Asymmetric Catalysis

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

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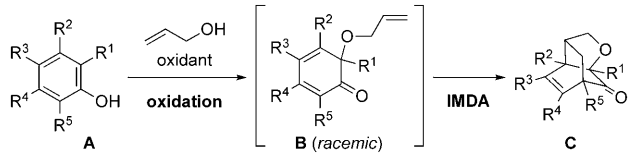
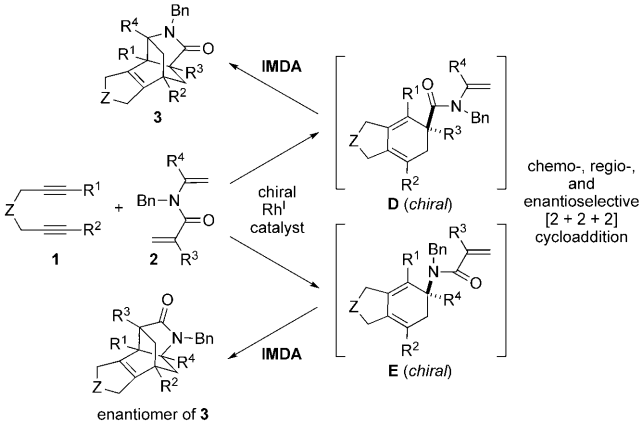
The intramolecular Diels–Alder (IMDA) reaction is a powerful strategy for the construction of complex multicyclic skeletons.[1] The construction of the bridged multicyclic skeleton **C,** from phenol **A,** has been reported to proceed through oxidative dearomatization to give allyl cyclohexadienyl ether **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]

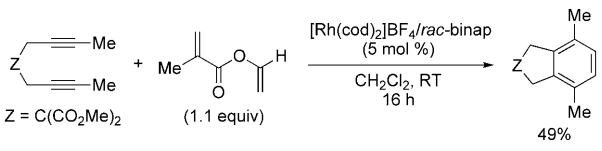
Chiral cyclohexadienes can be accessed with high yields and *ee* values through the enantioselective [2+2+2] cycloaddition[5,6] of 1,6-diynes with acrylates[7a] and enamides[7b,8] catalyzed by a cationic rhodium(I)/axially chiral biaryl bisphosphine complex. Importantly, the ester and amide moieties 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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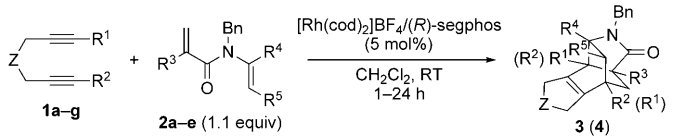
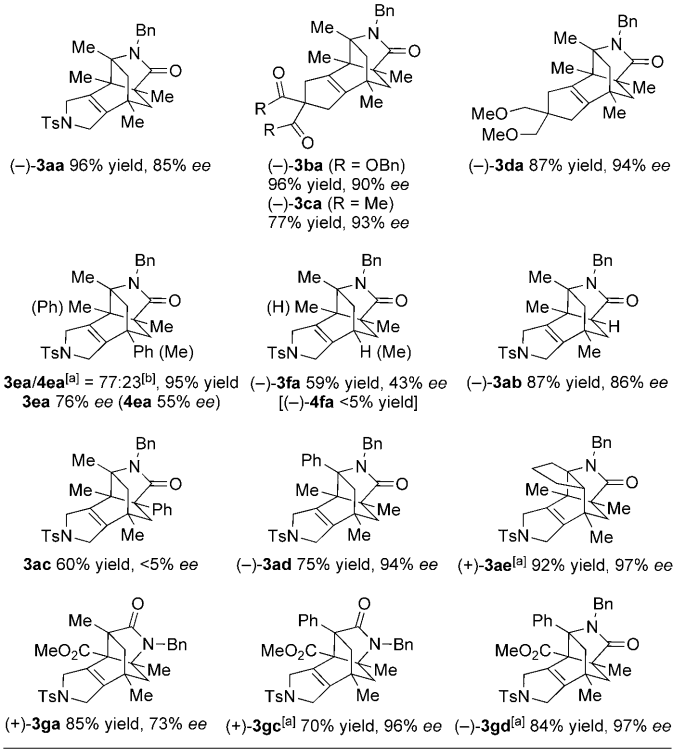


1a–g + **2a–e** (1.1 equiv) → **3** (**4**)

1a (Z = NTs, R^1 = R^2 = Me)
1b [Z = $C(CO_2Bn)_2$, R^1 = R^2 = Me]
1c (Z = CAc_2, R^1 = R^2 = Me)
1d [Z = $C(CH_2OMe)_2$, R^1 = R^2 = Me]
1e (Z = NTs, R^1 = Me, R^2 = Ph)
1f (Z = NTs, R^1 = Me, R^2 = H)
1g (Z = NTs, R^1 = CO_2Me, R^2 = Me)

2a (R^3 = R^4 = Me, R^5 = H)
2b (R^3 = R^5 = H, R^4 = Me)
2c (R^3 = Ph, R^4 = Me, R^5 = H)
2d (R^3 = Me, R^4 = Ph, R^5 = H)
2e [R^3 = Me, R^4,R^5 = $(CH_2)_3$]



(–)-**3aa** 96% yield, 85% *ee*

(–)-**3ba** (R = OBn) 96% yield, 90% *ee*
(–)-**3ca** (R = Me) 77% yield, 93% *ee*

(–)-**3da** 87% yield, 94% *ee*

3ea/**4ea**[a] = 77:23[b], 95% yield
3ea 76% *ee* (**4ea** 55% *ee*)

(–)-**3fa** 59% yield, 43% *ee*
[(–)-**4fa** <5% yield]

(–)-**3ab** 87% yield, 86% *ee*

3ac 60% yield, <5% *ee*

(–)-**3ad** 75% yield, 94% *ee*

(+)-**3ae**[a] 92% yield, 97% *ee*

(+)-**3ga** 85% yield, 73% *ee*

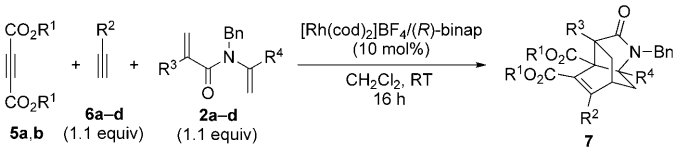
(+)-**3gc**[a] 70% yield, 96% *ee*

(–)-**3gd**[a] 84% yield, 97% *ee*

Scheme 4. Enantioselective cycloaddition cascade of 1,6-diynes **1a–g** with 1,5-dienes **2a–e**. A solution of **1** in CH_2Cl_2 was added to a solution of **2** and the Rh catalyst in CH_2Cl_2 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.

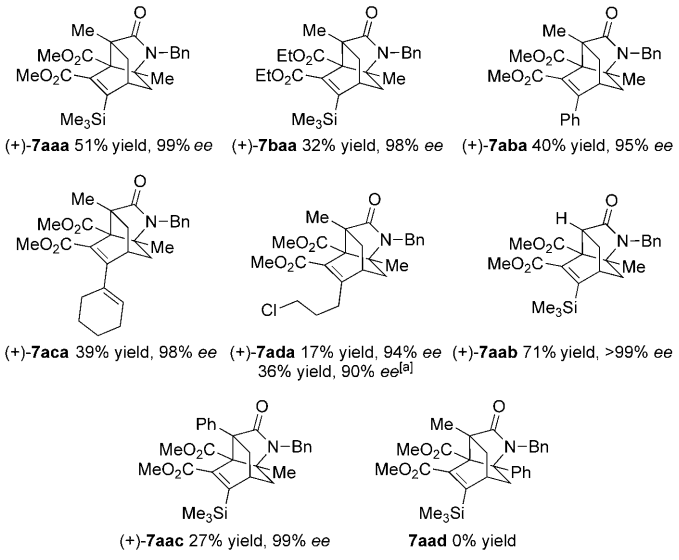
Next we investigated the enantioselective intermolecular [2+2+2] cycloaddition/IMDA reaction cascade as shown in Scheme 5, even though an enantioselective intermolecular



5a,**b** (1.1 equiv) + **6a–d** (1.1 equiv) + **2a–d** (1.1 equiv) → **7**

5a (R^1 = Me)
5b (R^1 = Et)

6a (R^2 = $SiMe_3$)
6b (R^2 = Ph)
6c (R^2 = 1-cyclohexenyl)
6d [R^2 = $(CH_2)_3Cl$]



(+)-**7aaa** 51% yield, 99% *ee*

(+)-**7baa** 32% yield, 98% *ee*

(+)-**7aba** 40% yield, 95% *ee*

(+)-**7aca** 39% yield, 98% *ee*

(+)-**7ada** 17% yield, 94% *ee*
36% yield, 90% *ee*[a]

(+)-**7aab** 71% yield, >99% *ee*

(+)-**7aac** 27% yield, 99% *ee*

7aad 0% yield

Scheme 5. Enantioselective cycloaddition cascade of alkynes **5a**,**b**, alkynes **6a–d**, and 1,5-dienes **2a–d**. A solution of **6** in CH_2Cl_2 was added to a solution of **2**, **5**, and the Rh catalyst in CH_2Cl_2 over 1 min. Cited yields are of isolated products. [a] A solution of **6d** (1.5 equiv) in CH_2Cl_2 was added to a solution of **2a**, **5a**, and the Rh catalyst in CH_2Cl_2 over 2 h by using a syringe pump.

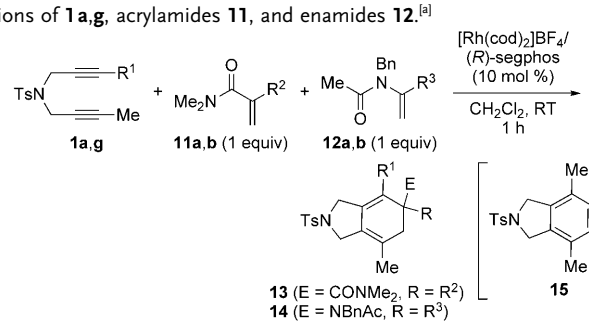
three-component co-cyclotrimerization has not been reported to date.[11–13] After screening substrate combinations and catalysts, we were pleased to find that a cationic rhodium(I)/(*R*)-binap complex effectively catalyzes the desired chemo-, regio-, and enantioselective cycloaddition cascade of dimethyl 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.

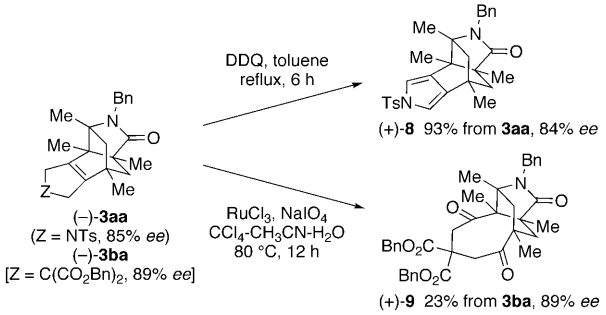
To clarify which alkene unit of the amide-linked 1,5-dienes **2** reacts with 1,6-diynes **1** in the [2+2+2] cycloaddition step, competition experiments were conducted as shown in Table 1. The electron-rich

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

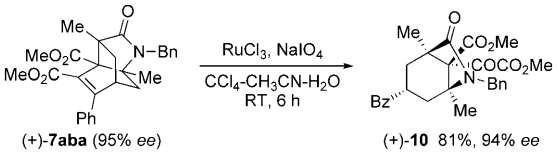


Entry	**1** (R^1)	**11** (R^2)	**12** (R^3)	**13** yield [%][b]	*ee* [%]	**14** or **15** yield [%][b]	*ee* [%]
1	**1a** (Me)	**11a** (Me)	**12a** (Me)	**13a**: 70	99	**14a**: 22	97
2	**1a** (Me)	**11b** (Ph)	**12a** (Me)	**13b**: 36	98	**15**: 40	–
3	**1a** (Me)	**11a** (Me)	**12b** (Ph)	**13a**: 82	99	**14b**: 7	–
4	**1g** (CO_2Me)	**11a** (Me)	**12a** (Me)	**13c**: 10	95	**14c**: 79	>99
5	**1g** (CO_2Me)	**11b** (Ph)	**12a** (Me)	**13d**: <5	–	**14c**: 63	>99
6	**1g** (CO_2Me)	**11a** (Me)	**12b** (Ph)	**13c**: 80	99	**14d**: <5	–

[a] A solution of **1** in CH_2Cl_2 was added to a solution of **11**, **12**, and Rh catalyst in CH_2Cl_2 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.



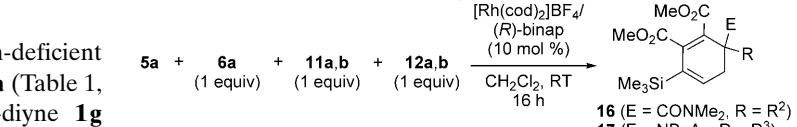
Scheme 7. Ruthenium-catalyzed oxidation of tricyclic amide **7aba**.

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** (R^2)	**12** (R^3)	**16** yield [%][b]	**17** yield [%][b]	*ee* [%]
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 CH_2Cl_2 was added to a solution of **5a**, **11**, **12**, and Rh catalyst in CH_2Cl_2 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.

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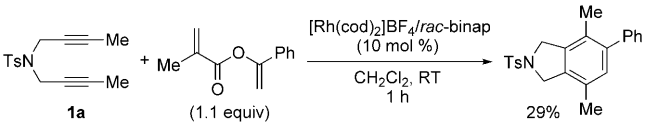

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[14] CCDC 782581 [(−)-**3aa**], CCDC 782582 [(+)-**3ae**], CCDC 782583 [(+)-**3gc**], and CCDC 782584 [(+)-**7ada**] contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15] A control experiment was conducted to see if the rhodium catalyst is required for the Diels–Alder reaction step. As a result of this control experiment, it was concluded that the rhodium catalyst is not necessary for the Diels–Alder reaction step. See the Supporting Information.

