

Rhodium-Catalyzed Chemo-, Regio-, and Enantioselective [2 + 2 + 2] Cycloaddition of Alkynes with Isocyanates

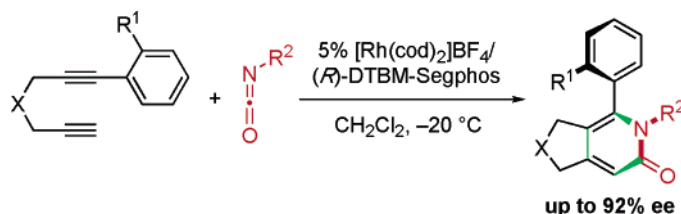
Ken Tanaka,^{*,†} Azusa Wada,[†] and Keiichi Noguchi[‡]

Department of Applied Chemistry, Graduate School of Engineering, and
Instrumentation Analysis Center, Tokyo University of Agriculture and Technology,
Koganei, Tokyo 184-8588, Japan

tanaka-k@cc.tuat.ac.jp

Received August 24, 2005

ABSTRACT



We have developed a cationic rhodium(I)/modified-BINAP complex-catalyzed chemoselective [2 + 2 + 2] cycloaddition of alkynes with isocyanates leading to a wide range of 2-pyridones. This method was successfully applied to the chemo-, regio-, and enantioselective synthesis of axially chiral 2-pyridones from unsymmetrical α,ω -diynes, bearing an ortho-substituted phenyl at one terminal position, and alkyl isocyanates.

Transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes with isocyanates is a valuable method to construct substituted 2-pyridones.¹ The pioneering work for such a catalytic formation of 2-pyridones was first reported by Yamazaki using Co catalysts² and by Hoberg using Ni catalysts.³ Vollhardt et al. developed Co-catalyzed partially intramolecular cycloaddition utilizing 5-isocyanatoalkynes.^{2c} Takahashi et al. developed the selective preparation of

pyridones from two different internal alkynes and isocyanates by formation of an azazirconacyclopentenone followed by transmetalation with $\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$ using stoichiometric amounts of Ni and Zr.⁴ Yamamoto, Itoh, and co-workers developed Ru-catalyzed cycloaddition of 1,6-diynes with isocyanates.⁵ Recently, Louie et al. demonstrated that $\text{Ni}(\text{cod})_2/\text{SIPr}$ [1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene] efficiently catalyzes cycloaddition of alkynes with isocyanates at room temperature.^{3d} However, the substrate scope, the efficiency, and the selectivity remain to be improved.

Although rhodium complexes are effective catalysts for cyclotrimerization of alkynes,⁶ the use of a neutral rhodium complex catalyzes only cycloaddition of tetrolic acid methyl ester with isocyanates in low yield.⁷ We recently reported

[†] Department of Applied Chemistry.

[‡] Instrumentation Analysis Center.

(1) For a review, see: Varela, J. A.; Saà, C. *Chem. Rev.* **2003**, *103*, 3787–3801.

(2) (a) Hong, P.; Yamazaki, H. *Synthesis* **1977**, 50–52. (b) Hong, P.; Yamazaki, H. *Tetrahedron Lett.* **1977**, 1333–1336. (c) Earl, R. A.; Vollhardt, K. P. C. *J. Org. Chem.* **1984**, *49*, 4786–4800. (d) Diversi, P.; Ingrosso, G.; Lucherini, A.; Malquori, S. *J. Mol. Catal.* **1987**, *40*, 267–280. (e) Bonaga, L. V. R.; Zhang, H.-C.; Gauthier, D. A.; Reddy, I.; Maryanoff, B. E. *Org. Lett.* **2003**, *5*, 4537–4540. (f) Bonaga, L. V. R.; Zhang, H.-C.; Moretto, A. F.; Ye, H.; Gauthier, D. A.; Li, J.; Leo, G. C.; Maryanoff, B. E. *J. Am. Chem. Soc.* **2005**, *127*, 3473–3485.

(3) (a) Hoberg, H.; Oster, B. W. *Synthesis* **1982**, 324–325. (b) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1982**, *234*, C35–C38. (c) Hoberg, H.; Oster, B. W. *J. Organomet. Chem.* **1983**, *252*, 359–364. (d) Duong, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438–11439.

(4) (a) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kitora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059–5067. (b) Li, Y.; Matsumura, H.; Yamanaka, M.; Takahashi, T. *Tetrahedron* **2004**, *60*, 1393–1400.

(5) (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117–2119. (b) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605–613.

Rh(I)⁺/H8-BINAP⁸-catalyzed cross-cyclotrimerization of terminal alkynes with dialkyl acetylenedicarboxylates.⁹ In this paper, we describe Rh(I)⁺/modified-BINAP-catalyzed chemo-, regio-, and enantioselective [2 + 2 + 2] cycloaddition of alkynes with isocyanates.

We first investigated the cycloaddition of terminal alkynes with isocyanates. After screening various rhodium(I) complexes, we found that [Rh(cod)₂]BF₄/H8-BINAP catalyzed this reaction at room temperature. Regioselectivity is highly dependent on the alkynes used (Table 1). Although the

Table 1. Rhodium-Catalyzed Regioselective [2 + 2 + 2] Cycloaddition of Terminal Monoynes with Isocyanates

entry	1	R ¹	2	R ²	yield ^a (%)			
					3	4	5	6
1	1a	1-cyclohexenyl	2a	Bn	47 ^b	1 ^b	0	0
2	1a	1-cyclohexenyl	2b	<i>n</i> -Bu	47 ^b	1 ^b	0	0
3	1b	<i>n</i> -C ₁₀ H ₂₁	2a	Bn	31	30	<5	0
4	1b	<i>n</i> -C ₁₀ H ₂₁	2c	Cy	31	31	<5	0
5	1c	Me ₃ Si	2b	<i>n</i> -Bu	0	0	65	0
6	1c	Me ₃ Si	2c	Cy	0	0	48	0

^a Isolated yield. ^b Isolated as a mixture of **3** and **4**.

reaction of conjugated alkyne **1a** furnished isomer **3** as a major product (entries 1 and 2), the reaction of nonconjugated alkyne **1b** furnished isomers **3** and **4** as major products (entries 3 and 4). On the other hand, the reaction of

(trimethylsilyl)acetylene (**1c**) furnished isomer **5** as a sole product (entries 5 and 6).

Next, the cycloaddition of both terminal and internal α,ω -diynes with isocyanates was investigated using 5% [Rh(cod)₂]-BF₄/H8-BINAP at room temperature (Table 2). The reaction

Table 2. Rhodium-Catalyzed [2 + 2 + 2] Cycloaddition of Symmetrical α,ω -Diynes with Isocyanates^a

entry	7	X	R ¹	2	R ²	8	yield ^b (%)
1	7a	C(CO ₂ Me) ₂	Me	2a	Bn	8aa	99
2	7a	C(CO ₂ Me) ₂	Me	2b	<i>n</i> -Bu	8ab	90
3	7a	C(CO ₂ Me) ₂	Me	2d	Ph	8ad	87
4	7b	C(CO ₂ Me) ₂	H	2a	Bn	8ba	84
5	7b	C(CO ₂ Me) ₂	H	2c	Cy	8bc	81
6	7c	NTs	Me	2a	Bn	8ca	93
7	7c	NTs	Me	2b	<i>n</i> -Bu	8cb	80
8 ^c	7d	CH ₂	H	2a	Bn	8da	64
9	7e	CH ₂ CH ₂	Me	2a	Bn	8ea	85
10	7f	CH ₂ CH ₂	Et	2a	Bn	8fa	98
11	7g	CH ₂ CH ₂	H	2a	Bn	8ga	65
12	7h	CH ₂ CH ₂ CH ₂	H	2a	Bn	8ha	48

^a Isocyanates (1.1 equiv: R¹ = Me or Et, 2.0 equiv: R¹ = H) were used. ^b Isolated yield. ^c BINAP was used as ligand.

of malonate-derived 1,6-diynes and diynes containing an internal amino group with a variety of isocyanates afforded the desired 2-pyridones in good yield (entries 1–7). 1,6-Heptadiyne, having no tertiary center on the tether chain, also reacted with an isocyanate to afford the expected 2-pyridone (entry 8). The formation of a six- or seven-membered ring was also possible (entries 9–12). In general, the reactions of internal α,ω -diynes proceeded in higher yield than those of terminal α,ω -diynes, due to the lower reactivity toward homo-cycloaddition.

The [2 + 2 + 2] cycloaddition of unsymmetrical α,ω -diynes, bearing an ortho-substituted phenyl at one terminal position, with alkyl isocyanates would install axial chirality during the formation of pyridone rings.¹⁰ As shown in Table 3, the reaction of unsymmetrical 1,6-diynes using [Rh(cod)₂]-BF₄/(R)-DTBM-Segphos¹¹ furnished a sterically demanding and axially chiral regioisomer as a sole product.¹² The reaction of 2-chlorophenyl-substituted 1,6-heptadiyne **9a** with various alkyl isocyanates furnished axially chiral 2-pyridones

(6) For rhodium-catalyzed cyclotrimerization of alkynes, see: (a) Müller, E. *Synthesis* **1974**, 761–774. (b) Grigg, R.; Scott, R.; Stevenson, P. *Tetrahedron Lett.* **1982**, 23, 2691–2692. (c) Grigg, R.; Scott, R.; Stevenson, P. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1357–1364. (d) Magnus, P.; Witty, D.; Stamford, A. *Tetrahedron Lett.* **1993**, 34, 23–26. (e) Baidossi, W.; Goren, N.; Blum, J. *J. Mol. Catal.* **1993**, 85, 153–162. (f) Doyle, M. P.; Shanklin, M. S. *Organometallics* **1994**, 13, 1081–1088. (g) McDonald, F. E.; Zhu, H. Y. H.; Holmquist, C. R. *J. Am. Chem. Soc.* **1995**, 117, 6605–6606. (h) Kotha, S.; Brahmachary, E. *Tetrahedron Lett.* **1997**, 38, 3561–3564. (i) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, 38, 2426–2430. (j) Grigg, R.; Sridharan, V.; Wang, J.; Xu, J. *Tetrahedron* **2000**, 56, 8967–8976. (k) Witulski, B.; Stengel, T.; Fernandez-Hernandez, J. M. *Chem. Commun.* **2000**, 1965–1966. (l) McDonald, F. E.; Smolentsev, V. *Org. Lett.* **2002**, 4, 745–748. (m) Witulski, B.; Zimmermann, A. *Synlett* **2002**, 1855–1859. (n) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, 41, 3281–3284. (o) Nishiyama, H.; Niwa, E.; Inoue, T.; Ishima, Y.; Aoki, K. *Organometallics* **2002**, 21, 2572–2574. (p) Yan, H.; Beatty, A. M.; Fehlner, T. P. *Organometallics* **2002**, 21, 5029–5037. (q) Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, 125, 7784–7785. (r) Flynn, S. T.; Hasso-Henderson, S. E.; Parkins, A. W. *J. Mol. Catal.* **1985**, 32, 101–105.

(8) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumabayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, 32, 7283–7286.

(9) (a) Tanaka, K.; Shirasaka, K. *Org. Lett.* **2003**, 5, 4697–4699. (b) Tanaka, K.; Toyoda, K.; Wada, A.; Shirasaka, K.; Hirano, M. *Chem. Eur. J.* **2005**, 11, 1145–1156.

(10) For enantioselective synthesis of axially chiral compounds through [2 + 2 + 2] cycloaddition, see: (a) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, 43, 3795–3797. (b) Shibata, T.; Fujimoto, T.; Yokota, K.; Takagi, K. *J. Am. Chem. Soc.* **2004**, 126, 8382–8383. (c) Tanaka, K.; Nishida, G.; Wada, A.; Noguchi, K. *Angew. Chem., Int. Ed.* **2004**, 43, 6510–6512. (d) Tanaka, K.; Nishida, G.; Ogino, M.; Hirano, M.; Noguchi, K. *Org. Lett.* **2005**, 7, 3119–3121.

(11) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumabayashi, H. *Adv. Synth. Catal.* **2001**, 343, 264–267.

Table 3. Rhodium-Catalyzed Regio- and Enantioselective [2 + 2] Cycloaddition of Unsymmetrical α,ω -Diyne with Isocyanates

Reaction scheme showing the [2 + 2] cycloaddition of unsymmetrical α,ω -diynes **9a-d** with isocyanates **2** (2 equiv) catalyzed by 5% $[\text{Rh}(\text{cod})_2]\text{BF}_4$ and (R) -DTBM-Segphos in CH_2Cl_2 at -20°C for 12–36 h to yield product **10**.

Structure of (R) -DTBM-SEGPHOS (Ar = 4-MeO-3,5-(*t*-Bu) $_2$ C $_6$ H $_2$) is shown below the reaction arrow.

entry	9	X	R ¹	2	R ²	10	yield ^a (%)	ee (%)
1	9a	CH ₂	Cl	2a	Bn	(+)- 10aa	81	87
2	9a	CH ₂	Cl	2b	<i>n</i> -Bu	(<i>R</i>)-(+)- 10ab	79	88
3	9a	CH ₂	Cl	2e	<i>n</i> -C ₈ H ₁₇	(+)- 10ae	75	90
4	9b	CH ₂	Br	2a	Bn	(+)- 10ba	83	85
5	9c	O	Cl	2a	Bn	(+)- 10ca	58	91
6	9d	C(CO ₂ Me) ₂	Cl	2a	Bn	(+)- 10da	89	92

^a Isolated yield.

in high yield with high enantioselectivity (entries 1–3). Not only 2-chlorophenyl- but also 2-bromophenyl (**9b**, entry 4)-

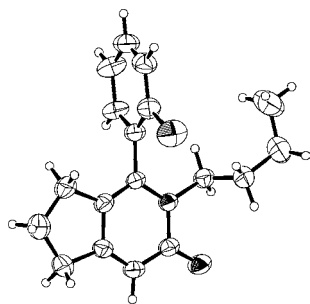
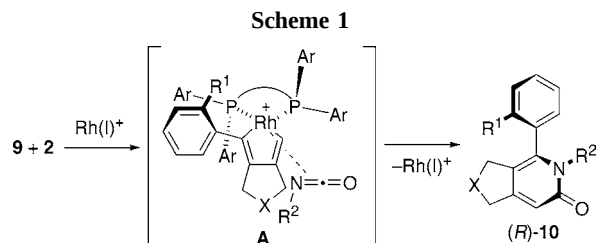


Figure 1. ORTEP diagram of (R) -(+)-**10ab**.

substituted 1,6-diynes were suitable substrates in this process. Furthermore, the reaction of dipropargyl ether derivative **9c** and malonate-derived 1,6-diyne **9d** also proceeded with high enantioselectivity (entries 5 and 6). The absolute configuration of (+)-**10ab** was determined to be *R* by the anomalous dispersion method (Figure 1).

The observed high regio- and enantioselectivity can be explained by the selective formation of rhodium complex **A** (Scheme 1). The unsymmetrical α,ω -diyne **9** and isocyanate



2 react with rhodium to form complex **A**, which can furnish (R) -**10**. Indeed, homo-[2 + 2 + 2] cycloaddition products of **9** were generated other than the desired cross-[2 + 2 + 2] cycloaddition products **10**.

In conclusion, we have developed a rhodium-catalyzed chemo-, regio-, and enantioselective [2 + 2 + 2] cycloaddition of alkynes with isocyanates leading to a wide range of 2-pyridones, including enantioenriched axially chiral 2-pyridones. Additional synthetic and mechanistic studies of this reaction are underway in our laboratory.

Acknowledgment. This work was supported by Uehara Memorial Foundation. We thank Takasago International Corp. for the gift of H8-BINAP and DTBM-Segphos.

Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic files (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL052041B

(12) The use of α,ω -diynes, bearing an ortho-halogenated phenyl at the terminal position, is important. The reaction of an *o*-methyl- or trifluoromethylphenyl-substituted α,ω -diyne furnished a mixture of regioisomers, and an axially chiral regioisomer **10** was a minor product.