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

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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.

Transiton-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 catalysts[2] 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 $Ni(PPh_3)_2Cl_2$ 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 $Ni(cod)_2$/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

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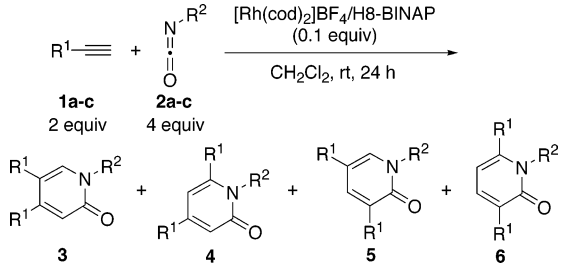
$Rh(I)^+$/H8-BINAP[8]-catalyzed cross-cyclotrimerization of terminal alkynes with dialkyl acetylenedicarboxylates.[9] In this paper, we describe $Rh(I)^+$/modified-BINAP-catalyzed chemo-, regio-, and enantioselective [2 + 2 + 2] cycloaddition of alkynes with isocyanates.

We first investigated the cycloaddition of terminal alkynes with isocyanates. After screening various rhodium(I) complexes, we found that $[Rh(cod)_2]BF_4$/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



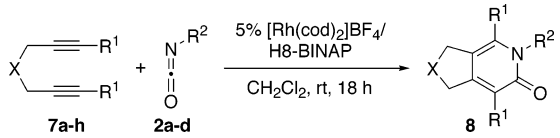
					yield[a] (%)			
entry	**1**	R^1	**2**	R^2	**3**	**4**	**5**	**6**
1	**1a**	1-cyclohexenyl	**2a**	Bn	47[b]	1[b]	0	0
2	**1a**	1-cyclohexenyl	**2b**	*n*-Bu	47[b]	1[b]	0	0
3	**1b**	*n*-$C_{10}H_{21}$	**2a**	Bn	31	30	<5	0
4	**1b**	*n*-$C_{10}H_{21}$	**2c**	Cy	31	31	<5	0
5	**1c**	Me_3Si	**2b**	*n*-Bu	0	0	65	0
6	**1c**	Me_3Si	**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% $[Rh(cod)_2]BF_4$/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**	$C(CO_2Me)_2$	Me	**2a**	Bn	**8aa**	99
2	**7a**	$C(CO_2Me)_2$	Me	**2b**	*n*-Bu	**8ab**	90
3	**7a**	$C(CO_2Me)_2$	Me	**2d**	Ph	**8ad**	87
4	**7b**	$C(CO_2Me)_2$	H	**2a**	Bn	**8ba**	84
5	**7b**	$C(CO_2Me)_2$	H	**2c**	Cy	**8bc**	81
6	**7c**	NTs	Me	**2a**	Bn	**8ca**	93
7	**7c**	NTs	Me	**2b**	*n*-Bu	**8cb**	80
8[c]	**7d**	CH_2	H	**2a**	Bn	**8da**	64
9	**7e**	CH_2CH_2	Me	**2a**	Bn	**8ea**	85
10	**7f**	CH_2CH_2	Et	**2a**	Bn	**8fa**	98
11	**7g**	CH_2CH_2	H	**2a**	Bn	**8ga**	65
12	**7h**	$CH_2CH_2CH_2$	H	**2a**	Bn	**8ha**	48

[a] Isocyanates (1.1 equiv: R^1 = Me or Et, 2.0 equiv: R^1 = 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 $[Rh(cod)_2]BF_4$/(*R*)-DTBM-Segphos[11] 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

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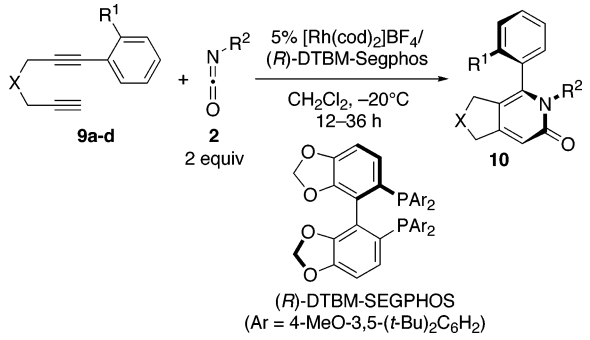
Table 3. Rhodium-Catalyzed Regio- and Enantioselective [2 + 2 + 2] Cycloaddition of Unsymmetrical α,ω-Diynes with Isocyanates



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**	*n*-Bu	(*R*)-(+)-**10ab**	79	88
3	**9a**	CH_2	Cl	**2e**	*n*-C_8H_{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**	$C(CO_2Me)_2$	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)-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).

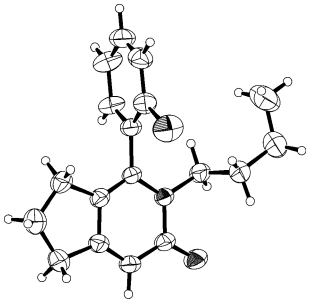
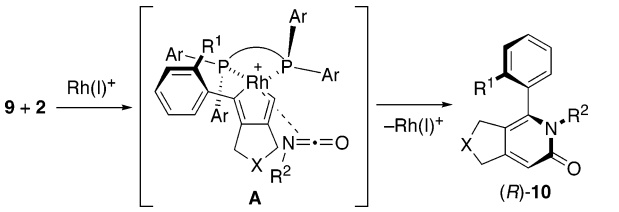


Figure 1. ORTEP diagram of (*R*)-(+)-**10ab**.

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**.

Scheme 1



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 enentioenriched axially chiral 2-pyridones. Additional synthetic and mechanistic studies of this reaction are underway in our laboratory.

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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.

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(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.