Cycloaddition

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Rh-Catalyzed [4+2] Annulation of 4-Alkynals with Isocyanates and Its Application to the Parallel Kinetic Resolution of Unfunctionalized 4-Alkynals**

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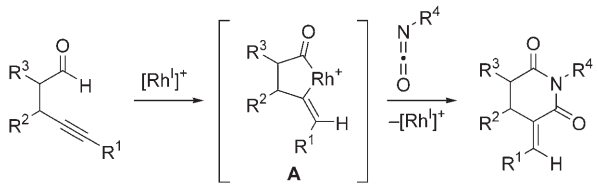
Transition-metal-catalyzed carbocyclizations are useful methods for the construction of carbocycles and heterocycles.[1] In particular, cycloadditions that use isocyanates are efficient methods for the construction of nitrogen-containing heterocycles.[2] For example, transition-metal-catalyzed [2+2+2] cycloadditions of alkynes with isocyanates to prepare substituted 2-pyridones have been widely examined with Co,[3] Ni,[4] Ru,[5] and Rh[6,7] catalysts. However, to the best of our knowledge, transition-metal-catalyzed [4+2] cycloadditions that use isocyanates to prepare six-membered nitrogen-containing heterocycles have not been reported.

We recently reported the rhodium-catalyzed regio- and enantioselective intermolecular [4+2] carbocyclization of 4-alkynals with *N,N*-dialkyl acrylamides for the synthesis of enantioenriched cyclohexanones through five-membered acyl rhodium intermediates **A**, which are formed by the intramolecular hydroacylation of alkynes.[8–11] Herein, we establish a rhodium-catalyzed intermolecular [4+2] annulation of 4-alkynals with isocyanates for the preparation of 4-alkylideneglutarimides (Scheme 1), and its application to a parallel kinetic resolution of unfunctionalized 4-alkynals.[12]

The rhodium-catalyzed [4+2] annulation of 3-methyl-4-nonynal (**1a**) with *n*-butyl isocyanate (**2a**) was examined using various mono- or bidentate phosphine ligands. The



Scheme 1. Intermolecular [4+2] annulation of 4-alkynals with isocyanates.

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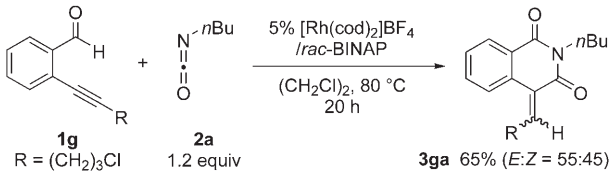
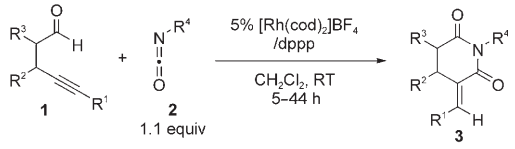
study revealed that the use of bidentate phosphine ligands with large P-M-P natural bite angles (1,3-propanediylbis-[(diphenyl)phosphine] (dppp), 1,4-butanediylbis[(diphenyl)-phosphine] (dppb), 1,1′-bis(diphenylphosphino)ferrocene (dppf), and (1,1′-binaphthalene)-2,2′-diylbis(diphenylphosphine) (*rac*-BINAP)) gave glutarimide **3aa**, which was produced in the highest yield with dppp. The reactions of **1a** with a series of isocyanates **2a–f** were examined by using Rh^I/dppp as the catalyst (Table 1, entries 1–6). The reactions



Scheme 2. Intermolecular [4+2] annulation of 2-alkynylbenzaldehyde **1g** with isocyanate **2a**. cod = 1,5-cyclooctadiene.

Table 1: Rhodium-catalyzed [4+2] annulation of 4-alkynals with isocyanates to give 2-alkylideneglutarimides.[a]



Entry	1	R^1	R^2	R^3	2	R^4	3	Yield [%][b]
1	**1a**	*n*Bu	Me	H	**2a**	*n*Bu	**3aa**	82
2	**1a**	*n*Bu	Me	H	**2b**	*n*Oct	**3ab**	75
3	**1a**	*n*Bu	Me	H	**2c**	Cy	**3ac**	67
4	**1a**	*n*Bu	Me	H	**2d**	Bn	**3ad**	79
5	**1a**	*n*Bu	Me	H	**2e**	4-MeOBn	**3ae**	75
6	**1a**	*n*Bu	Me	H	**2f**	Ph	**3af**	45
7[c,d]	**1b**	*n*Bu	H	Me	**2a**	*n*Bu	**3ba**	63
8	**1c**	Cy	Me	H	**2a**	*n*Bu	**3ca**	87
9[d]	**1d**	$SiMe_3$	Me	H	**2a**	*n*Bu	**3da**	91
10[e]	**1e**	1-cyclohexenyl	Me	H	**2a**	*n*Bu	**3ea**	83
11[e]	**1f**	Ph	Me	H	**2a**	*n*Bu	**3fa**	71

[a] Reactions were carried out with **1** (0.40 mmol), **2** (0.44 mmol), $[Rh(cod)_2]BF_4$ (0.020 mmol), dppp (0.020 mmol), and CH_2Cl_2 (1.0 mL). [b] Yields of the isolated products. [c] Ligand = dppb. [d] Catalyst = 10 mol%. [e] Ligand = *rac*-BINAP. Cy = cyclohexyl.

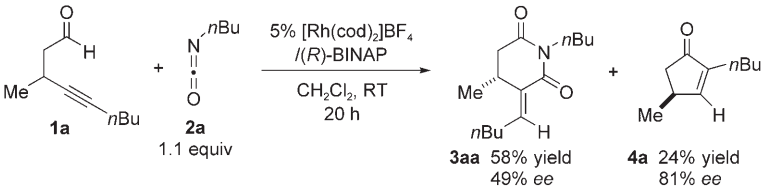
of **1a** with alkyl (entries 1–3), benzyl (entry 4), methoxybenzyl (entry 5), and aryl (entry 6) isocyanates afforded the corresponding glutarimides in moderate-to-high yields. We also explored the scope of this process in respect to 4-alkynals (entries 1 and 7–11). A variety of 4-alkynals were subjected to this process by employing appropriate bidentate phosphine ligands. The reactions tolerated substitutions at both the 3 and 2 positions (entries 1 and 7, respectively). 5-Alkyl-, 5-trimethylsilyl-, 5-alkenyl-, and 5-aryl-substituted 4-alkynals with **2a** afforded the corresponding glutarimides in high yields (entries 1 and 8–11, respectively). Importantly, a single olefin isomer described in Table 1 was produced for all of these annulations. On the other hand, the reaction of 2-alkynylbenzaldehyde **1g** with **2a** furnished a mixture of *E*/*Z* isomers of glutarimide **3ga** at an elevated temperature (80 °C) in the presence of 5 mol% Rh^I/*rac*-BINAP as the catalyst (Scheme 2).[13,14]

During the screening of ligands for the reaction of **1a** with **2a**, the use of *rac*-BINAP afforded a significant amount of the cyclopentenone **4a** as a by-product to the desired glutarimide **3aa**. We anticipated that parallel kinetic resolution of 4-alkynal **1a** for the preparation of the enantioenriched glutarimide **3aa** and cyclopentenone **4a** might proceed.[12] We were pleased to find that enantioenriched **3aa** and **4aa** were obtained in 58 and 24% yield with 49 and 81% *ee*, respectively, when the same reaction was conducted using 5% Rh^I/(*R*)-BINAP (Scheme 3).

After screening a variety of chiral bidentate phosphine ligands, (*S*)-segphos[15] was found to be the ligand of choice in terms of yield and enantioselectivity of the products. We therefore examined the scope of the Rh^I/(*S*)-segphos-catalyzed parallel kinetic resolution of 4-alkynals in the presence of 0.5 equivalents of isocyanates (Table 2).[16] Alkyl, benzyl, and aryl isocyanates could be employed for this resolution process (entries 1–4, respectively). We also extended the scope of this process with respect to 4-alkynals (entries 5–9). The reactions tolerated both alkyl and aryl substitutions at the 3-position (entries 1, 5, and 6) and alkyl, alkenyl, and aryl groups substitutions at the 5-position (entries 5 and 7–9).[17]

Interestingly, the reaction of 5-trimethylsilyl-4-alkynal **1j** with isocyanate **2a** using 20 mol% Rh^I/(*R*)-BINAP afforded enantioenriched glutarimide **3ja** and aziridine **5** in 17 and 16% yield with 62 and 7% *ee*, respectively (Scheme 4).

Scheme 5 shows a plausible mechanism for this reaction. The rhodium catalyst oxidatively inserts into the aldehyde C–H bond, thus affording a rhodium acyl hydride **B**. The *cis*

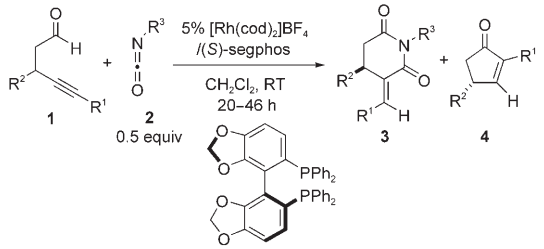


Scheme 3. The parallel kinetic resolution of 3-methyl-4-nonynal (**1a**), which leads to enantioenriched 2-alkylideneglutarimide **3aa** and cyclopentenone **4a**.

addition of the rhodium hydride to the metal-bound alkyne then provides the five-membered acyl rhodium intermediate **A**.[18] Complexation of the isocyanate is followed by insertion to form metallacycle **C**. Reductive elimination from **C** furnishes the glutarimide **3** and regenerates the Rh catalyst. The cyclopentenone **4** can be obtained through the rhodium-catalyzed *trans* hydroacylation of **1**.[19]

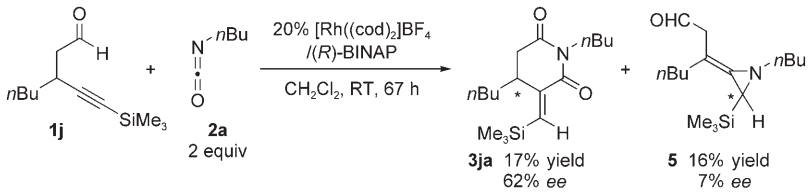
In conclusion, we have developed a rhodium-catalyzed intermolecular [4+2] annulation of 4-alkynals with isocyanates for the preparation of 2-alkylideneglutarimides and applied this approach to the parallel kinetic resolution of unfunctionalized 4-alkynals. This method serves as an attractive new route to enantioenriched 2-alkylideneglutarimides and cyclopentenones given the one-step access to 4-alkynals from readily available terminal alkynes.

Table 2: Rhodium-catalyzed parallel kinetic resolution of 3-substituted 4-alkynals to yield enantioenriched 2-alkylideneglutarimides and cyclopentenones.[a]

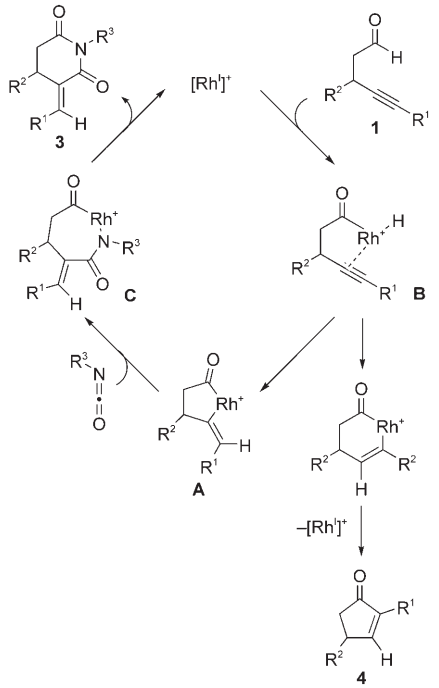


Entry	1	R^1	R^2	2	R^3	3		4	
						Yield [%][b]	*ee* [%][c]	Yield [%][b]	*ee* [%][c]
1	**1h**	*n*Bu	*n*Bu	**2a**	*n*Bu	34	91	28	92
2	**1h**	*n*Bu	*n*Bu	**2b**	Cy	30	81	38	94
3	**1h**	*n*Bu	*n*Bu	**2c**	Bn	36	88	26	91
4	**1h**	*n*Bu	*n*Bu	**2d**	Ph	20	52	38	94
5	**1a**	*n*Bu	Me	**2a**	*n*Bu	38	87	39	83
6[d]	**1i**	*n*Bu	Ph	**2a**	*n*Bu	22	97	36	78
7[d]	**1c**	Cy	Me	**2a**	*n*Bu	33	64	30	98
8	**1e**	1-cyclohexenyl	Me	**2a**	*n*Bu	49	56	26	85
9[d]	**1f**	Ph	Me	**2a**	*n*Bu	35	72	31	76

[a] Reactions were carried out with **1** (0.40 mmol), **2** (0.20 mmol), $[Rh(cod)_2]BF_4$ (0.020 mmol), (*S*)-segphos (0.020 mmol), and CH_2Cl_2 (2.0 mL). [b] Yields of the isolated products. [c] The *ee* values were determined by chiral HPLC or GC analysis. [d] Catalyst = 10 mol%.



Scheme 4. Intermolecular [4+2] annulation of 5-trimethylsilyl-4-alkynal **1j** with isocyanate **2a**.



Scheme 5. Plausible reaction mechanism for the rhodium-catalyzed intermolecular [4+2] annulation of 4-alkynals with isocyanates.

Experimental Section

Representative procedure (Table 2, entry 5): In an Ar atmosphere, a solution of (*S*)-segphos (12.2 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL) was added to a solution of $[Rh(cod)_2]BF_4$ (8.1 mg, 0.020 mmol) in CH_2Cl_2 (1.0 mL), and the resulting mixture was stirred for 5 min. H_2 was introduced to the reaction solution in a Schlenk tube. The resulting solution was concentrated to dryness after stirring for 0.5 h at room temperature. 3-Methylnon-4-ynal (**1a**; 60.9 mg, 0.400 mmol) and *n*-butyl isocyanate (**2a**; 19.8 mg, 0.20 mmol) were added to the residue by using CH_2Cl_2 (2.0 mL), and the reaction mixture was stirred at room temperature for 20 h. The resulting solution was concentrated and purified by chromatography on silica gel (hexane/EtOAc 12:1), which furnished (*R*)-(+)-1-butyl-4-methyl-3-pentylidenepiperidine-2,6-dione ((*S*)-(+)-**3aa**; 38.5 mg, 0.153 mmol, 38% yield, 87% *ee*) as a pale-yellow oil and (*S*)-(+)-2-butyl-4-methylcyclopent-2-enone ((*R*)-(+)-**4a**; 23.9 mg, 0.157 mmol, 39% yield, 83% *ee*) as a colorless oil. (*S*)-(+)-**3aa**: $[\alpha]_D^{25}$ +56.3° ($CHCl_3$, $c = 1.625$, 87% *ee*); IR (neat) 2920, 2855, 1710, 1662, 1635, 1430, 1330, 1176, 1122, 728 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 6.92$ (t, $J = 7.8$ Hz, 1H), 3.70–3.93 (m, 2H), 3.06–3.20 (m, 1H), 2.71 (dd, $J = 16.2$ and 5.4 Hz, 1H), 2.62 (dd, $J = 16.2$ and 2.4 Hz, 1H), 2.10–2.33 (m, 2H), 1.24–1.59 (m, 8H), 1.10 (d, $J = 7.2$ Hz, 3H), 0.93 ppm (t, $J = 7.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 171.5$, 165.9, 142.7, 131.8, 39.8, 39.3, 30.8, 30.1, 27.7, 26.2, 22.5, 20.3, 20.0, 13.82, 13.76 ppm; HRMS (EI) calcd for $C_{15}H_{25}NO_2$: $[M]^+$ 251.1885, found 251.1847; chiralpak AS, hexane/*i*PrOH (98:2), 1.0 mL min^{-1}, retention times: 4.9 min (minor isomer) and 5.6 min (major isomer). (*R*)-(+)-**4a**: $[\alpha]_D^{25}$ +84.6° ($CHCl_3$, $c = 0.950$, 83% *ee*); ^1H NMR ($CDCl_3$, 300 MHz) $\delta = 7.13$–7.21 (m, 1H), 2.81–2.94 (m, 1H), 2.63 (dd, $J = 18.9$ and 6.3 Hz, 1H), 2.08–2.19 (m, 2H), 1.96 (dd, $J = 18.9$ and 2.1 Hz, 1H), 1.26–1.52 (m, 4H), 1.17 (d, $J = 6.9$ Hz, 3H), 0.91 ppm (t, $J = 6.6$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) $\delta = 209.8$, 162.5, 145.4, 43.3, 33.3, 29.8, 24.2, 22.4, 20.4, 13.8 ppm; chiraldex G-TA column, 90 °C isothermal, retention times: 19.5 min (major isomer) and 21.4 min (minor isomer).[20]

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