Transition Metal-Catalyzed Intramolecular [4 + 2] Cycloadditions: A Novel Method for the Assembly of Nitrogen Heterocycles and Its Application to Yohimban Alkaloid Synthesis

Paul A. Wender* and Thomas E. Smith

Department of Chemistry, Stanford University, Stanford, California 94305

Received November 8, 1995

The transition metal-catalyzed intramolecular [4 + 2] cycloaddition between dienes and unactivated π-systems has been shown to offer several advantages over the corresponding Diels−Alder reaction.[1] Proceeding through a distinct multistep reaction sequence, it is exempt from the often restrictive electronic requirements that govern the concerted Diels−Alder process. As a result, in many cases where the Diels−Alder reaction[2] fails, or proceeds only slowly, even at elevated temperatures, *the former process occurs efficiently and rapidly, often at room temperature,* accommodating functionality too labile for the uncatalyzed, thermal process. Moreover, in contrast to the Diels−Alder reaction, in which chemo- and stereoselectivity are dictated principally by the diene and dienophile substrates, *the selectivity of the metal-catalyzed reaction can be controlled and reversed by the catalyst*.[1d] While ester-, ether-, and silicon-containing functional groups have been shown to participate in these reactions without complication, the ability of the catalytic cycle to tolerate nitrogen functionality has not been addressed.[3] We describe herein the first study of nickel(0)-catalyzed intramolecular [4 + 2] cycloadditions of nitrogen-containing dienynes, providing a novel method for the synthesis of hydroisoindoles and hydroisoquinolines, ring systems common to a variety of natural and non-natural polycycles.[4] The application of this methodology to the synthesis of the yohimban skeleton, the pentacyclic framework of the medicinally active Rauwolfia alkaloids, such as reserpine, is also reported.[5]

In order to attenuate the donor ability of the nitrogen atom lone pair and minimize complications brought about by its capacity to coordinate with a metal center and potentially interfere with catalyst function, our initial studies employed amines protected with electron-withdrawing groups. The efficacy of the Ni-catalyzed cycloaddition for the assembly of nitrogen-containing bicycles is illustrated in Table 1. Treatment of dienyne sulfonamide **1**[6] with a typical Ni(0) catalyst derived from Ni(COD)$_2$ and tri-*o*-biphenylyl phosphite *at room temperature* provided the tetrahydroisoindole **2** in 91% yield.[7] The Boc-protected amine **4** exhibited similar reactivity, providing the corresponding cycloadduct **5** in 86% yield. Importantly, when the tether length between the reactive partners was increased by one methylene unit as in **7** and **10**, a modification that often leads to diminished reaction rates and/or yields in metal-catalyzed reactions, the regioisomeric hydroisoquinoline derivatives **8** and **11**, respectively, were formed in high yields.[8]

In marked contrast to these efficient metal-catalyzed[9] transformations, the corresponding (Diels−Alder) control reactions require temperatures from 100 to 150 °C (Table 1: thermal control) to effect conversion of **1**, **4**, and **13** to their respective cycloadducts. For the four-atom-tether-containing dienynes **7** and **10**, the Diels−Alder reaction fails while the metal-catalyzed process occurs at room temperature to afford cycloadducts **8** and **11**, respectively.

Of further consequence to the utility of the transition metal-catalyzed process is the facile aromatization of the 1,4-cyclohexadiene products. As shown in Table 1, [4 + 2] cycloadduct **2** is smoothly dehydrogenated by DDQ to give the aromatized product **3** in 88% yield.[10] Corresponding transformations are indicated for the other cycloadducts. The combination of these two procedures provides a concise route to the dihydroisoindole and tetrahydroisoquinoline ring systems.

The effect of an amide linkage between the reactive subunits was initially investigated with substrate **13**. The Martin group has shown that such systems undergo Diels−Alder cycloadditions to produce hydroisoquinolines.[11] Temperatures between 140 and 275 °C and reaction times from 24 to 96 h are required for these uncatalyzed processes. In contrast, treatment of the methylpropargylhexadienamide **13** (Table 1) with the Ni(0) catalyst at 60 °C provided the desired cycloadduct in 81% yield.

A simple extension of this method to the assembly of the DE-ring system of the yohimbine skeleton (Scheme 1) was initiated by the preparation of tryptophyl-substituted amide **15** in three steps by the sequential

(1) For the most recent work in this area see: (a) Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. For the original work on intramolecular diene−diene and diene−alkyne cycloadditions, see: (b) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678 and (c) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6433−6434. For extensions to diene−alkene and diene−allene cycloadditions and other metal catalysts, see: (d) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843−1844. (e) McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145 and references cited therein. For extensions to homologous vinylcyclopropane−alkyne systems see: (f) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720−4721.

(2) For a recent review of the intramolecular Diels−Alder reaction, see: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 5, pp 513−550.

(3) For Ni(0)-mediated cyclizations of diynes with nitrogen linkers see: (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539−546 and references therein. (b) Tsuda, T.; Morikawa, S.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 3140−3145. (c) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570−8572.

(4) *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, 1951−1994; Vols. 1−45.

(5) For an excellent review see: Baxter, E. W.; Mariano, P. S. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Springer-Verlag: New York, 1992; Vol. 8, pp 197−319.

(6) Dienyne substrates were prepared by alkyl halide alkylation of *p*-toluenesulfonamides, using NaH in DMF (Kataoka, T.; Yoshimatsu, M.; Noda, Y.; Sato, T.; Shimizu, H.; Hori, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 121), derived from sulfonylation of the corresponding amines using TsCl and pyr in THF (Luo, F.-T. and Wang, R.-T. *Heterocycles* **1991**, *32*, 2365−2372) or Mitsunobu reaction of the corresponding alcohol with TsNHBoc using DEAD and PPh_3 in THF (Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709−5712).

(7) In a representative procedure, dienyne **1** (60.6 mg, 0.174 mmol, 1 equiv), freshly distilled oxygen-free THF (17.4 mL), and tri-*o*-biphenylyl phosphite (28.2 mg, 0.052 mmol, 0.3 equiv) were added sequentially to an acid-washed, base-washed, oven-dried 25-mL Schlenk flask under a positive argon flow. Bis(1,5-cyclooctadiene)nickel (218 μL, 0.080 M stock solution in THF, 0.017 mmol, 0.1 equiv) was added *via* gastight syringe. The reaction was stirred at rt overnight, and the clear solution slowly changed to a golden yellow color. The reaction was quenched by opening to air and stirring for 30 min. The crude reaction mixture was purified by flash filtration through a 1-in. plug of silica (20% EtOAc/hexanes) followed by flash chromatography (15% Et_2O/hexanes) to give the tetrahydroisoindole **2** (55.2 mg, 91%) as a white powder. All new compounds were characterized by IR and NMR spectroscopy and provided satisfactory elemental or exact mass analyses.

(8) The highly electron-withdrawing ligand tris(hexafluoroisopropyl) phosphite has an accelerating effect in these cycloadditions. For the electronic and steric parameters of this versatile ligand, see: Van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973. For the best synthetic preparation, see: Sakatsume, O.; Yamane, H.; Takaku, H.; Yamamoto, N. *Nucleic Acids Res.* **1990**, *18*, 3327.

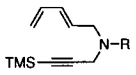
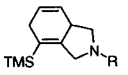
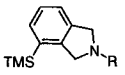
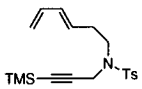
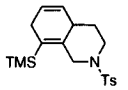
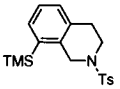
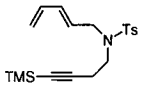
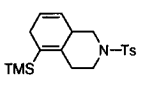
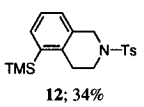
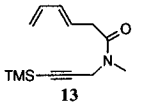
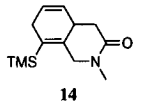
(9) For a mechanistic interpretation of the nickel-catalyzed reactions see refs 1a and 1c.

(10) Following the protocol of: Hayakawa, K.; Takewaki, M.; Fujimoto, I.; Kanematsu, K. *J. Org. Chem.* **1986**, *51*, 5100−5105.

(11) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.

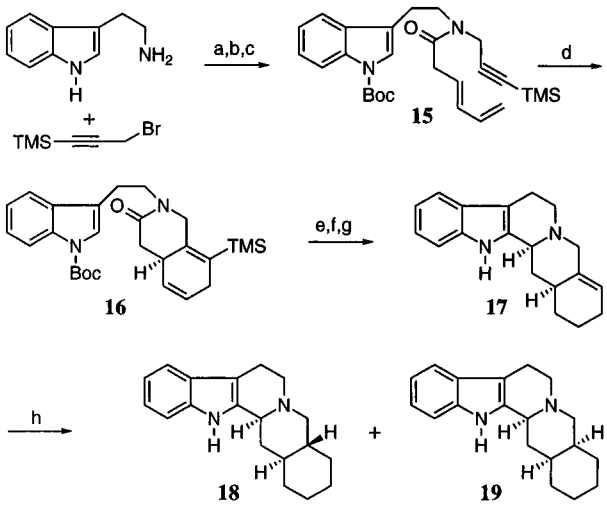
0022-3263/96/1961-0824$12.00/0

Table 1. Nickel-Catalyzed and Control Cycloadditions of Nitrogen-Tethered Dienynes and Their Aromatization Products

Dienyne	Reaction Conditions	Product	Ni(0)–catalyzed % yield / temp[a]	Thermal Control $t_{1/2}$ (h) / temp[b]	Aromatized Derivative[c]
 **1**: R = Ts	10% $Ni(COD)_2$, $P(O\text{-}oBiPh)_3$, 3:1, THF	 **2**: R = Ts	91% / 25 °C	4.8 / 100 °C	 **3**: R = Ts; 88%
4: R = Boc	10% $Ni(COD)_2$, $P(O\text{-}oBiPh)_3$, 3:1, THF	**5**: R = Boc	86% / 25 °C	17.6 / 100 °C	**6**: R = Boc; 82%
 **7**	20% $Ni(COD)_2$, $P(O\text{-}iC_3HF_6)_3$, 3:1, cyclohexane	 **8**	87% / 25 °C	26.3 / 100 °C (decomposition)	 **9**; 60%
 **10**	20% $Ni(COD)_2$, $P(O\text{-}iC_3HF_6)_3$, 3:1, cyclohexane	 **11**	82% / 25 °C	12.9 / 150 °C (decomposition)	 **12**; 34%
 **13**	20% $Ni(COD)_2$, $P(O\text{-}iC_3HF_6)_3$, 3:1, cyclohexane	 **14**	81% / 60 °C	2.6 / 150 °C	

[a] Dienyne 0.01 M; 3:1 ratio of added ligand to nickel(0) catalyst. [b] Thermal control reactions were run in resealable medium-walled NMR tubes. Disappearance of SM was monitored by reference to an internal standard of 1,4-diacetylbenzene. Half-life values and the reported temperatures are for conversion of starting dienyne at the temperature where Diels–Alder products were initially observed. [c] Aromatizations were carried out with 1.1 equiv of DDQ in *p*-dioxane at 60 °C.

Scheme 1[a]



[a] Reaction Conditions: (a) Na_2CO_3, EtOH, rt (5 equiv. tryptamine), 62%; (b) 3,5-hexadienoyl chloride, Et_3N, CH_2Cl_2, −78 °C, 88%; (c) $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 99%; (d) 20 mol % $Ni(COD)_2$, 60 mol % $P(O\text{-}i\text{-}C_3HF_6)_3$, THF, 0.01 M, 25 °C, 88%; (e) $RhCl(PPh_3)_3$, 50 psi H_2, CH_2Cl_2, rt, 93%; (f) 2 M TsOH, CH_3CN, THF, H_2O (3:3:1), reflux, 69%; (g) (i) $POCl_3$, benzene, reflux; (ii) $NaBH_4$, MeOH, 86%; (h) PtO_2, 1 atm of H_2, EtOH; 33% **20**, 34% **21**.

alkylation,[12] acylation,[11] and Boc protection[13] of tryptamine. *Nickel-catalyzed cycloaddition of* ***15*** *proceeded to give* ***16*** *in an optimized yield of 88% at room temperature, while the alternative preparative thermal reaction required a temperature of 150 °C, caused cleavage of the Boc protecting group, and gave only a 45% yield of the 1,4-cyclohexadiene product.* Elaboration of the resulting product by selective hydrogenation of the sterically less-encumbered olefin, protiodesilylation[14] of the vinylsilane with concomitant removal of the Boc protecting group, and Bischler–Napieralski closure of the C-ring[15] provided the pentacyclic 19,20-didehydroyohimban **17** in 86% yield. Confirmation of structure of **17** was established by its catalytic hydrogenation over PtO_2[16] to give (±)-yohimban **18** and (±)-alloyohimban **19** in a 1:1 ratio.[17]

In summary, this study establishes the nickel(0)-catalyzed intramolecular [4 + 2] cycloaddition as a mild, efficient, and practical method for the assembly of hydroisoindole and hydroisoquinoline derivatives. The reaction has been shown to tolerate amide, sulfonamide, and carbamate functionalities. The 1,4-cyclohexadiene products of these reactions are smoothly aromatized by DDQ, effectively providing an efficient route to the corresponding aromatic heterocycles. Finally, the utility of this methodology has been demonstrated by its application to the expedient synthesis of (±)-19,20-didehydroyohimban, a simplified analog of yohimbine containing a desired site of unsaturation difficult to introduce by other means.[18] Further studies are in progress.

Acknowledgment. This research was supported by a grant (CHE-9321676) from the National Science Foundation. Mass spectra were provided by the Mass Spectrometry Facility, University of California–San Francisco.

Supporting Information Available: IR, NMR, and mass spectrometry data for compounds **1**–**14**, **16**, **17**, and **19** (11 pages).

JO9519827

(12) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336–3346.

(13) Lounasmaa, M.; Karvinen, E.; Jokela, R. *Tetrahedron* **1987**, *43*, 2135–2146.

(14) Fujikara, S.; Inoue, M.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 1999–2002.

(15) (a) Aubé, J.; Ghosh, S.; Tanol, M. *J. Am. Chem. Soc.* **1994**, *116*, 9009–9018. (b) Aubé, J.; Wang, Y.; Hammond, M.; Tanol, M.; Takusagawa, F.; Vander Velde, D. *J. Am. Chem. Soc.* **1990**, *112*, 4879–4891.

(16) Naito, T.; Miyata, O.; Tada, Y.; Nishiguchi, Y.; Kiguchi, T.; Ninomiya, I. *Chem. Pharm. Bull.* **1986**, *34*, 4144–4149.

(17) The products of the hydrogenation had spectra consistent with those from yohimban and alloyohimban: (a) Hua, D. H.; Bharathi, S. N.; Panagadan, J. A. K.; Tsujimoto, A. *J. Org. Chem.* **1991**, *56*, 6998–7007. (b) Reference 15b. (c) Wenkert, E.; Chang, C.-J.; Chawla, H. P. S.; Cochran, D. W.; Hagaman, E. W.; King, J. C.; Orito, K. *J. Am. Chem. Soc.* **1976**, *98*, 3645–3655.

(18) Naito, T.; Hirata, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2219–2225 and references therein.