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Enantioselective Synthesis of cis-Fused Cyclooctanoids via Rhodium(I)-Catalyzed [4 + 2 + 2] Cycloadditions

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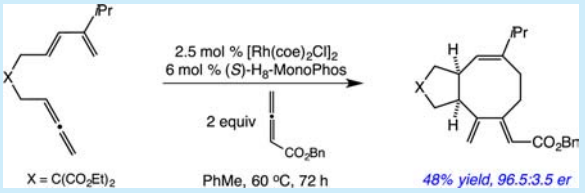
Supporting Information

ABSTRACT: Catalytic multicomponent [*m* + *n* + *o*]-type cycloadditions offer efficient, atom-economical routes to diverse complex carbocycles. Recently, such transformations have emerged as unique strategies for medium ring carbocycle synthesis. Despite the important developments in this area, however, highly enantioselective [*m* + *n* + *o*]-type processes accessing medium ring carbocycles have yet to be developed. Herein, a rhodium-catalyzed [4 + 2 + 2] cycloaddition of allenedienes with allenes enabling the direct stereoselective synthesis of cis-fused cyclooctanoids is reported. These cycloadditions are successful with a diverse range of π-components and demonstrate the potential for high levels of enantioselectivity in a [4 + 2 + 2] process.

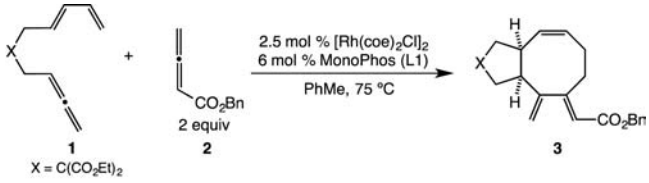


Catalytic, multicomponent [*m* + *n* + *o*]-type cycloadditions are applicable to the concise synthesis of diverse carbocycles and heterocycles. Foremost among these cycloadditions are [2 + 2 + 2] processes, with particularly attractive applications in the preparation of benzenoid systems.[1] Recent work has extended the use of multicomponent cycloadditions to the synthesis of medium-ring systems via [3 + 2 + 2] and [4 + 2 + 2] approaches.[2] These transformations offer unique strategies toward seven- and eight-membered carbocycles that remain a formidable synthetic challenge.[3] However, in contrast to [2 + 2 + 2] processes, enantioselective variants of these cycloadditions are not known.[4] The successful development of reactions accomplishing this goal would constitute powerful tools for the direct, enantioselective synthesis of these challenging carbocycles.

We have previously reported Rh- and Ni-catalyzed [2 + 2 + 2] cycloadditions of alkenes and allenes for the construction of stereochemically complex cyclohexanoids, including enantioselective variants.[5] Herein, the development of a Rh-catalyzed [4 + 2 + 2] cycloaddition of allenedienes with allenes for the stereoselective construction of cis-fused cyclooctanoids is reported. Through the use of chiral phosphoramidites as ligands in our catalytic system, we have successfully developed the first examples of highly enantioselective multicomponent cycloadditions for the synthesis of medium ring carbocycles.

Our initial efforts targeted the identification of an effective catalytic system for the [4 + 2 + 2] cycloaddition of allenediene **1** and benzyl allenoate **2** (Table 1). Phosphoramidite MonoPhos (**L1**) proved to be an excellent ligand for the reaction and, in conjunction with 2.5 mol % $[Rh(coe)_2Cl]_2$, provided cyclooctanoid **3** in 70% yield as a single diastereomer (entry 1). The simple intramolecular [4 + 2] cycloaddition of the allenediene substrate was not observed under these conditions.[6] Reactions using either standard monodentate phosphines (PPh_3), or bidentate phosphines (BINAP) in the presence or absence of AgOTf provided no cycloadduct (entries 2−4). Increasing the amount of MonoPhos in the catalytic system led to a decrease in yield (entry 5). Reactions in the absence of ligand or metal both provided no product (entries 6 and 7).

Table 1. Rh-Catalyzed [4 + 2 + 2] Cycloaddition of Allenediene 1



entry	variations from standard conditions	yield **3** (%)[a]
1	–	**70**
2	$RhCl(PPh_3)_3$ instead of $[Rh(coe)_2Cl]_2$ + ligand	<2
3	BINAP instead of MonoPhos, 100 °C	<2
4	BINAP instead of MonoPhos, with 5 mol % AgOTf, 100 °C	<2
5	10 mol % instead of 6 mol % MonoPhos	54
6	no ligand	<2
7	no metal or ligand	<2

[a]Isolated yield.

Prior to our studies of enantioselective variants of the [4 + 2 + 2], we elected to perform an initial survey of the substrate scope (Table 2). The cycloaddition was successful using a variety of allenediene tether units (entries 1−3). The identity of the cis-fused cyclooctanoid **7** was confirmed by X-ray crystallography (Figure 1). Importantly, substrates benefiting from the Thorpe−Ingold effect were not required in the process, as demonstrated by the reaction of methylene-tethered substrate **8**, which proceeded in 75% yield (entry 4). Substitution of the diene at the 2-position in allenediene **10** provided cycloadduct **11** in moderate yield (49%); we also observed allenediene [4 + 2]

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Table 2. Scope of Rhodium-Catalyzed [4 + 2 + 2] Allenediene-Allene Cycloaddition[a]

entry	substrate	allene	product	yield (%)[b]
1[c]	**1**: X = $C(CO_2Et)_2$	**2**	**3**: X = $C(CO_2Et)_2$	70
2[c]	**4**: X = O		**5**: X = O	70
3[c]	**6**: X = NTs		**7**: X = NTs	59
4[c]	**8**		**9**	75
5[c]	**10**		**11**	49
6				59
7	**12**		**13**	50
8	**14**: R = Me		**15**: R = Me	55
9	**16**: R = CO_2Et		**17**: R = CO_2Et	63
10	**18**		**19**	59
11	**1**	**20**: R = *n*Hex	**21**: R = *n*Hex	36
12		**22**: *p*-$(CO_2Me)C_6H_4$	**23**: *p*-$(CO_2Me)C_6H_4$	78
13		**24**: R = Bpin	**25**: R = Bpin	47
14[d]	**1**	**26**	**27**	40

[a]Reactions performed using **1** equiv of allenediene and **2** equiv of allene in the presence of 2.5 mol % $[Rh(coe)_2Cl]_2$ and 6 mol % $P(OEt)_3$ in PhMe at 100 °C for 72 h. X = $C(CO_2Et)_2$ unless otherwise noted. [b]Isolated yield. [c]6 mol % MonoPhos used as ligand. [d]Reaction temperature 130 °C.

cycloaddition (28%), however. This selectivity issue was easily addressed by substituting $P(OEt)_3$ for MonoPhos as ligand. The intramolecular allenediene [4 + 2] process was not observed in any cases using $P(OEt)_3$ as ligand.

Our studies continued with allenediene substrates containing substitution at the 1- and 3-positions of the diene (entries 7−9), which were also well tolerated, providing the cyclooctanoid

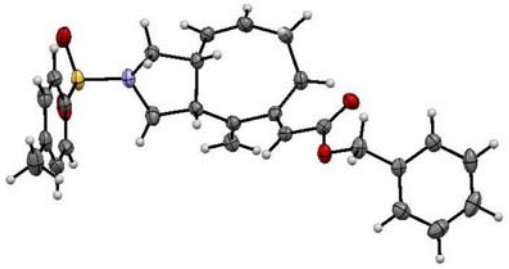
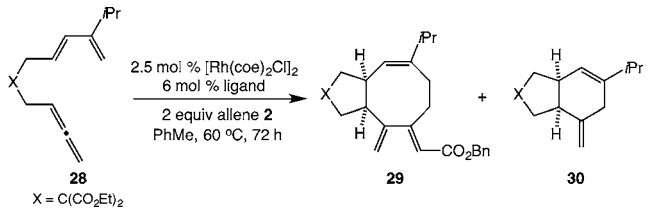


Figure 1. ORTEP diagram of cycloaddition product **7** (thermal ellipsoids set at 50% probability).

products in moderate yield as single diastereomers. The reaction of dienoate **16** demonstrated the viability of electron-poor dienes in the [4 + 2 + 2] process. We next sought to investigate the scope of the cycloaddition with respect to substitution of the allene components. Cycloaddition of 1,1-disubstituted allenediene **18** produced cyclooctanoid **19** containing a quaternary stereogenic center as a single diastereomer (entry 10). The exogenous allene is not limited to benzyl allenoate, as demonstrated by the reactions of entries 11−13 involving allenes containing aliphatic, aromatic, and heteroatom substitution, respectively. Furthermore, cycloaddition of **1** with 1,1-disubstituted allenoate **26** delivered cyclooctanoid **27** containing a tetrasubstituted alkene as a single stereoisomer.

We next turned our focus to the development of a highly enantioselective variant of the [4 + 2 + 2] process (Table 3). Our initial studies involved substrate **28**, as 2-substitution of the diene component had been shown to increase levels of undesired [4 +

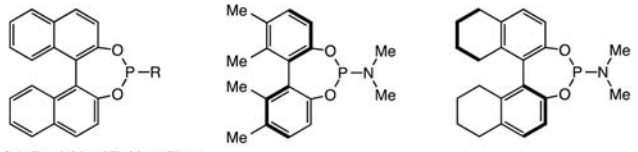
Table 3. Optimization Studies of Enantioselective Rh-Catalyzed [4 + 2 + 2] Allenediene-Allene Cycloaddition



28 X = $C(CO_2Et)_2$ **29** **30**

entry	ligand	deviation from above conditions	er **29**	yield **29** (%)[a]	yield **30** (%)[b]
1	L1	–	97.5:2.5	39	31
2	L1	75 °C instead of 60 °C	97:3	27	43
3	L1	5 mol % AgOTf added	72.5:27.5	45	6
4	L1	5 mol % AgOTs added	56.5:43.5	31	4
5	L2	–	99:1	20	55
6	L3	–	97:3	25	39
7	L4	–	97:3	38	25
8	**L5**	–	**96.5:3.5**	**47 (48)**[c]	**30**
9	L5	dioxane instead of PhMe	97:3	36	23
10	L5	$ClCH_2CH_2Cl$ instead of PhMe	97.5:2.5	41	32

[a]Isolated yield. [b]Calculated by ^1H NMR spectroscopy of crude reaction mixtures using an internal standard. [c]Reaction performed on 0.5 mmol scale.



L1: R = NMe_2 (*R*)-MonoPhos
L2: R = $N(CH_2)_5$ (*S*)-PipPhos
L3: R = NMeBn (*S*)-(Bz)-MonoPhos
L4
L5: (*S*)-H_8-MonoPhos

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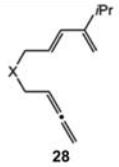
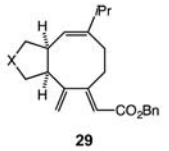
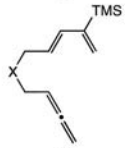
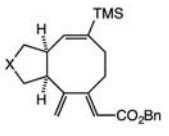
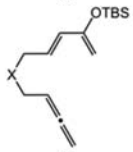
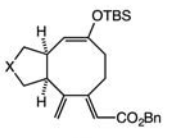
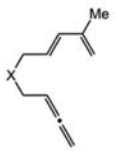
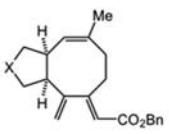
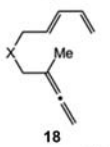
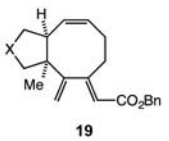
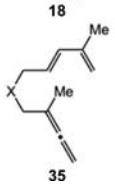
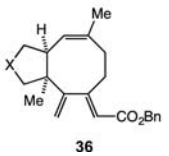
2] cycloaddition (e.g., Table 1, entry 5). Our rationale was that this choice would allow for the simultaneous determinination of reaction enantioselectivity and chemoselectivity with a challenging allenediene substrate. We were pleased to discover that the reaction of **28** with allenoate **2** using (*R*)-MonoPhos as ligand provided [4 + 2 + 2] product **29** in a highly enantioselective fashion (97.5:2.5 er, entry 1). The cyclooctanoid product was formed in moderate yield (39%), however, with a significant amount of **30** produced. Increasing the reaction temperature led to a predominance of the [4 + 2] pathway (entry 2), and lowering the reaction temperature further (e.g., 40 °C) resulted in low conversions. Encouraged by these initial results, we next performed experiments involving modified catalytic systems. The addition of silver salts as halide abstractors increased the reaction chemoselectivity at the expense of enantioselectivity (entries 3 and 4). A survey of phosphoramidite ligands was performed, and altering substitution on the amine moiety with the bulkier piperidine (**L2**) and methylbenzylamine (**L3**) moieties maintained reaction enantioselectivity, but decreased product selectivity (entries 5 and 6). A large increase in the diol dihedral angle (**L4**) provided no improvement over **L1** (entry 7); however, a modest increase in dihedral angle with (*S*)-H_8-MonoPhos (**L5**) led to a somewhat improved level of product selectivity (47% yield of cyclooctanoid), while maintaining high enantioselectivity (entry 8). Solvent modifications had minimal effect on the reaction outcome (entries 9 and 10).

With our optimized conditions for the enantioselective [4 + 2 + 2] in hand, we studied a range of allenediene substrates (Table 4). Increasing the steric bulk of the 2-position of the diene from isopropyl (entry 1) to trimethylsilyl (entry 2) did not reduce the reaction enantioselectivity, but did somewhat decrease chemoselectivity. Cycloaddition of −OTBS diene **33** delivered silyl enol ether product **34** in modest yield (and high enantioselectivity); in this case the cyclooctanoid was the major product (entry 3). Decreasing the size of the 2-substituent (entry 4) noticeably improved product selectivity, but at the expense of enantioselectivity (85:15 er). While there are limitations with respect to the diene substitution in these enantioselective reactions, the vinyl silane and silyl enol ether functionality of products **32** and **34** are expected to enable access to a variety of derivatives via standard synthetic manipulations.[7]

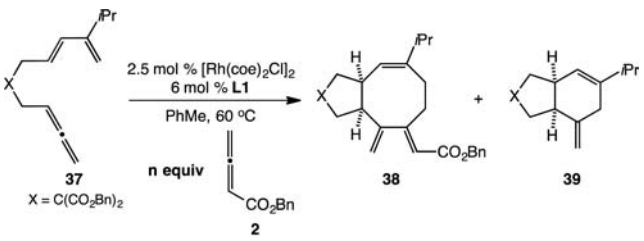
The reaction of allenediene **18**, containing a 1,1-disubstituted allene, yielded [4 + 2 + 2] product **19** with high chemoselectivity but modest enantioselectivity (entry 5). Interestingly, a synergistic effect was observed when this allene substitution pattern was combined with 2-substitution on the diene. In the event, reaction of **35** delivered cyclooctanoid **36**, bearing a quaternary center at the ring fusion, in high enantioselectivity (97.5:2.5). The enantioselectivity of this process was higher than the reactions of either substituent in isolation (entries 4 and 5).

In order to gain insight into a potential reaction mechanism, we sought to verify whether the undesired [4 + 2] cycloadduct was formed with an identical level of enantioselectivity as the [4 + 2 + 2] product. This would be consistent with a common enantiodetermining step. However, the [4 + 2] pathway proceeded with lower enantioselectivity than the [4 + 2 + 2] pathway (77.5:22.5 vs 96.5:3.5, Figure 2). The removal of exogenous allene from the system provided a high yield of [4 + 2] product **39** in nearly racemic fashion. These results suggest that the enantiodetermining steps of the two cycloadditions are not identical and that the added allene component is a factor in determining the enantioselectivity of both pathways.

Table 4. Enantioselective Rh-Catalyzed [4 + 2 + 2] Cycloadditions of Allenedienes with Allene 2

entry	substrate	product	er	yield (%)[a]	yield [4+2] (%)[b]
1	 **28**	 **29**	96.5:3.5	47	30
2	 **31**	 **32**	96:4	34	47
3[c]	 **33**	 **34**	95.5:4.5	34	23
4	 **10**	 **11**	85:15	60	23
5	 **18**	 **19**	65:35	55	2
6	 **35**	 **36**	97.5:2.5	33	27

[a]Isolated yield. [b]Calculated by ^{1}H NMR spectroscopy of crude reaction mixtures using an internal standard. [c]Reaction temperature 100 °C.



allene	yield 38 (%)[a]	er 38	yield 39 (%)[a]	er 39
–	–	–	84	42:58
2 equiv	48	96.5:3.5	37	77.5:22.5

Figure 2. Enantioselectivity of [4 + 2] pathway.

Given the complete cis-diastereoselectivity of these cycloadditions, we propose that both the [4 + 2 + 2] and [4 + 2] pathways proceed via a cis-fused metallacyclopentane intermediate (B and B′, Figure 3). The cis-diastereoselectivity of the allenediene oxidative coupling has previously been attributed to the higher strain energy of a trans-fused metallacycle.[6] We

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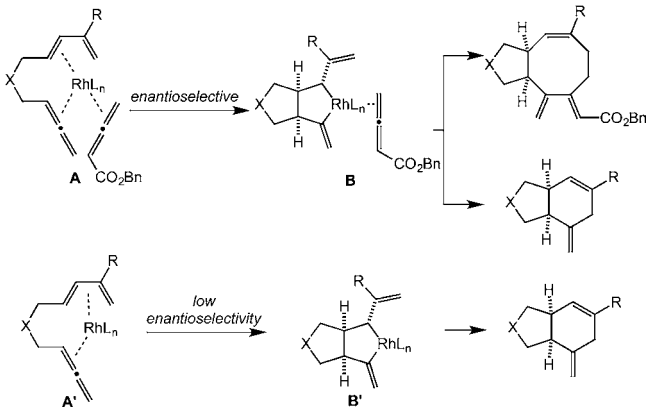

Figure 3. Mechanistic rationale for inequivalent enantioselectivities in [4 + 2 + 2] and [4 + 2] pathways.

propose that two pathways with inequivalent enantioselectivities lead to the cycloadducts formed. The first route involves an enantioselective oxidative coupling of allene-bound coordination complex A to form metallacycle B. This pathway subsequently produces the [4 + 2 + 2] and [4 + 2] products with high enantioselectivity. Alternatively, a pathway solely involving the allenediene can simultaneously deliver the [4 + 2] product with poor enantioselectivity. Consistent with this hypothesis is the observed increase in enantioselectivity of the [4 + 2] process with added allene and the near racemic product formed in its absence (Figure 2).

In conclusion, a Rh-catalyzed [4 + 2 + 2] cycloaddition of allenedienes and allenes for the construction of fused cyclooctanoids is reported. This catalytic cycloaddition is successful with a diverse set of diene and allene components and provides unique 5−8 cis-fused carbocycles in a highly stereoselective fashion. The use of phosphoramidite ligands has enabled the development of asymmetric variants of this process, which represent the first examples of highly enantioselective multicomponent cycloadditions in medium ring carbocycle synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Tanaka, K., Ed. *Transition-Metal-Mediated Aromatic Ring Construction*; John Wiley & Sons: Hoboken, NJ, 2013. (b) Broere, D. L. J.; Ruitjer, E. *Synthesis* **2012**, *44*, 2639. (c) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(2) (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (b) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784. (c) Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150. (d) Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63. (e) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354. (f) Hilt, G.; Janikowski, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5243. (g) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480. (h) Saya, L.; Bhargava, G.; Navarro, M. A.; Gulías, M.; López, F.; Fernández, I.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9886. (i) Canlas, G. M. R.; Gilbertson, S. R. *Chem. Commun.* **2014**, *50*, 5007. (j) Araya, M.; Gulías, M.; Fernández, I.; Bhargava, G.; Castedo, L.; Mascareñas, J. L.; López, F. *Chem.—Eur. J.* **2014**, *20*, 10255.

(3) (a) López, F.; Mascareñas, J. L. *Chem.—Eur. J.* **2007**, *13*, 2172. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (c) Butenschön, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5287. (d) Yu, Z.-X.; Wang, Y.; Wang, Y. *Chem.—Asian J.* **2010**, *5*, 1072.

(4) Using an alkyne-alkyne-diene [4 + 2 + 2], Gilbertson has reported a moderately enantioselective reaction (70.5:29.5 er) yielding an eight-membered carbocycle: DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. Rovis has reported a highly enantioselective approach to azocine *heterocycles* via a [4 + 2 + 2] of dienyl isocyanates and alkynes: Yu, R. T.; Friedman, R. K.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13250.

(5) (a) Noucti, N. N.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8424. (b) Brusoe, A. T.; Edwankar, R. V.; Alexanian, E. J. *Org. Lett.* **2012**, *14*, 6096. (c) Brusoe, A. T.; Alexanian, E. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6596.

(6) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843.

(7) (a) Fleming, I.; Dunoguès, J.; Smithers, R. The Electrophilic Substitution of Allylsilanes and Vinylsilanes. In *Organic Reactions*; John Wiley & Sons, Inc.: New York, 2004; pp 57−575. (b) Oshima, K. Vinylsilanes. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, Germany, 2002; Vol. 4, pp 713−754. (c) Kobayashi, S.; Manabe, K.; Ishitani, H.; Matsuo, J.-I. Silyl Enol Ethers. In *Science of Synthesis*; Fleming, I., Ed.; Thieme: Stuttgart, Germany, 2002; Vol. 4, pp 317−369.

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