Asymmetric Catalysis

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Highly Chemo-, Regio-, and Enantioselective Rhodium-Catalyzed Cross-Cyclotrimerization of Two Different Alkynes with Alkenes**

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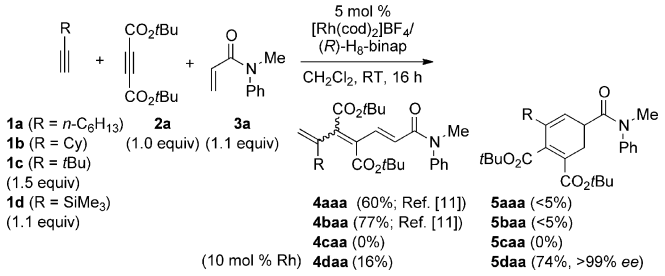
Abstract: *It has been established that a cationic rhodium(I)/(R)-tol-binap complex catalyzes the cross-cyclotrimerization of silylacetylenes, di-tert-butyl acetylenedicarboxylates, and acrylamides with excellent chemo-, regio-, and enantioselectivities. Unsymmetrical alkynoates can also be employed in place of di-tert-butyl acetylenedicarboxylate for this process, but with reduced chemoselectivity.*

Transition-metal-catalyzed cross-[2+2+2] cyclotrimerization reactions of three different unsaturated compounds are efficient and atom-economical methods for the synthesis of substituted six-membered compounds.[1] However, such transformations have been accomplished in only a few examples because of the difficulty in achieving high chemo- and regioselectivities. For examples of the cross-cyclotrimerization of three different alkynes,[2] Ikeda and co-workers reported a nickel-catalyzed reaction[2a] and Kondoh and co-workers reported a ruthenium-catalyzed reaction.[2b] For examples of the cross-cyclotrimerization of two different alkynes with alkenes,[3–10] Ikeda and co-workers reported the nickel-catalyzed reaction[3] and Obora and co-workers reported the niobium-catalyzed reaction.[4] Saito and co-workers reported the nickel-catalyzed [3+2+2] cyclotrimerization of two different alkynes and ethyl cyclopropylideneacetate.[5] Our research group also reported the rhodium-catalyzed cross-cyclotrimerization of terminal alkynes, acetylenedicarboxylates, and alkenyl acetates.[6] However, in these reports, at least one component is in large excess so as to obtain the three-component cyclotrimerization products in acceptable yields. In addition, regioselectivities are insufficient in some cases. Recently, our research group accomplished the rhodium-catalyzed enantioselective cross-cyclotrimerization of electron-rich terminal alkynes, acetylenedicarboxylates, and enamides, however the product yields were low to moderate.[7,8] Herein, we disclose the unprecedented highly chemo-, regio-, and enantioselective catalytic cross-cyclotrimerization of two different alkynes with an alkene.

Recently, our research group reported the chemo- and regioselective synthesis of substituted trienes by the rhodium-catalyzed intermolecular linear cross-trimerization of terminal alkynes, acetylenedicarboxylates, and acrylamides.[11,12] For example, a CH_2Cl_2 solution of *N*-methyl-*N*-phenylacrylamide (**3a**), di-*tert*-butyl acetylenedicarboxylate (**2a**), and *n*-hexylacetylene (**1a**) or cyclohexylacetylene (**1b**) were sequentially added to a CH_2Cl_2 solution of the cationic rhodium(I)/H_8-binap catalyst at room temperature to give either the linear trimerization product **4aaa** or **4baa** in good yield (Scheme 1).[11] However, *tert*-butyl acetylene (**1c**) failed to react with **2a** and **3a** (Scheme 1). Surprisingly, trimethylsilylacetylene (**1d**) reacted with **2a** and **3a** to give cyclotrimerization product **5daa** in a good yield with an excellent *ee* value, along with the linear trimerization product **4daa** (Scheme 1).



Scheme 1. Rhodium-catalyzed linear trimerization versus cyclotrimerization. cod = cyclo-1,5-octadiene.

Thus, various axially chiral biaryl bisphosphine ligands (Figure 1) were screened (Table 1, entries 1–5), and the use of (*R*)-tol-binap afforded **5daa** in the highest yield with an excellent *ee* value (entry 4). Pleasingly, the simple addition of a CH_2Cl_2 solution of **1d**, **2a**, and **3a** to a CH_2Cl_2 solution of a reduced amount of the catalyst (5 mol%) afforded **5daa** without erosion of the product yield and *ee* value (entry 6).

The substrate scope is shown in Scheme 2. With respect to acrylamides, not only *N*-methyl-*N*-phenylacrylamide (**3a**) but also *N*,*N*-dimethyl (**3b**), *N*,*N*-dibutyl (**3c**), *N*,*N*-tetramethylene (**3d**), and Weinreb (**3e**) acrylamides could be employed. With respect to alkynoates, not only **2a**, but also the

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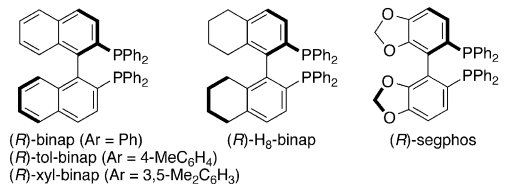
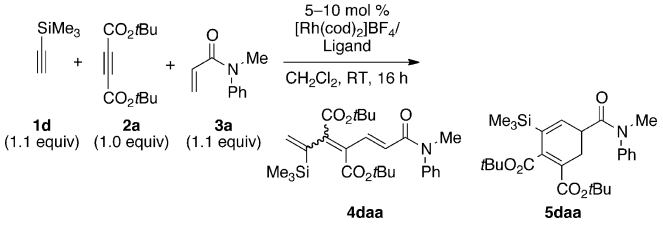


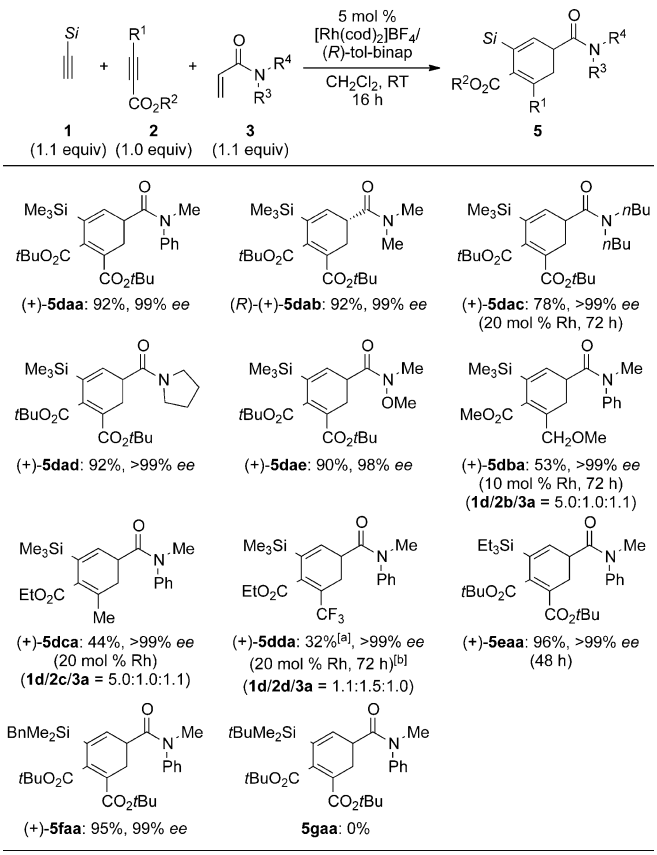
Figure 1. Structures of axially chiral biaryl bisphosphine ligands.

Table 1: Optimization of reaction conditions for rhodium-catalyzed enantioselective cross-cyclotrimerization of **1d**, **2a**, and **3a**.[a]



Entry	Ligand	Catalyst (mol%)	**4daa** Yield [%][b]	**5daa** Yield [%][b] (*ee* [%])
1	(*R*)-H_8-binap	10	16	74 (>99, +)
2	(*R*)-binap	10	<5	71 (95, +)
3	(*R*)-segphos	10	6	42 (>99, +)
4	(*R*)-tol-binap	10	<5	91 (99, +)
5	(*R*)-xyl-binap	10	56	20 (95, +)
6[c]	(*R*)-tol-binap	5	<5	92 (99, +)

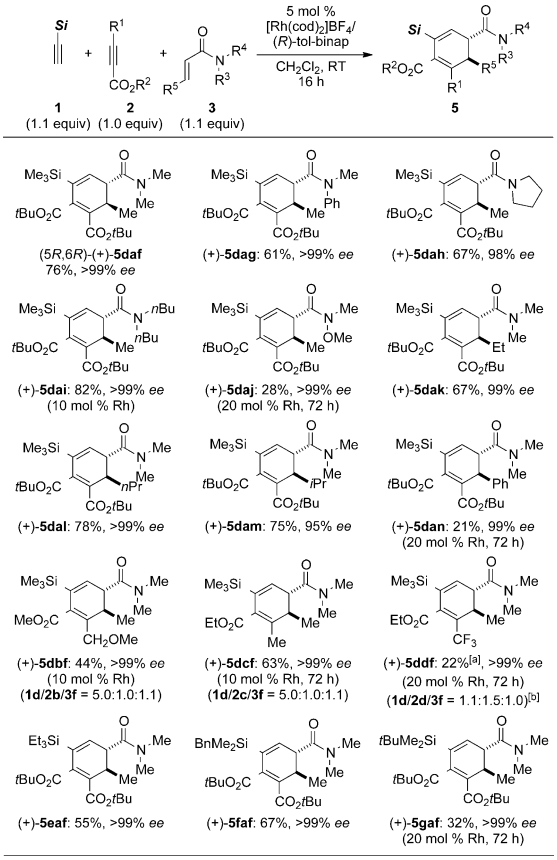
[a] $[Rh(cod)_2]BF_4$/ligand (0.010 mmol), **1d** (0.11 mmol), **2a** (0.10 mmol), **3a** (0.11 mmol), and CH_2Cl_2 (2.0 mL) were used. Solutions of **3a**, **2a**, and **1d** in were added in this order to a solution of the Rh catalyst in CH_2Cl_2. [b] Yield of isolated product. [c] A solution of **1d** (0.22 mmol), **2a** (0.20 mmol), and **3a** (0.22 mmol) in CH_2Cl_2 was added to a solution of the Rh catalyst in CH_2Cl_2.



Scheme 2. Rhodium-catalyzed asymmetric cross-cyclotrimerization of **1d–g**, **2a–d**, and **3a–e**. $[Rh(cod)_2]BF_4$ (0.010–0.040 mmol), (*R*)-tol-binap (0.010–0.040 mmol), **1** (0.22–1.00 mmol), **2** (0.20 mmol), **3** (0.22 mmol), and CH_2Cl_2 (2.0 mL) were used. Cited yields are of isolated products. [a] Conv. of **3a**: ca. 60%. [b] $[Rh(cod)_2]BF_4$ (0.030 mmol), (*R*)-tol-binap (0.030 mmol), **1d** (0.165 mmol), **2d** (0.225 mmol), **3a** (0.150 mmol), and CH_2Cl_2 (2.0 mL) were used.

unsymmetrical alkynoates **2b**,**c** reacted with **1d** and **3a** to give cyclohexadienes **5dba** and **5dca** in moderate yields, however an increased amount of **1d** and the catalyst were necessary. A slight excess of the trifluoromethyl-substituted alkynoate **2d** also reacted with **1d** and **3a** to give the cyclohexadiene **5dda** with an excellent *ee* value, however the reaction was sluggish. With respect to silylacetylenes, not only trimethylsilylacetylene (**1d**) but also triethylsilyl (**1e**) and benzyldimethylsilyl (**1f**) acetylenes could be employed, while *tert*-butyldimethylsilylacetylene (**1g**) failed to react with **2a** and **3a**. Importantly, the present three-component cyclotrimerizations proceeded with excellent regio- and enantioselectivities. The absolute configuration of (+)-**5dab** was unambiguously determined to be *R* by the anomalous dispersion methods.[13]

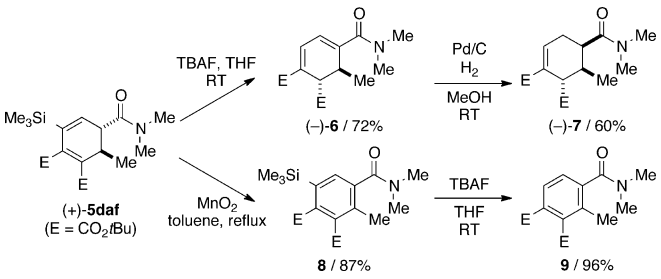
Next, the use of crotonamides in place of acrylamides was attempted (Scheme 3).[14,15] We were pleased to find that the reaction of **1d**, **2a**, and the *N*,*N*-dimethylcrotonamide **3f** in the presence of the cationic rhodium(I)/(*R*)-tol-binap catalyst (5 mol%) at room temperature affords the cyclotrimerization product **5daf** as a single diastereomer in a high yield with an excellent *ee* value. With respect to crotonamides, *N*-methyl-*N*-phenyl (**3g**) and *N*,*N*-tetramethylene (**3h**) crotonamides could also be employed. However, *N*,*N*-dibutyl (**3i**) and Weinreb (**3j**) crotonamides showed low reactivities and required high catalyst loadings. Importantly, sterically more demanding ethyl-, *n*-propyl-, and isopropyl-substituted acrylamides (**3k–m**) reacted with **1d** and **2a** to give the cyclohexadienes **5dak–m**, the yields of which were comparable to that of **5daf**. Unfortunately, the reaction of the phenyl-substituted acrylamide **3n**, **1d**, and **2a** afforded the cyclohexadiene **5dan** in low yield despite employing high catalyst loading. With respect to alkynoates, not only the symmetrical acetylenedicarboxylate **2a** but also the unsymmetrical alkynoates **2b**,**c** reacted with **1d** and **3f** to give cyclohexadienes **5dbf** and **5dcf** in moderate yields, although increasing amounts of **1d** and the rhodium catalyst were necessary. Unfortunately, the trifluoromethyl-substituted alkynoate **2d** showed poor reactivity. With respect to silylacetylenes, not only trimethylsilylacetylene (**1d**) but also triethylsilyl (**1e**) and benzyldimethylsilyl (**1f**) acetylenes could be employed. *tert*-Butyldimethylsilylacetylene (**1g**) could also react with **2a** and **3f** by using an increasing amount of the catalyst, although the yield of **5gaf** was low. Importantly, the present three-component cyclotrimerization reactions proceeded with excellent regio-, diastereo-, and enantioselectivities. The absolute configuration of (+)-**5daf** was unambiguously determined to be (5*R*,6*R*) by the anomalous dispersion methods.[13]



Scheme 3. Rhodium-catalyzed asymmetric cross-cyclotrimerization of **1d–g**, **2a–d**, and **3f–n**. $[Rh(cod)_2]BF_4$ (0.010–0.040 mmol), (*R*)-tol-binap (0.010–0.040 mmol), **1** (0.22–1.00 mmol), **2** (0.20 mmol), **3** (0.22 mmol), and CH_2Cl_2 (2.0 mL) were used. Cited yields are of isolated products. [a] Conv. of **3f**: ca. 30%. [b] $[Rh(cod)_2]BF_4$ (0.030 mmol), (*R*)-tol-binap (0.030 mmol), **1d** (0.165 mmol), **2d** (0.225 mmol), **3f** (0.150 mmol), and CH_2Cl_2 (2.0 mL) were used. THF = tetrahydrofuran.

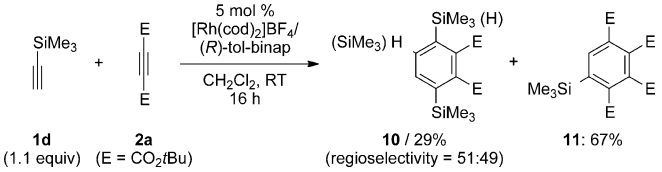
Transformations of the reaction product were briefly examined (Scheme 4). Desilylation and diene isomerization of (+)-**5daf** proceeded by treatment with TBAF (tetra-*n*-butylammonium fluoride) to give te cyclohexadiene (−)-**6**. Hydrogenation of (−)-**6** with Pd/C afforded (−)-**7**.[16] Dehydrogenation of (+)-**5daf** with MnO_2 afforded the pentasubstituted benzene **8**. Desilylation of **8** with TBAF afforded tetrasubstituted benzene **9**.

Reactivities of **1d**, **2a**, and **3a** were examined in the presence of $[Rh(cod)_2]BF_4$/(*R*)-tol-binap catalyst at room

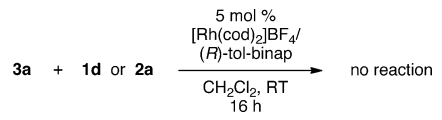


Scheme 4. Transformations of (+)-**5daf**. TBAF = tetra-*n*-butylammonium fluoride.

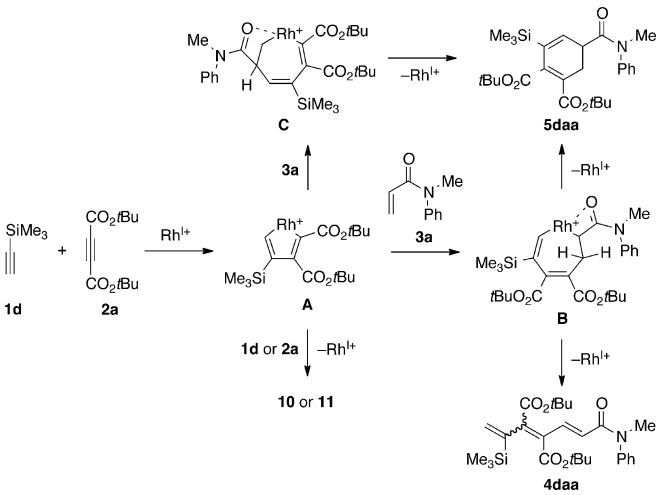
temperature. Cross-cyclotrimerization of **1d** and **2a** proceeded smoothly to give the substituted benzenes **10** and **11** (Scheme 5),[17] while **3a** failed to react with both **1d** and **2a** (Scheme 6).



Scheme 5. Treatment of **1d** and **2a** with the rhodium catalyst.



Scheme 6. Treatment of **3a** and **1d** or **3a** and **2a** with the rhodium catalyst.

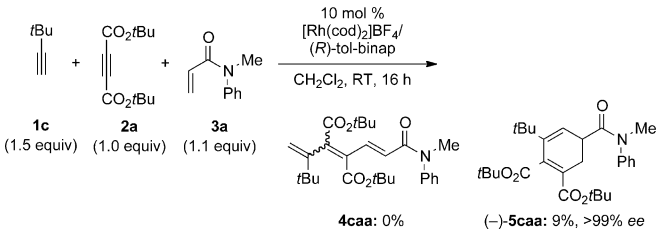


Scheme 7. Possible reaction pathways.

Possible reaction pathways for the formation of **5daa** from **1d**, **2a**, and **3a** are shown in Scheme 7. The reaction of **1d** and **2a** with rhodium generates the rhodacyclopentadiene **A**. Insertion of **3a** into **A** generates the intermediate **B**. Reductive elimination would furnish **5daa** and β-hydride elimination with subsequent reductive elimination would furnish **4daa**. In contrast, the reaction of **A** with **1d** or **2a** would furnish the either of the major by-products **10** or **11**, respectively. Alternatively, the formation of **5daa** can be explained by the formation of **C** through insertion of **3a** into the sterically less demanding Rh–C bond of **A**. Chelation of the amide carbonyl to rhodium would suppress β-hydride elimination.[18] However, given that 1) no linear trimerization from β-hydride elimination of **C** was observed, 2) **C** has a strained [4.2.1] bicyclic system, and 3) the insertion of the Rh–C bond across **3a** would have to occur at the less electrophilic site of the alkene, make this pathway unlikely. Therefore, the formation of **B** is more likely, although the precise mechanism cannot be identified at the present stage. The bulky silyl groups would accelerate the reductive

elimination from **B** as a result of steric repulsion between the silyl and *tert*-butylcarbonyl groups.

The experimental support of the former possibility is that the reaction of sterically demanding *tert*-butylacetylene (**1c**) with **2a** and **3a** afforded the cyclotrimerization product **5caa** without formation of the linear trimerization product **4caa**, however, the yield of **5caa** was low (Scheme 8).



Scheme 8. Rhodium-catalyzed reaction of **1c**, **2a**, and **3a**.

In conclusion, we have achieved the unprecedented highly chemo-, regio-, and enantioselective catalytic cross-cyclotrimerization of two different alkynes with alkenes. When di-*tert*-butyl acetylenedicarboxylate was employed, excess amounts of cycloaddition partners are not required to obtain three-component cyclotrimerization products in high yields. Future work will focus on further exploration of the rhodium-catalyzed intermolecular multicomponent reactions.

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[13] CCDC 972328 [(+)-**5dab**] and CCDC 972329 [(+)-**5daf**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] The use of methacrylamide, acrylate, and vinyl ketone did not afford three-component cyclotrimerization products.

[15] See the Supporting Information for optimization of reaction conditions of **1d**, **2a**, and **3f**.

[16] Hydrogenation of another double bond and that of two double bonds also proceeded in about 15% and 10% yield (NMR), respectively. Cyclohexadiene (−)-**7** (74% NMR yield) was isolated as a mixture of these by-products and pure (−)-**7** was isolated in 60% yield by GPC.

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