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COMMUNICATION

Rhodium(I)-catalysed "ene-type" cycloisomerization of *N*-[2-(2-alkyn-1-yl)phenyl]carbodiimides leading to 3-(*cis*-alken-1-yl)-2-aminoquinolines

Takashi Otani,*[ab] Misato Onishi,[a] Takafumi Seino,[a] Naoki Furukawa[a] and Takao Saito*[a]

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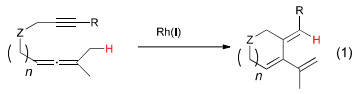
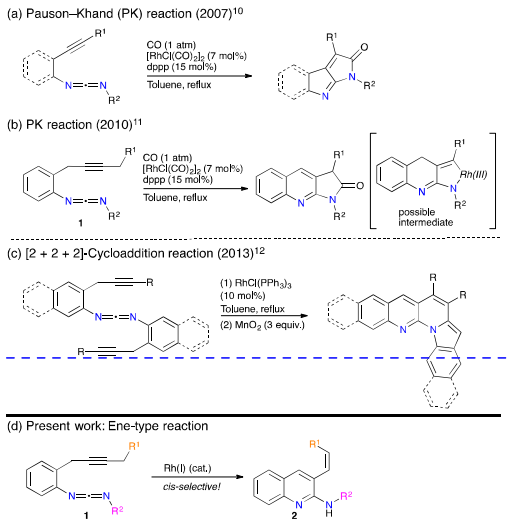
Cycloisomerization of *N*-[2-(2-alkyn-1-yl)phenyl]carbodiimides 1 catalysed by Rh(dppp)$_2$Cl under heating conditions afforded 3-(*cis*-alken-1-yl)-2-(substituted amino)quinolines in up to 87% yield with high *cis*-selectivity. Scope, limitations, a proposed mechanism for these reactions, and a one-pot synthesis of their *trans*-isomers from 1 with iodine-promoted olefin isomerization are described.

Transition metal-catalysed ene-type cycloisomerization of α,ω-enynes is a facile and highly atom-economical method to access carbo- and heterocycles containing 1,4-diene moieties.[1,2] This ene-type reaction is also applicable to allene-ynes for the construction of a cross-conjugated triene system (eq. 1),[3–7] which participates in various Diels–Alder (DA) reactions,[5a–c,6] including diene-transmissive DA reactions.[5b,c,8] Malacria and co-workers reported the first example of cycloisomerization of allene-ynes by using a stoichiometric amount of [CpCo(CO)$_2$].[4] Brummond and co-workers succeeded in a catalytic version of this reaction for the first time by using cationic rhodium(I) and iridium(I) catalysts.[5d] Around the same time, Shibata and co-workers also succeeded with a rhodium-catalysed ene-type cycloisomerization of allene-ynes and proposed their reaction mechanism.[6] Since then, several research groups have developed their own reactions leading to various carbo- and heterocycles with a cross-conjugated triene system.[7] However, as far as we are aware, the use of *heterocumulene*-ynes instead of allene-ynes has not yet been explored, except in our own research.



As part of our continuing programme on the synthesis of nitrogen heterocycles using functionalized heterocumulenes,[9–12] we have been investigating rhodium-catalysed cycloaddition reactions of carbodiimide-ynes.[13] For example, we reported rhodium(I)-catalysed Pauson–Khand (PK)-type reactions of *N*-alkynyl-, *N*-(*o*-alkynylphenyl)-, and *N*-[2-(2-alkyn-1-yl)phenyl]carbodiimides or *N*-(3-propyn-1-yl)carbodiimides leading to pyrrole-, indole-, or quinoline-fused pyrrolin-2-ones, respectively (Schemes 1a,b).[10,11] We also achieved full intramolecular [2 + 2 + 2]-cycloaddition of *N*,*N*′-bis-[2-(2-alkyn-1-yl)phenyl]carbodiimides that deliver structurally unique penta- to heptacyclic L-shaped compounds (Scheme 1c).[12] Schemes 1b and 1c suggest that the possible intermediates, nitrogen-containing rhodacycles, are ~~useful~~ attractive synthetic intermediates ~~for constructing~~to access variously functionalized quinoline ring systems. To exploit ~~their~~their diverse ~~utility~~reactivity, we investigated Rh(I)-catalysed "ene-type" cycloisomerization of **1**. Herein, we report a unique type of cycloisomerization to access 3-(*cis*-alken-1-yl)-2-aminoquinolines **2** with high control of olefin geometry (Scheme 1d).



Scheme 1 Our previous contributions and present work on heterocycle synthesis using carbodiimide-ynes via rhodium-catalysed cycloaddition and cycloisomerization reactions.

To examine the feasibility of the hetero-ene-type cycloisomerization reactions, we selected *N*-isopropyl-*N*′-(2-(octyn-2-yl)phenyl)carbodiimide (**1a**) as the test substrate, with **1a** being heated in the presence of several rhodium catalysts

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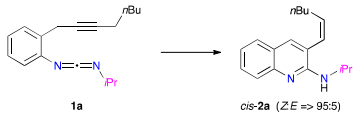
(Table 1). A phosphine-free rhodium catalyst, $[Rh(cod)Cl]_2$, was ineffective, and **1a** was recovered with 95% yield after heating in xylene at 130 °C for 2 h (entry 1). Next, we examined Wilkinson's catalyst ($Rh(PPh_3)_3Cl$), which exhibited high catalytic activities in the [2 + 2 + 2]-cycloaddition of carbodiimide-diynes[12] (Scheme 1c) and in the cycloisomerization reaction of allene-ynes;[6] however, the reaction of **1a** provided only complex mixtures (entry 2). Then, we explored a bidentate phosphine ligand, 1,3-bis(diphenylphosphino)propane (dppp), because it showed high catalytic activity in the previously reported PK reactions of carbodiimide-ynes (Schemes 1a,b).[10,11] When $[Rh(cod)Cl]_2$ and dppp were mixed, we were delighted to obtain the cycloisomerization product, 3-(*cis*-1-hexenyl)-2-(isopropylamino)quinoline (*cis*-**2a**), albeit with a low yield of 25% (entry 3). While switching the rhodium complex from $[Rh(cod)Cl]_2$ to $[Rh(cod)OH]_2$ slightly improved the yield (entry 4 *vs* 3), the use of $Rh(dppp)_2Cl$ significantly improved the yield of **2a** (entry 5, 64% yield). The reaction in di-*n*-butyl ether (entry 6), at a lower temperature of 110 °C (entry 7), or with 6 mol% of the catalyst (entry 8) resulted in lower yields of **2a** than under conditions in entry 5. Interestingly, *cis*-**2a** was formed exclusively over the *trans*-isomer in entries 3–8. The structure of the phosphine ligand is critical for this reaction; the use of a one-carbon longer or shorter bidentate ligand, such as 1,2-bis(diphenylphosphino)ethane (dppe) and 1,4-bis(diphenylphosphino)butane (dppb), failed to form **2a** (entries 9 and 10). The use of a cationic rhodium complex, $Rh(dppp)_2BF_4$, completely suppressed the formation of **2a** (entry 11).

Table 1 Screening of reaction conditions



1a *cis*-**2a** (*Z*:*E* => 95:5)

Entry	Catalyst (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$[Rh(cod)Cl]_2$ (5)[a]	xylene	130	2.0	N.R.[b]
2	$Rh(PPh_3)_3Cl$ (10)	xylene	130	2.0	N.D.[c]
3	$[Rh(cod)Cl]_2$ (5) + dppp (22)[d]	xylene	130	1.0	25[e]
4	$[Rh(cod)OH]_2$ (5) + dppp (20)	xylene	130	1.0	33
5	$Rh(dppp)_2Cl$ (12)	xylene	130	1.0	64
6	$Rh(dppp)_2Cl$ (12)	nBu_2O	130	1.0	55[e]
7	$Rh(dppp)_2Cl$ (12)	toluene	110	1.5	55
8	$Rh(dppp)_2Cl$ (6)	xylene	130	1.0	40[e]
9	$Rh(dppe)_2Cl$ (10)[f]	xylene	130	1.0	N.D.
10	$Rh(dppb)_2Cl$ (10)[g]	xylene	130	1.0	N.D.
11	$Rh(dppp)_2BF_4$ (10)	xylene	130	1.0	N.D.

[a] cod: 1,5-cyclooctadiene. [b] No reaction. [c] Not detected. [d] dppp: 1,3-bis(diphenylphosphino)propane. [e] Based on NMR. [f] dppe: 1,2-bis-(diphenylphosphino)ethane. [g] dppb: 1,4-bis(diphenylphosphino)butane.

With the optimized reaction conditions (Table 1, entry 5) in hand, we explored the scope of the cycloisomerization reaction of carbodiimide-ynes **1** (Table 2). Prominent features observed are as follows. (a) The *cis*-alkenyl quinolines were formed nearly exclusively in all entries. (b) With regard to the substituent at the alkyne terminus (CH_2R^1), the benzyl group (R^1 = Ph) is the most suitable for this reaction (entries 16–20) compared with *n*-pentyl (R^1 = *n*Bu, entries 1–5), methyl (R^1 = H, entries 6–10), and isobutyl (R^1 = *i*Pr, entries 11–15) groups. (c) With regard to the substituent of the carbodiimide terminus (R^2), a relatively larger substituent such as isopropyl (Table 1, entry 5; Table 2, entries 8, 13, and 18) or cyclohexyl (entries 3, 9, 14, and 19) resulted in a better yield; however, the *t*-butyl group seems to be too bulky for the reaction (entry 4).

To clarify the effects of substituents adjacent to the alkynyl carbon, the cycloisomerization reactions of **3** and **5** were examined. The reaction of **3** bearing a methyl group at the benzylic position, proceeded to form 4-methylquinoline derivative **4**, albeit with a lower yield than that of 4-unsubstituted quinoline **2i** (eq. 2 vs. Table 2, entry 8). Meanwhile, the cycloisomerization reactions of **5**, in which a methyl group was introduced to the other adjacent carbon to the C≡C bond, were completely suppressed, and the formation of **6** was not detected (eq. 3). Accordingly, it is suggested that the presence of a *trans*-substituent with regard to the quinolyl group in the product is unfavourable for this reaction, and causes selective formation of *cis*-**2** (vide infra).

We further evaluated the reaction of naphthyl analogues **7** as substrates. The reactions of **7** proceeded under the above optimized conditions to produce 2-(substituted amino)-4-(*cis*-hexen-1-yl)benzo[*g*]quinolines **8** with acceptable yields (54–59%) and high *cis*-selectivity (Scheme 2).

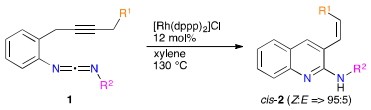
To probe a preliminary mechanistic consideration, we performed *N*-[2-(1,1-dideuterio-2-alkyn-1-yl)phenyl]-*N*′-isopropylcarbodiimide (**1a**-d_2) under the above optimized reaction conditions (eq. 4). The reaction produced 2-isopropylamino-3-(*cis*-1-deuterio-1-hexenyl)-4-deuterioquinoline (*cis*-**2a**-d_2) with high D-content, indicating that one of the benzylic deuterium atoms in **1a**-d_2 migrates to the 1-alkenyl position of *cis*-**2a**-d_2 *via* formal internal [1,3] migration during the cyclization.

Based on the above observations, a possible mechanistic pathway for the formation of **2** is shown in Fig. 1a. (i) Co-ordination of the rhodium complex to the alkyne bond and the external C=N bond to form **A**, from which (ii) oxidative cyclization takes place to construct rhodacycle **B**. (iii) Formal [1,3]-migration of the benzylic proton produces intermediate **C**, concurrent with gaining pyridine aromatic stabilization energy, from which (iv) β-hydride migration to the rhodium leads stereoselectively to *cis*-alkenyl quinoline intermediate *cis*-**D**. (v) Finally, reductive elimination of the rhodium species from *cis*-**D** results in formation of *cis*-**2** and regeneration of the catalyst. Notably, in the present ene-type reaction, the alkynyl function ($C{\equiv}CCH_2R^1$) serves as an "ene" unit and the external heterocumulenic C=N bond serves as an "enophile" unit. This is quite a contrast to the ene-type reaction of allene-ynes, in which the alkynyl group function (C≡C) and the allenyl function ($C{=}CCH_2R$) serve as an "enophile" and an "ene" unit, respectively (eq. 1).

As a possible rationale for the observed *cis*-selectivity, transition states (TSs) of β-hydride migration in **C** to *cis*- and *trans*-alkenyl quinoline complex **D** are depicted in Fig. 1b. In the *E*-TS, the substituent on the alkyne terminus (R^1) may constitute a barrier to the phenyl group on the dppp, hampering the *syn*-hydride migration. Meanwhile, in the *Z*-TS, R^1 faces the opposite side of the ligand and hence the hydride would more smoothly

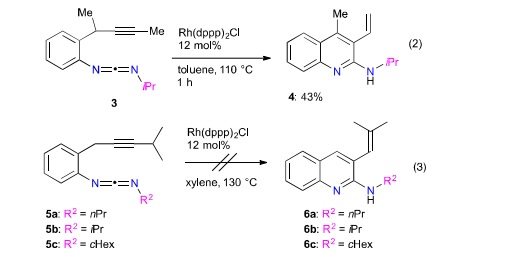
migrate with *syn*-elimination leading to *cis*-**D**.

Table 2 Scope of substituents of **1**

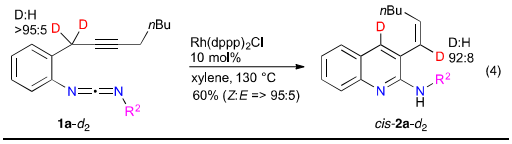


Entry	**1**	R^1	R^2	Time (h)	Yield (%)
1	**1b**	*n*Bu	*n*Pr	1	25
2	**1c**	*n*Bu	Bn	0.5	30
3	**1d**	*n*Bu	*c*Hex	1	48
4	**1e**	*n*Bu	*t*Bu	1	N.R.
5	**1f**	*n*Bu	Ph	1	34
6	**1g**	H	*n*Pr	1	25
7	**1h**	H	Bn	1.5	9
8[a]	**1i**	H	*i*Pr	1	48
9[a]	**1j**	H	*c*Hex	2	54
10[a]	**1k**	H	Ph	1	18
11	**1l**	*i*Pr	*n*Pr	1.5	16
12	**1m**	*i*Pr	Bn	0.5	55
13	**1n**	*i*Pr	*i*Pr	0.5	55
14	**1o**	*i*Pr	*c*Hex	1	43
15	**1p**	*i*Pr	Ph	0.5	67
16	**1q**	Ph	*n*Pr	1	67
17	**1r**	Ph	Bn	1	49
18	**1s**	Ph	*i*Pr	0.8	77
19	**1t**	Ph	*c*Hex	1	73
20	**1u**	Ph	Ph	0.1	87

[a]In toluene at 110 °C.



Scheme 2 Rhodium-catalysed cycloisomerization of **7**



Finally, we found that molecular iodine[14] effectively promotes cis- to trans-isomerization of **2**. For example, stirring *cis*-**2s** and iodine (3 equiv.) in dichloromethane at room temperature for 24 h afforded *trans*-**2s** with 94% yield. In addition, *trans*-**2** was obtained using a one-pot reaction from **1** (Scheme 3), and the yields compared favourably with those of the ene-type reaction (Scheme 3 vs Table 2), implying high yield of the olefin-isomerization step. The progress of isomerization confirms that the *trans*-isomer is more thermodynamically stable than the corresponding *cis*-isomer, and hence the present cycloisomerization is the kinetically controlled reaction.

In conclusion, rhodium(I)-catalysed cycloisomerization of *N*-(propargylphenyl)carbodiimides **1** results in formation of 3-(*cis*-alken-1-yl)-2-(substituted amino)quinolines **2** with high *cis*-selectivity. This reaction constitutes the first example of a metal-catalysed "ene-type" cycloisomerization of heterocumulene-ynes, featuring the alkynyl function–"ene" unit and one heterocumulenic C=N bond–"enophile" unit. Facile access to 2-(*trans*-alkenyl)-3-aminoquinoline derivatives from **1** was also developed.

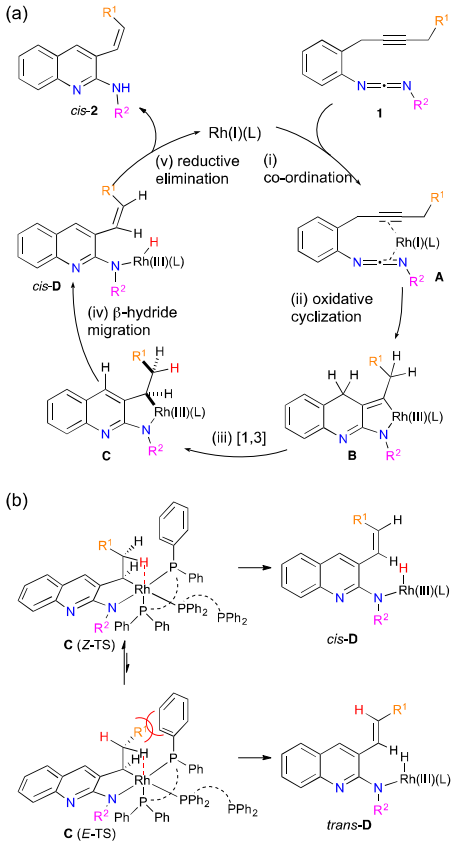
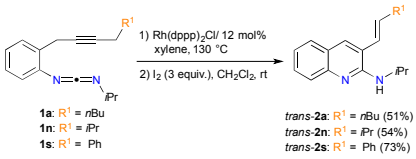


Fig. 1 (a) Assumed reaction mechanism. (b) Assumed TSs for β-hydride migration to form *cis*- and *trans*-alkenyl groups.



Scheme 3 One-pot synthesis of *trans*-alkenylquinolines **2**.

Notes and references

[a] Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku, Tokyo 162-8601, Japan. E-mail: tsaito@rs.kagu.tus.ac.jp (T.S.); Fax: +81 (0)3-5261-4631
[b] Research Center for Chirality, Research Institute for Science & Technology, Tokyo University of Science, Kagurazaka, Shinjuku, Tokyo 162-8601, Japan. E-mail: totani@rs.tus.ac.jp (T.O.); Fax: +81 (0)3-5261-4631

† Electronic supplementary information (ESI) available: Experimental details and other electronic format see DOI: 10.1039/b000000x//

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