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Highly Selective Cobalt-Mediated [6 + 2] Cycloaddition of Cycloheptatriene and Allenes

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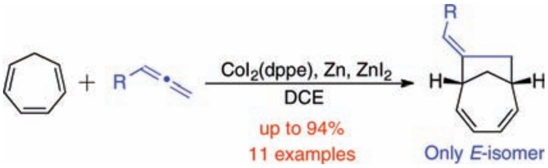
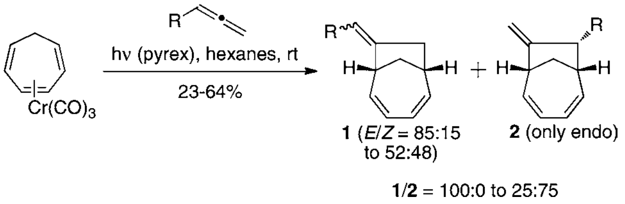
ABSTRACT



[6 + 2] Cycloadditions between cycloheptatrienes with allenes have been investigated. Cobalt salts were found to promote this transformation efficiently. Moreover, this reaction was found to be highly selective since only one regioisomer was obtained with an excellent *E*/*Z*-selectivity.

Although less commonly encountered in nature than six-membered rings or smaller, eight-membered carbocycles have attracted particular attention for their synthesis due to their biological relevance.[1] Among the synthetic strategies developed for the construction of medium-sized ring targets, transition-metal-mediated higher-order cycloaddition reactions have emerged as one of the most powerful.[2] In this context, chromium(0)-promoted [6π + 2π] cycloadditions with cycloheptatrienes (CHT) have been extensively studied via both thermal and photochemical ways with various 2π partners,[3] such as alkynes,[4] isocyanates, or ketenes.[5] More recently, Rigby and co-workers reported the photoinduced [6π + 2π] cycloadditions of allenes with (η^6-CHT)tricarbonylchromium(0) (Scheme 1).[6] This reaction was found to be efficient and tolerant to various functional groups; however it suffered from moderate yields, regioselectivity issues, and low *E*/*Z*-selectivity.

Scheme 1. Photoinduced [6π + 2π] Cycloadditions of Allenes with Cr(0)(η^6-CHT)(CO)$_3$



As an alternative to the photoinduced Cr(0)(η^6-CHT)(CO)$_3$ system, our group developed cobalt(I)-catalyzed [6 + 2]

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(1) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Chemistry*, Vol. 3; Atta-ur-Rahman, Ed.; Elsevier Science Publishers: New York, 1989; pp 73−115.

(2) Yu, Z.-X.; Wang, Y.; Wang, Y. *Chem.—Asian J.* **2010**, *5*, 1072–1088.

(3) For a review, see: Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521–4538.

(4) (a) Fischler, I.; Grevels, F. W.; Leitich, J.; Özkar, S. *Chem. Ber.* **1991**, *124*, 2857–2861. (b) Chaffee, K.; Sheridan, J. B.; Aistars, A. *Organometallics* **1992**, *11*, 18–19. (c) Chaffee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lanlancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900–1907.

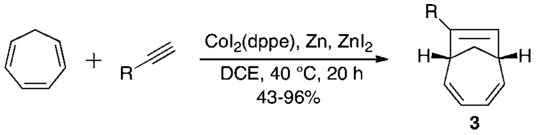
(5) Rigby, J. H.; Ahmed, G.; Ferguson, M. D. *Tetrahedron Lett.* **1993**, *34*, 5397–5400.

(6) Rigby, J. H.; Laurent, S. B.; Kamal, Z.; Heeg, M. J. *Org. Lett.* **2008**, *10*, 5809–5812.

10.1021/ol102783x

cycloadditions with alkynes (Scheme 2).[7] The catalytic system including cobalt(II) iodide, 1,2-bis(diphenylphosphino)ethane (dppe), zinc metal as a reducing agent, and zinc iodide as a Lewis acid showed good activity and an excellent tolerance to various functional groups. Moreover, it could be applied to cyclooctatriene and cyclooctatetraene.[8]

Scheme 2. Cobalt-Mediated [6 + 2] Cycloaddition with Alkynes



Importantly, an enantioselective version of this reaction was developed using phosphoramidite ligands as chirality inductors.[7,9] Thus, chiral phosphoramidites based on 3,3′-disubstituted (*R*)-BINOL allowed affording the corresponding cycloadducts with up to 92% ee.

These results prompted us to investigate the cobalt-catalyzed [6 + 2] cycloaddition of cycloheptatriene using allenes as 2π partners. Indeed, we believed a cobalt-based catalytic system could significantly improve yields of cycloadducts and both regioselectivity and geometric isomerism issues.

We have optimized the cobalt-mediated [6 + 2] cycloaddition using the benchmark substrates cycloheptatriene and phenylallene **4a** and determined that, through the appropriate choice of conditions, reaction can be achieved with both high efficiency and selectivity (Table 1). Thus, during all the experiments of this optimization study, only the *E*-isomer of 7-benzylidenebicyclo[4.2.1]nona-2,4-diene **1a** was observed. Neither *Z*-cycloadduct nor product **2** resulting from the contribution of the internal allene double bond could be detected. Whereas CoI$_2$(dppe) with zinc powder and zinc iodide at 60 °C allowed for the formation of 85% of cycloadduct **1a** in only 5 h (entry 1), the reaction did not proceed at room temperature (entry 2) and was found slower at 40 °C (entries 3 and 4). Importantly, we checked that the [6 + 2] cycloaddition could not be achieved under thermal activation at 60 °C (entry 5). It was also noticed that the nature of the zinc salt was more important than the one of the cobalt salt. In the presence of zinc chloride, only small amounts of **4a** were isolated, no matter which cobalt halide was used: CoCl$_2$ or CoI$_2$ (entries 6 and 8). On the other hand, the combination of CoCl$_2$ with ZnI$_2$ led to a good yield (entry 7). The ligand itself was equally found to be a key parameter (entry 10); bis(diphenylphosphino)methane (dppm) or 1,3-bis(diphenylphosphino)propane (dppp) appeared to be inefficient (entries 11 and 12). Without zinc metal as a reducing agent, the cycloaddition could not be accomplished (entry 13). Whereas tetrabutylammonium borohydride was successfully used for [6 + 2] cycloaddition involving alkynes,[7] with phenylallene **4a**, only polymerization of allene was observed (entry 14). This probably resulted from the formation of cobalt hydride species promoting the polymerization process.

Table 1. Cobalt-Catalyzed [6 + 2] Cycloaddition of CHT with Phenylallene **4a**: Effect of Reaction Parameters[a]

entry	change from “the standard conditions”	isolated yield (%)
1	None	85
2	25 °C, 72 h instead of 60 °C, 5 h	<5
3	40 °C, 5 h instead of 60 °C, 5 h	27
4	40 °C, 20 h instead of 60 °C, 5 h	83
5	No CoI$_2$(dppe)	NR
6	CoCl$_2$(dppe), ZnCl$_2$ instead of CoI$_2$(dppe), ZnI$_2$	9
7	CoCl$_2$(dppe), ZnI$_2$ instead of CoI$_2$(dppe), ZnI$_2$	79
8	CoI$_2$(dppe), ZnCl$_2$ instead of CoI$_2$(dppe), ZnI$_2$	<5
9	No ZnI$_2$	NR
10	No dppe	NR
11	dppm instead of dppe	NR
12	dppp instead of dppe	NR
13	No Zn	NR
14	*n*-Bu$_4$NBH$_4$ instead of Zn	NR[b]

[a] Reaction conditions: Allene **4a** (1 mmol), CHT (2 mmol), CoI$_2$(dppe) (5 mol %), Zn (15 mol %), ZnI$_2$ (10 mol %), DCE (3 mL, 0.3 M), 60 °C, 5 h. [b] Allene polymerization. NR = No reaction.

Having established the optimal reaction conditions, we investigated further the scope of the catalytic system with a range of monosubstituted allenes (Table 2). Phenylallene substituted with methoxy or methyl groups in the *para*- or *ortho*-positions are well tolerated, and only *E*-isomers were isolated (entries 1−4). [6 + 2] Cycloaddition could also be achieved with benzylallene **4e**, and the *E*-7-benzylidenebicyclo[4.2.1]nona-2,4-diene **1e** was obtained as a single product (entry 5). We then examined allenes bearing free hydroxyl groups (entries 6−9). Neither α-allenol **4f** nor β-allenol **4g** reacted under standard conditions. Nevertheless using trifluoroethanol (TFE) instead of DCE afforded cycloadduct **1g** in moderate yield (entry 9); this solvent being beneficial to cationic species.[10] Unfortunately, with α-allenol **4f**, reaction did not work even when performed in TFE. For this reason, protected analogues were tested (entries 10−12). Whereas tetrahydropyranyl protected α-allenol **4h** or benzoate protected β-allenol **4j** led to excellent yields, only 54%

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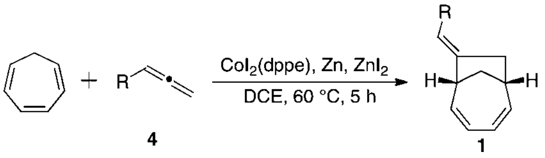
(7) Achard, M.; Tenaglia, A.; Buono, G. *Org. Lett.* **2005**, *7*, 2353–2356.

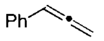
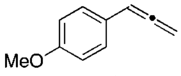
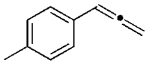
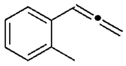
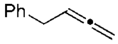
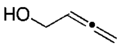
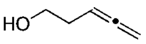
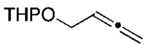
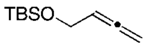
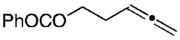
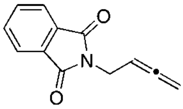
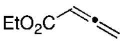
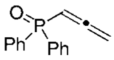
(8) Achard, M.; Mosrin, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2006**, *71*, 2907–2910.

(9) (a) Toselli, N.; Martin, D.; Achard, M.; Tenaglia, A.; Bürgi, T.; Buono, G. *Adv. Synth. Catal.* **2008**, *350*, 280–286. (b) Toselli, N.; Fortrie, R.; Martin, D.; Buono, G. *Tetrahedron: Asymmetry* **2010**, *21*, 1238–1245.

(10) Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925–2943.

Table 2. Cobalt-Mediated [6 + 2] Cycloaddition of CHT with Various Monosubstituted Allenes[a]



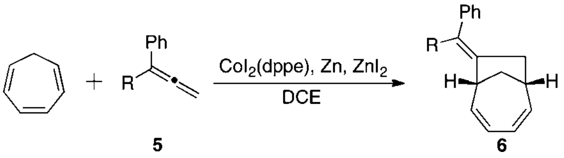
entry	allene 4	adduct	isolated yield (%)
1	 **4a**	**1a**	85
2	 **4b**	**1b**	76
3	 **4c**	**1c**	75
4	 **4d**	**1d**	87
5	 **4e**	**1e**	82
6	 **4f**	-	NR
7			NR[b]
8	 **4g**	**1g**	NR
9			45[b]
10	 **4h**	**1h**	93
11	 **4i**	**1i**	54
12	 **4j**	**1j**	94
13	 **4k**	**1k**	Traces
14			66[c]
15	 **4l**	-	NR[d]
16	 **4m**	-	NR[d]

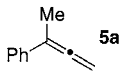
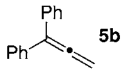
[a] Reaction conditions: Allene (1 mmol), CHT (2 mmol), CoI$_2$(dppe) (5 mol %), Zn (15 mol %), ZnI$_2$ (10 mol %), DCE (3 mL, 0.3 M), 60 °C, 5 h. [b] TFE, 16 h. [c] 72 h. [d] 90 °C, 16 h. NR = No reaction.

of **1i** using *tert*-butyldimethylsilyl as a protecting group was isolated, likely due to a degradation of allene **4i** during the catalytic cycle. For phtalimide-based allene **4k**, traces of **1k** were detected after 5 and 72 h of reaction at 60 °C were required to achieve an acceptable yield (entries 13 and 14). Cycloaddition did not work with electron-deficient allenes such as **4l** and **4m** despite more drastic conditions: 90 °C for 16 h (entries 15−16). This showed clearly that the thermal process did not occur under the reaction conditions since these allenes are well-known to be good enophiles.

We then studied disubstituted allenes (Table 3). None of allenes **5a** and **5b** reacted at 60 °C (entries 1 and 4); therefore the reaction temperature was increased to 90 °C. After 5 h, cycloadduct **6a** was obtained in a respectable yield, and increasing the reaction duration gave a good yield (entries 2 and 3). We were pleased to see that the *E*- cycloadduct was still mainly obtained since only traces of the *Z*-isomer were detected. Unfortunately, under these conditions [6 + 2] cycloaddition with diphenylallene **5b** could not be achieved (entry 5).

Table 3. Cobalt-Mediated [6 + 2] Cycloaddition of CHT with Disubstituted Allenes **5**[a]

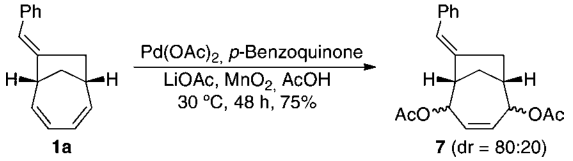


entry	allene 5	conditions	adduct	isolated yield (%)	*E*/*Z* ratio
1	 **5a**	60 °C, 16 h	**6a**	NR	-
2		90 °C, 5 h		65	> 95:5
3		90 °C, 16 h		82	> 95:5
4	 **5b**	60 °C, 16 h	-	NR	-
5		90 °C, 16 h		Traces	-

[a] Reaction conditions: Allene (1 mmol), CHT (2 mmol), CoI$_2$(dppe) (5 mol %), Zn (15 mol %), ZnI$_2$ (10 mol %), DCE (3 mL, 0.3 M). NR = No reaction.

The synthetic potential of bicyclo[4.2.1]nonatrienes has been already demonstrated through electrophilic activations and *in situ* trapping by water or alcohols allowing for the introduction of various functional groups.[11] To also illustrate the synthetic usefulness of 7-alkylidenebicyclo-[4.2.1]nona-2,4-diene, compound **1a** was engaged in a palladium-catalyzed 1,4-diacetoxylation of the diene moiety.[12] As shown in Scheme 3, the reaction of **1a** with Pd(OAc)$_2$, *p*-benzoquinone, lithium acetate, and manganese oxide in acetic acid proceeded slowly since 2 days were required to complete the reaction and obtain 75% yield. Two diastereomers were detected in a ratio of 80:20 (Scheme 3).

Scheme 3. Palladium-Catalyzed 1,4-Diacetoxylation of 7-Benzylidenebicyclo[4.2.1]nona-2,4-diene **1a**



A simple recrystallization in a hexanes/Et$_2$O mixture allowed for isolation of the major diastereomer as white crystals, which were found suitable for X-ray determination. The major diastereomer resulted from the 1,4-*cis*-addition

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[11] Toselli, N.; Martin, D.; Achard, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2009**, *74*, 3783–3791.

[12] (a) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619–4631. (b) Bäckvall, J.-E.; Anderson, P. G. *J. Am. Chem. Soc.* **1990**, *112*, 3683–3685.

of acetoxy groups on the methylene bridge side, leading to an *exo*-product (Figure 1). This is consistent with Bäckvall's observations on cycloheptadiene derivatives.[12] Moreover, this X-ray structure also allowed confirmation of the *E* conformation of the exocyclic C−C double bond. According to the literature results showing only *cis*-addition for seven-membered rings, we presumed the minor diastereomer to be the *endo*-product (Figure 2) resulting from the *cis*-addition of the acetoxy groups on the opposite face of the methylene bridge.

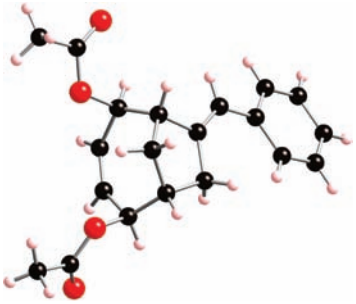
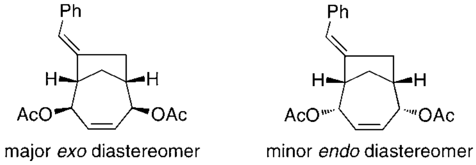


Figure 1. Ball-and-stick representation of major diastereomer.



major *exo* diastereomer   minor *endo* diastereomer

Figure 2. Structures of the diastereomers of **7**.

Allenes have been used in various cycloadditions catalyzed by transition metals such as molybdenum, rhodium, ruthenium, palladium, platinum, or gold.[13,14] However, to the best of our knowledge, we have reported herein the first cobalt-catalyzed [$6\pi + 2\pi$] cycloaddition involving allenes. Optimal catalytic conditions and key parameters have been identified. Thus, excellent yields have been reached, up to 94%, for various allenes including nonprotected allenol (54% yield). As we expected, the use of cobalt for this cycloaddition allowed for both regioselectivity and *E*/*Z* selectivity control. The *E*-isomer was obtained exclusively in all reactions performed with the exception of methylphenylallene **5a** where traces of the *Z*-isomer where observed. Additionally, the synthetic value of the cycloadducts formed was demonstrated through a reaction of 1,4-diacetoxylation on the 1,3-diene. An enantioselective version and mechanism investigations are currently underway in our laboratory.

Acknowledgment. We acknowledge the CNRS for fundings. We are grateful to Christophe Chendo and Valérie Monnier for mass spectroscopy analyses and Alain Giorgi for X-ray determination (Spectropole, Fédération des Sciences Chimiques de Marseille).

Supporting Information Available: Experimental procedures, compounds characterization results, NMR spectra of new compounds, and CIF of *endo*-product **7** (CCDC-798241). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For reviews, see: (a) Brummond, K. M.; Chen, H. In *Modern Allene Chemistry*, Vol. 2; Krause, N.; Hashmi, S. K., Eds.; Wiley-VCH: 2004; pp 1041−1089. (b) Ma, S. *Chem. Soc. Rev.* **2005**, *105*, 2829–2871. (c) Croatt, M. P.; Wender, P. A. *Eur. J. Org. Chem.* **2010**, 19–32. (d) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev. Rev.* **2010**, *39*, 783–816.

(14) For selected recent examples, see: (a) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951–954. (b) Trillo, B.; López, F.; Montserrat, S.; Ujaque, G.; Castedo, L.; Lledós, A.; Mascareñas, J. L. *Chem.−Eur. J.* **2009**, *15*, 3336–3339. (c) Mauleón, P.; Zeldin, R. M.; González, A. Z.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 6348–6349. (d) Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124–4126. (e) Kusama, H.; Ebisawa, M.; Funami, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2009**, *131*, 16352–16353. (f) Li, W.; Yuan, W.; Shi, M.; Hernandez, E.; Li, G. *Org. Lett.* **2010**, *12*, 64–67. (g) González, A. Z.; Toste, F. D. *Org. Lett.* **2010**, *12*, 200–203.