,4-dimethyl-2-pentyne in 96% yield.

Kinetic Studies of the Catalytic Hydroamination of 4-Methyl-2-pentyne by 2,6-Dimethylaniline. These experiments were carried out as described earlier using ^1H NMR spectrometry to follow the disappearance of 2,6-dimethylaniline.[1] Bis(amide) **8** was the catalyst, and *p*-dimethoxybenzene was employed as an internal standard. The disappearance of amine was monitored as the reaction progressed at 95 °C.

Two stock solutions were prepared. Stock solution 1 contained 150.3 mg (3.25×10^{-3} mol, 3.25×10^{-2} M) of bis(amide) **8** in C_6D_6 in a 10.00-mL volumetric flask. Stock solution 2 contained 194.1 mg (1.60×10^{-3} mol, 1.60×10^{-1} M) of 2,6-dimethylaniline and 223.3 mg (1.62×10^{-3} mol, 1.62×10^{-1} M) of *p*-dimethoxybenzene internal standard in C_6D_6 in a 10.00-mL volumetric flask. These solutions were stored in the drybox at −30 °C between uses.

In a typical run, a 1.00 ± 0.01 mL volumetric flask was charged with 0.037 mL (3.22×10^{-3} mol) of 4-methyl-2-pentyne, 0.20 ± 0.005 mL of stock solution 1, and 0.20 ± 0.005 mL of stock solution 2, and C_6D_6 was added to bring the total volume to 1.00 mL. The concentrations of all materials during the initial stages of each run were confirmed by ^1H NMR integration as described earlier.[1] The sample was then heated at 140 °C, and the procedure described earlier was used to take spectra at time intervals of 50 min throughout the run. The data were then analyzed according to eq 6. The rate constant data are presented in Table III.

Relative Temperature Dependence of Protonation and Reversion for 4-Methyl-2-pentyne. In a typical experiment, the mixture of metallacycles **2** and **3** (R_L = *i*-Pr, R_S = Me) was generated by the addition of *i*-PrCCMe (0.215 mL, 1.88×10^{-3} mol, 6 equiv), via syringe to a stirring solution of $Cp_2(THF)Zr(NAr)$ (128.7 mg, 3.12×10^{-4} mol) in 8 mL of toluene. The solution turned purple immediately. After 5 min, the volatile materials were removed under reduced pressure. In a separate 25-mL Schlenk flask in the drybox, 2,6-dimethylaniline (70.2 mg, 5.80×10^{-4} mol, 10 equiv) was dissolved in 2.05 mL of toluene. The flask was equipped with a Teflon thermometer adapter. The metallacycle mixture (24.3 mg, 5.76×10^{-5} mol) was loaded into a spatula which was suspended above the amine solution in the thermometer adapter. The flask was taken out of the drybox this way and submerged in a constant-temperature bath (100 °C), and the contents were allowed to equilibrate for at least 45 s before the flask was shaken so that the metallacycles and amine were mixed together. After the addition was complete, the flask was removed from the bath and cooled under cold water. The solution was bright yellow at this time. The thermometer adapter was removed, and immediately 1 mL of diethyl ether, 2 mL of 10% CF_3COOH, and 5.0 μL of methylcyclohexane were added. The colorless mixture was transferred to a large scintillation vial and stirred for at least 1.5 h, after which 5 mL of saturated $NaHCO_3$ was added to the solution. A 2-μL sample of the diethyl ether layer was then analyzed by GC. The ratio of alkyne to the two ketones was corrected for differing response factors by calibration of the GC integrator using methylcyclohexane as a standard. The experiments were run at 25, 60, and 100 °C. Experiments with both 10 and 20 equiv of amine were run at 60 and 100 °C. The data from each temperature point are presented in Table V.

Table V. Experimental Data for the Temperature Dependence of k_3 (Protonation) and k_{-2} (Reversion) in the Reaction of **2** and **3** (R_L = *i*-Pr, R_S = Me; R_L = R_S = Ph) with 2,6-Dimethylaniline

alkyne	temp (°C)	[2] (M)	$[H_2NAr]$ (M)	% ketones	% alkyne	k_3/k_{-2}
i-PrCCMe	100	0.0281	0.283	71	29	8.5
i-PrCCMe	100	0.0320	0.337	79	22	11
i-PrCCMe	100	0.0312	0.314	81	19	13
i-PrCCMe	100	0.0307	0.306	73	27	8.7
i-PrCCMe	100	0.0276	0.552	80	20	7.4
i-PrCCMe	60	0.0322	0.335	97	3	110
i-PrCCMe	60	0.0297	0.584	96	4	47
PhCCPh	119	0.0220	0.224	99.6	0.4	1100
PhCCPh	119	0.0225	0.236	99.7	0.3	1400
PhCCPh	94	0.0253	0.268	99.9	0.1	3700
PhCCPh	94	0.0224	0.235	99.9	0.1	4300

Relative Temperature Dependence of Protonation and Reversion for Diphenylacetylene. In a typical experiment, 2,6-dimethylaniline (64.4 mg, 5.32×10^{-4} mol, 10.5 equiv) was dissolved in 1.5 mL of toluene, and the mixture was loaded into a 25-mL Schlenk flask with a rubber septum. Metallacycle **2** (R_L = R_S = Ph) (26.2 mg, 5.06×10^{-5} mol) was dissolved in 0.75 mL of toluene, and the mixture was loaded into a syringe. The tip of the syringe was inserted into the septum of the Schlenk flask, and both were brought out of the drybox this way. The flask was submerged in a constant-temperature bath (119 °C) and allowed to equilibrate for at least 45 s before the metallacycle was added slowly down the sides of the flask. After addition was complete, the solution was yellow, and the flask was removed from the bath and attached to a Schlenk line. The solvent was removed under reduced pressure, and 1 mL of diethyl ether was added under nitrogen. The flask was then opened to air, and 0.5 mL of 50% CF_3COOH and the internal standard, benzophenone (9.2 mg, 5.05×10^{-5} mol), were added. A 1-mL sample of the ether layer was injected into the GC column. The ratio of ketone to alkyne was corrected for differing response factors by calibration of the GC integrator using benzophenone as a standard.

Competitive Addition of 2,6-Dimethylaniline and 4-Methyl-2-butyne to $Cp_2Zr(NHAr)_2$. A vial was charged with 2,6-dimethylaniline (21.2 mg, 1.75×10^{-4} mol, 16 equiv), 4-methyl-2-pentyne (0.017 mL, 1.48×10^{-4} mol, 13 equiv), and 0.5 mL of toluene-d_8. $Cp_2(THF)Zr{=}NAr$ (**1**, 15.1 mg, 3.66×10^{-5} mol) was dissolved in 1 mL of toluene-d_8, and 0.3 mL of this solution was added to the stirring solution of amine and alkyne. The solution turned light yellow. By ^1H NMR, only $Cp_2Zr(NHAr)_2$ was seen as a product.

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