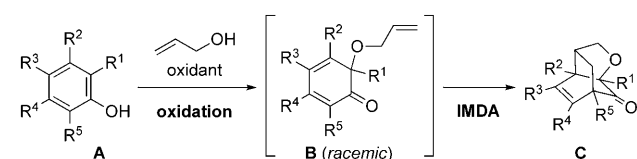


Enantioselective Construction of Bridged Multicyclic Skeletons: Intermolecular [2+2+2] Cycloaddition/Intramolecular Diels–Alder Reaction Cascade**

Masayuki Kobayashi, Takeshi Suda, Keiichi Noguchi, and Ken Tanaka*

The intramolecular Diels–Alder (IMDA) reaction is a powerful strategy for the construction of complex multicyclic skeletons.^[1] The construction of the bridged multicyclic skeleton **C**, from phenol **A**, has been reported to proceed through oxidative dearomatization to give allyl cyclohexadienyl ether **B**, which then undergoes the IMDA reaction to yield **C** (Scheme 1).^[2,3] This novel strategy was successfully

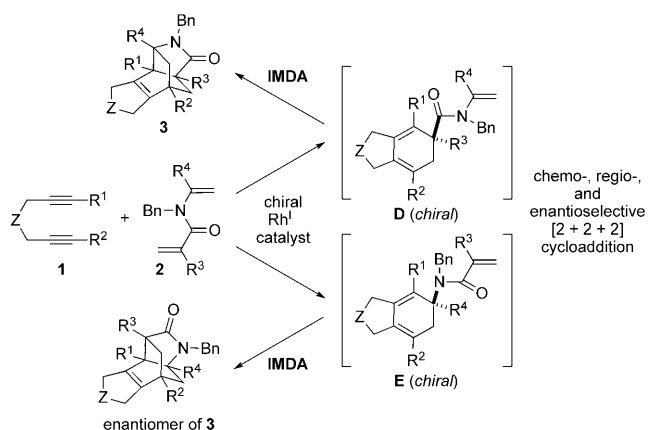


Scheme 1. Oxidative dearomatization/IMDA reaction cascade.

applied to the synthesis of various complex natural products,^[3a,b,d,e] but an asymmetric variant has not yet been developed because of the difficulty of the enantioselective dearomatization of phenols.^[4]

Chiral cyclohexadienes can be accessed with high yields and *ee* values through the enantioselective [2+2+2] cycloaddition^[5,6] of 1,6-diynes with acrylates^[7a] and enamides^[7b,8] catalyzed by a cationic rhodium(I)/axially chiral biaryl bisphosphine complex. Importantly, the ester and amide moieties of these chiral cyclohexadienes possessed the same absolute configurations relative to starting material. Therefore, in the presence of a chiral cationic rhodium(I) catalyst, chiral cyclohexadienes **D** or **E**, containing the required pendant alkene unit, could be generated from the selective

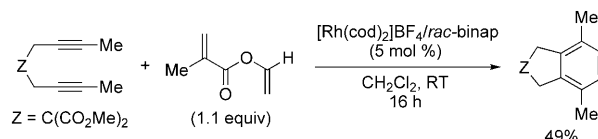
reaction of 1,6-diynes **1** with the amide-linked 1,5-dienes **2**, which bear two sterically and/or electronically different alkene units. A subsequent IMDA reaction would furnish the desired chiral bridged multicyclic compound **3** or its enantiomer (Scheme 2).^[9] The use of an ester-linked 1,5-diene



Scheme 2. Chemo-, regio-, and enantioselective [2+2+2] cycloaddition/IMDA reaction cascade. Bn = benzyl.

should furnish a chiral bridged multicyclic compound, which is similar to compound **C**. However, we have already reported that rapid aromatization through the selective [2+2+2] cycloaddition of the enol double bond and subsequent elimination of methacrylic acid proceeds in the reaction of a 1,6-diyne and vinyl methacrylate, catalyzed by the cationic rhodium(I)/*rac*-binap complex (Scheme 3).^[8c,10] Therefore, the amide-linked 1,5-dienes **2** were selected for this cascade reaction.

We first examined the reaction of the tosylamide-linked 1,6-diyne **1a** and amide-linked 1,5-diene **2a** as shown in Scheme 4. Pleasingly, a cationic rhodium(I)/(*R*)-segphos complex effectively catalyzes the desired enantioselective cycloaddition cascade at room temperature to yield amide **3aa** with a high yield and *ee* value. In addition to **1a**,

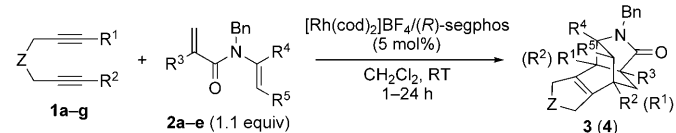


Scheme 3. Rhodium-catalyzed [2+2+2] cycloaddition/aromatization of a 1,6-diyne with vinyl methacrylate.^[8c] binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

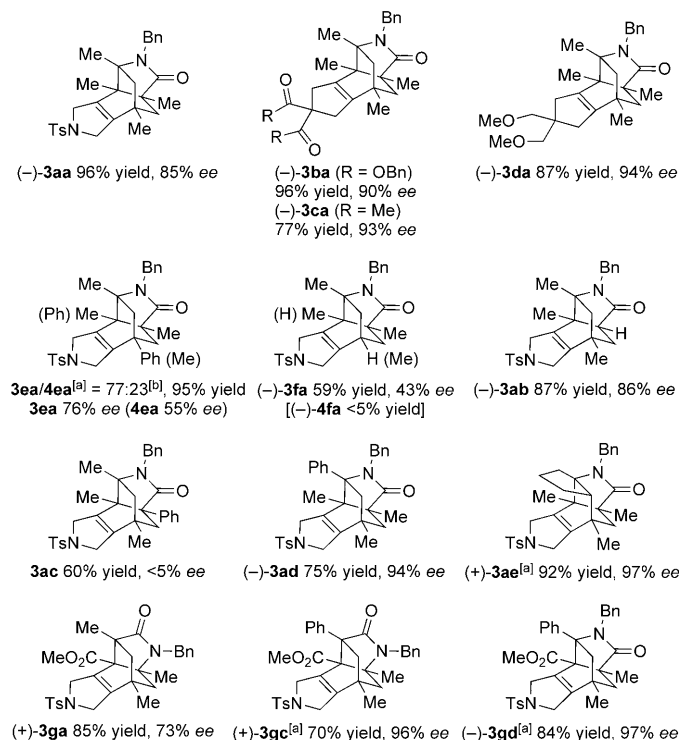
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[**] This work was supported partly by the Grants-in-Aid for Scientific Research (Nos. 20675002 and 20-8746) from MEXT (Japan). We thank Dr. Hidetomo Imase and Maho Takahashi (TUAT) for their preliminary experiments, Takasago Int. Co. for the gift of segphos, and Umicore for generous support in supplying a rhodium complex.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201004150>.



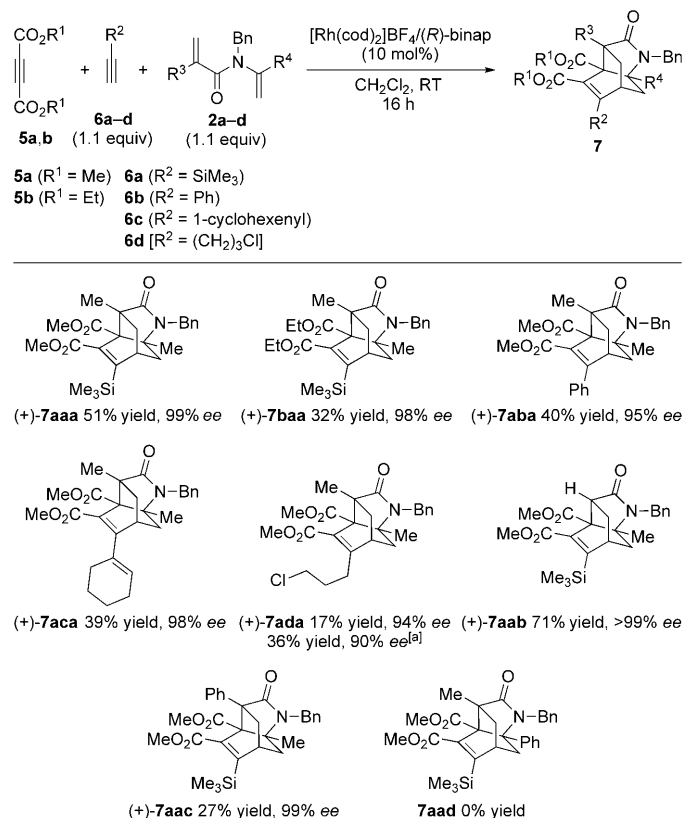
- 1a** (Z = NTs, R¹ = R² = Me) **2a** (R³ = R⁴ = Me, R⁵ = H) **1b** (Z = C(CO₂Bn)₂, R¹ = R² = Me) **2b** (R³ = R⁵ = H, R⁴ = Me) **1c** (Z = CAC₂, R¹ = R² = Me) **2c** (R³ = Ph, R⁴ = Me, R⁵ = H) **1d** (Z = C(CH₂OMe)₂, R¹ = R² = Me) **2d** (R³ = Me, R⁴ = Ph, R⁵ = H) **1e** (Z = NTs, R¹ = Me, R² = Ph) **2e** [R³ = Me, R⁴, R⁵ = (CH₂)₃] **1f** (Z = NTs, R¹ = Me, R² = H) **1g** (Z = NTs, R¹ = CO₂Me, R² = Me)



Scheme 4. Enantioselective cycloaddition cascade of 1,6-diynes **1a–g** with 1,5-dienes **2a–e**. A solution of **1** in CH₂Cl₂ was added to a solution of **2** and the Rh catalyst in CH₂Cl₂ over 1 min. Cited yields are of isolated products. [a] At 40 °C. [b] Catalyst: 10 mol%. Isolated as a mixture of **3ea** and **4ea**. cod = 1,5-cyclooctadiene, segphos = 5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole, Ts = 4-toluenesulfonyl.

malonate- (**1b**), acetyl acetone- (**1c**), and dimethoxypropane-linked (**1d**) 1,6-diynes also reacted with **2a** to yield amides **3ba**, **3ca**, and **3da**, respectively, with high yields and *ee* values. The unsymmetrical 1,6-diynes **1e** and **1f**, yielded the corresponding pairs of regioisomeric products, **3ea/4ea** and **3fa/4fa** with moderate regio- and enantioselectivities. With respect to 1,5-dienes, not only methacrylamide **2a** but also acrylamide **2b**, *N*-styryl **2d**, and *N*-cyclopentenyl **2e** derivatives reacted with **1a** to yield amides **3ab**, **3ad**, and **3ae**, respectively, with high yields and *ee* values. Unfortunately, the phenyl substitution of the acrylamide moiety (**2c**) resulted in the formation of the racemic amide **3ac**. The reactions of unsymmetrical electron-deficient 1,6-diyne **1g** and 1,5-dienes **2a**, **2c**, and **2d** proceeded with high regioselectivity to yield the corresponding amides **3ga**, **3gc**, and **3gd** with good to high yields and *ee* values.

Next we investigated the enantioselective intermolecular [2+2+2] cycloaddition/IMDA reaction cascade as shown in Scheme 5, even though an enantioselective intermolecular



Scheme 5. Enantioselective cycloaddition cascade of alkynes **5a,b**, alkynes **6a–d**, and 1,5-dienes **2a–d**. A solution of **6** in CH₂Cl₂ was added to a solution of **2**, **5**, and the Rh catalyst in CH₂Cl₂ over 1 min. Cited yields are of isolated products. [a] A solution of **6d** (1.5 equiv) in CH₂Cl₂ was added to a solution of **2a**, **5a**, and the Rh catalyst in CH₂Cl₂ over 2 h by using a syringe pump.

three-component co-cyclotrimerization has not been reported to date.^[11–13] After screening substrate combinations and catalysts, we were pleased to find that a cationic rhodium(I)/(*R*)-binap complex effectively catalyzes the desired chemo-, regio-, and enantioselective cycloaddition cascade of dimethyl acetylenedicarboxylate (**5a**), trimethylsilylacetylene (**6a**), and 1,5-diene **2a** at room temperature to yield the corresponding tricyclic amide **7aaa** as a single regioisomer with an excellent *ee* value. The reaction employing diethyl acetylenedicarboxylate (**5b**) gave **7baa** in a lower yield, but the *ee* value was still high. The conjugated terminal alkynes **6b** and **6c** were also suitable substrates for this process yielding **7aba** and **7aca**, respectively. Although the initial yield of **7ada** was very low, by adding the aliphatic terminal alkyne **6d** over a period of 2 hours to a solution of 1,5-diene **2a**, **5a**, and the Rh catalyst, the yield was significantly improved from 17% to 36%. With respect to the 1,5-dienes, acrylamide **2b** could also be employed to give amide **7aab** with a high yield and high *ee* value. Phenyl substitution of the acrylamide

moiety (**2c**) gave the amide **7aac** with an excellent *ee* value, but phenyl substitution of the enamide moiety (**2d**) did not deliver the expected **7aad**.

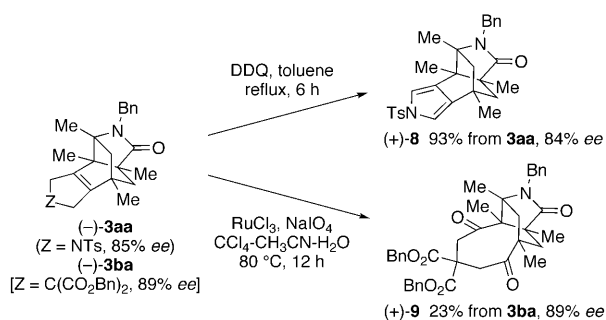
The transformation of bridged chiral multicyclic amides was briefly examined. Treatment of the tetracyclic amide **3aa** with DDQ furnished the pyrrole derivative **8** (Scheme 6). The ruthenium-catalyzed oxidation of the tetracyclic amide **3ba** and of tricyclic amide **7aba** furnished the tricyclic amide **9** (Scheme 6) and bicyclic amide **10** (Scheme 7), respectively.

To clarify which alkene unit of the amide-linked 1,5-dienes **2** reacts with 1,6-diynes **1** in the [2+2+2] cycloaddition step, competition experiments were conducted as shown in Table 1. The electron-rich

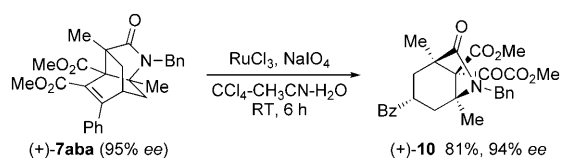
Table 1: Reactions of **1a,g**, acrylamides **11**, and enamides **12**.^[a]

Entry	1 (<i>R</i> ¹)	11 (<i>R</i> ²)	12 (<i>R</i> ³)	13 yield [%] ^[b]	<i>ee</i> [%]	14 or 15 yield [%] ^[b]	<i>ee</i> [%]
1	1a (Me)	11a (Me)	12a (Me)	13a : 70	99	14a : 22	97
2	1a (Me)	11b (Ph)	12a (Me)	13b : 36	98	15 : 40	–
3	1a (Me)	11a (Me)	12b (Ph)	13a : 82	99	14b : 7	–
4	1g (CO ₂ Me)	11a (Me)	12a (Me)	13c : 10	95	14c : 79	> 99
5	1g (CO ₂ Me)	11b (Ph)	12a (Me)	13d : < 5	–	14c : 63	> 99
6	1g (CO ₂ Me)	11a (Me)	12b (Ph)	13c : 80	99	14d : < 5	–

[a] A solution of **1** in CH₂Cl₂ was added to a solution of **11**, **12**, and Rh catalyst in CH₂Cl₂ over 1 min. [b] Yield of isolated product.



Scheme 6. DDQ oxidation of tetracyclic amide **3aa** and ruthenium-catalyzed oxidation of tetracyclic amide **3ba**. DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone.



Scheme 7. Ruthenium-catalyzed oxidation of tricyclic amide **7aba**.

1,6-diyne **1a** preferentially reacted with the electron-deficient acrylamide **11a** over the electron-rich enamide **12a** (Table 1, entry 1). In contrast, the electron-deficient 1,6-diyne **1g** preferentially reacted with electron-rich **12a** over electron-deficient **11a** (Table 1, entry 4). Phenyl substitution of the alkenes improved the chemoselectivity (Table 1, entries 3, 5, and 6), which accounts for higher *ee* values of (–)-**3ad** and (+)-**3gc** relative to those of (–)-**3aa** and (+)-**3ga** (Scheme 4). Phenyl-substituted acrylamide **11b** and methyl-substituted enamide **12a** showed similar reactivity (Table 1, entry 2), therefore the reaction involving substrate **2c**, which contains

both these olefinic units, results in the formation of racemic **3ac**. 1,6-Diyne **1g** preferentially reacted with enamide **12a** over acrylamides **11a,b** (Table 1, entries 4 and 5), thus accounting for the absolute configuration observed for amides (+)-**3ga** and (+)-**3gc**, which are presumably generated via intermediate **E** (Scheme 2). The remaining amides in Scheme 4 have the opposite configuration because they are thought to have been generated via intermediate **D** (Scheme 2). Indeed, the opposite absolute configurations were confirmed by the X-ray crystallographic analysis of (–)-**3aa**,^[14] (+)-**3ae**,^[14] and (+)-**3gc**.^[14]

The same competition experiments were conducted in the intermolecular [2+2+2] cycloaddition as shown in Table 2. As enamide **12a** is the only substrate that could participate in this reaction, the same enantioselection as (+)-**3ga** and (+)-**3gc** would be expected for **7** (Scheme 5). Again, the expected absolute configuration was confirmed by the X-ray crystallographic analysis of (+)-**7ada**.^[14]

In conclusion, we have determined that a cationic rhodium(I)/segphos or binap complex catalyzes the intermo-

Table 2: Reactions of **5a**, **6a**, acrylamides **11**, and enamides **12**.^[a]

Entry	11 (<i>R</i> ²)	12 (<i>R</i> ³)	16 yield [%] ^[b]	17 yield [%] ^[b]	<i>ee</i> [%]
1	11a (Me)	12a (Me)	16a : –	17a : 24	99
2	11b (Ph)	12a (Me)	16b : –	17a : 28	99
3	11a (Me)	12b (Ph)	16a : –	17b : –	–

[a] A solution of **6a** in CH₂Cl₂ was added to a solution of **5a**, **11**, **12**, and Rh catalyst in CH₂Cl₂ over 1 min. [b] Yield of isolated product.

lecular [2+2+2] cycloaddition/intramolecular Diels–Alder reaction^[15] cascade of alkynes and amide-linked 1,5-dienes with high chemo-, regio-, and enantioselectivity. Future studies will focus on expanding the reaction scope and its application to natural product synthesis.

Received: July 7, 2010

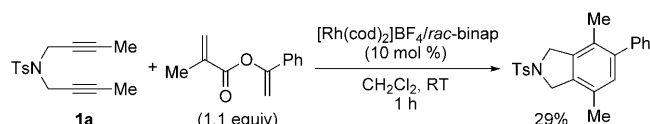
Revised: November 22, 2010

Published online: January 11, 2011

Keywords: asymmetric catalysis · cascade reactions · cycloaddition · Diels–Alder reaction · rhodium

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