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Desymmetrization of 1,4-Cyclohexadienyltriisopropoxysilane Using Copper Catalysis

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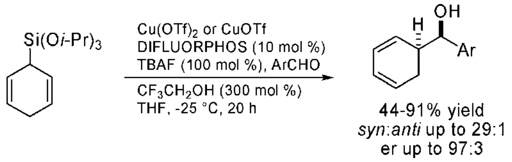
ABSTRACT



The first catalytic desymmetrization in the field of allylsilane chemistry is presented. Desymmetrization of cyclohexadienyltriisopropoxysilane is achieved using coppper catalysis. High diastereo- and enantioselectivities are obtained, and the product dienes are highly valuable building blocks for natural product synthesis.

Various allylmetal compounds have been successfully used for the asymmetric allylation of aldehydes.[1] Allylsilanes have often been applied as nucleophiles in these reactions. They are stable compounds, and some of them are commercially available. Importantly, allylsilanes are nontoxic and generally stable toward moisture. However, most of the allylsilanes are not reactive enough to undergo spontaneous addition to an aldehyde, and Lewis acid activation of the aldehyde is necessary.[2] Activation of allylsilanes can also be achieved by Lewis bases.[3] A third option is the transmetalation of an allylsilane to generate a reactive allylmetal species that is able to react with an aldehyde. In fact, Cu(I)-[4] and Ag(I)-catalyzed[5] enantioselective allylations of various aldehydes using readily available allyltrialkoxysilanes have been published. Achiral Cd(II) complexes have also been reported to catalyze the allylation of aldehydes using trialkoxyallylsilanes.[6] Moreover, hydrazones and activated imines were successfully allylated by allylsilanes using chiral Zn[7] and Cu complexes.[8]

We have recently reported the desymmetrization[9] of 1,4-cyclohexadiene using the chiral Ti(IV) complex **1**. The synthetically highly valuable 1,3-cyclohexadienes **2** were obtained with high diastereo- and enantioselectivities (Scheme 1).[10] In these reactions the differentiation of the two

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(1) (a) In *Houben-Weyl*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21 b, pp 1357−1602. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

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(6) (a) Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 676. (b) Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Org. Chem.* **2003**, *68*, 7329.

(7) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927.

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(10) (a) Schleth, F.; Studer, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 313. (b) Schleth, F.; Vogler, T.; Harms, K.; Studer, A. *Chem. Eur. J.* **2004**, *10*, 4171.

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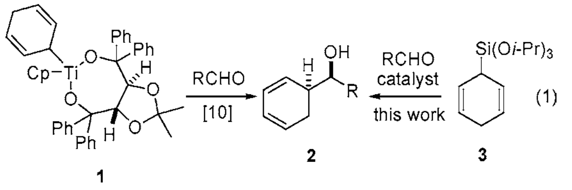
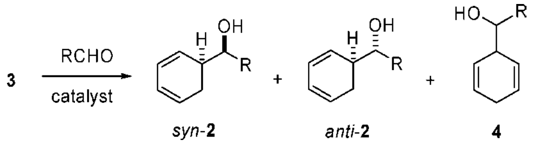
Scheme 1. Stoichiometric and Catalytic Desymmetrization of 1,4-Cyclohexadienes



enantiotopic double bonds (desymmetrization of the 1,4-cyclohexadiene) was achieved and the diastereoselectivity was perfectly controlled. A drawback of the developed method is the fact that stoichiometric amounts of the chiral complex **1** have to be used. Herein we present first results on the catalytic desymmetrization of 1,4-cyclohexadienes.

As a suitable substrate to run the desymmetrization catalytically, we identified the silylated cyclohexadiene **3**, which is readily prepared on a multigram scale by Birch reduction of triisopropoxysilylbenzene.[11] Benzaldehyde was used as electrophile to screen various catalysts. The reactions were performed in THF using **3** (2 equiv), MeOH (1 equiv), a catalyst (10 mol %), PPh_3 (40 mol %), and tetrabutylammonium fluoride (TBAF, 1 equiv) at room temperature. The products *syn*-**2**, *anti*-**2**, and **4** were isolated by chromatography on SiO_2, and the isomer ratio was determined by ^1H NMR spectroscopy and GC analysis (Scheme 2, Table 1).

Scheme 2. Desymmetrization of the Cyclohexadiene **3**



Importantly, the background reaction induced by TBAF without any catalyst was slow (entry 1). Pleasingly, AgF in combination with PPh_3 was able to catalyze the "allylation", and the products were obtained in 85% combined yield as a mixture of the three isomers (entry 2). The best result was obtained with AgOTf (entry 3). A lower but still satisfactory yield was achieved using $Cu(OTf)_2$ (entry 4). However, as compared to the Ag^+-catalyzed processes, the reaction took longer. An improvement of the yield and the selectivity resulted for the CuOTf-catalyzed reaction (entry 5). Surprisingly, worse results were obtained for the CuBr- and CuI-mediated reactions (entries 6 and 7). The addition of $Zn(OTf)_2$ did not show any effect (entry 8). Moderate yields were obtained for the $Yb(OTf)_3$- and $InBr_3$-catalyzed reactions (entries 9 and 10). For all of these processes, Lewis acid type catalysis cannot be excluded. Addition of Ru or Rh catalysts revealed some effects on the isomer ratio; however, low yields were obtained (entries 11 and 12). From these initial studies, AgOTf, Cu(I) salts, and $Cu(OTf)_2$ were identified as the best catalysts. Various chiral ligands **5**−**10** were then tested in the desymmetrization of **3** (Figure 1).

Table 1. Screening of Various Metal Salts as Catalysts Using Benzaldehyde as Electrophile (R = Ph)

entry	catalyst	time (h)	ratio (*syn*-**2**:*anti*-**2**:**4**)	yield (%)[a]
1[b]		20	43:07:50	29
2	AgF	2	46:13:41	85
3	AgOTf	2	42:15:43	91
4	$Cu(OTf)_2$	20	41:25:34	75
5	CuOTf[c]	20	76:08:16	88
6	CuBr	20	54:24:22	47
7	CuI	20	41:32:27	47
8	$Zn(OTf)_2$	20	43:04:53	26
9	$Yb(OTf)_3$	20	30:13:57	54
10	$InBr_3$	20	44:11:45	38
11[b]	$Ru(PPh_3)_3Cl_2$	20	32:17:51	30
12[b]	$Rh(PPh_3)_3Cl$	20	12:09:79	38

[a] Combined yield. [b] The reaction was carried out without PPh_3. [c] $[CuOTf]_2$-benzene complex was used.

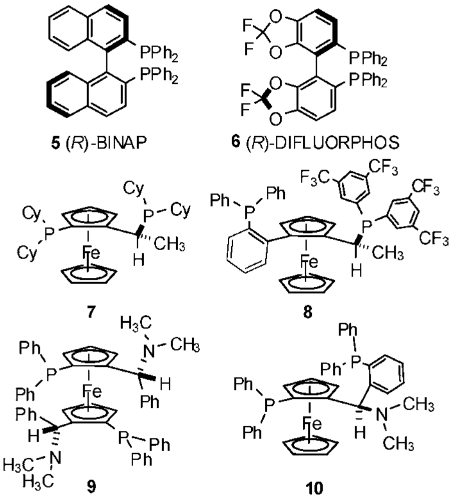


Figure 1. Chiral ligands **5**−**10** used in this study.

The reactions were run in THF at −25 °C for 20 h using **3** (2 equiv), 10 mol % of the Ag or Cu salt, and the chiral ligand (10 mol %) in the presence of TBAF (1 equiv) and MeOH (1 equiv). The enantiomeric ratio (er) of the *syn*-isomer was determined by GC (see Supporting Information).[12]

Excellent yields were obtained for all of the AgOTf-catalyzed reactions (Table 2). Unfortunately, the undesired regioisomer **4** was formed as the major product using BINAP, **6**, **8**, and **9** (entries 1, 2, 4, and 5). The best result in the AgOTf series was achieved using ligand **7**, where **2**

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(11) Kammel, T.; Pachaly, B.; Weidner, R.; Studer, A.; Alvarez-Garcia, L.; Herrera-Gonzalez, A. DE Patent 10326577 A, 2004.

(12) The assignment of the absolute configuration of the *syn* isomer is based on literature data; see ref 10.

Table 2. Screening of Various Chiral Ligands L (R = Ph; see Scheme 2)

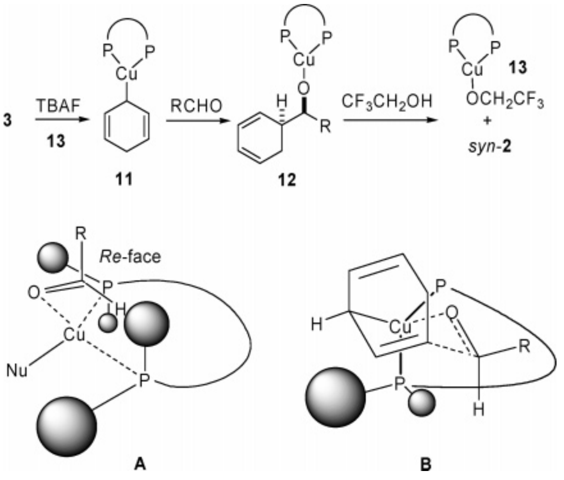
entry	catalyst	L	ratio (*syn*-**2**:*anti*-**2**:**4**)	er *syn*-**2**	yield (%)[a]
1	AgOTf	**5**	31:09:60	71:29	87
2	AgOTf	**6**	29:08:63	77:23	95
3	AgOTf	**7**	74:05:21	77:23	99
4	AgOTf	**8**	22:22:56	49:51	99
5	AgOTf	**9**	36:18:46	40:60	99
6	AgOTf	**10**	50:05:45	41:59	99
7	CuBr	**5**	43:10:47	57:43	38
8	CuI	**5**	42:09:49	54:46	59
9	CuOTf[b]	**5**	79:13:08	86:14	26
10	CuOTf[b]	**6**	80:11:09	92:08	36
11	CuOTf[b]	**7**	88:09:03	84:16	36
12	CuOTf[b]	**8**	88:04:08	74:26	21
13	CuOTf[b]	**9**	68:17:15	46:54	31
14	CuOTf[b]	**10**	83:11:06	22:78	36
15	$Cu(OTf)_2$	**5**	88:10:02	86:14	32
16	$Cu(OTf)_2$	**6**	88:11:01	94:06	38
17	$Cu(OTf)_2$	**7**	83:11:06	83:17	54
18	$Cu(OTf)_2$	**8**	76:09:15	68:32	43
19	$Cu(OTf)_2$	**9**	46:14:40	47:53	36
20	$Cu(OTf)_2$	**10**	63:08:29	28:72	32
21[c]	$Cu(OTf)_2$	**5**	89:09:02	86:14	38
22[d]	$Cu(OTf)_2$	**5**	90:08:02	85:15	44
23[e]	$Cu(OTf)_2$	**5**	89:09:02	86:14	60
24[f]	$Cu(OTf)_2$	**5**	89:09:02	86:14	83
25[f]	$Cu(OTf)_2$	**6**	90:08:02	94:06	83
26[f]	CuOTf[b]	**6**	86:11:03	94:06	83

[a] Combined yield. [b] $[CuOTf]_2$-benzene complex was used. [c] Three equivalents of MeOH were added. [d] CF_3CH_2OH (1 equiv) instead of MeOH. [e] CF_3CH_2OH (3 equiv) instead of MeOH. [f] CF_3CH_2OH (3 equiv) instead of MeOH using 3 equiv of **3**.

was formed with high *syn*:*anti* selectivity but moderate enantioselectivity (entry 3). The CuBr- and CuI-mediated reactions using BINAP afforded only low levels of enantioselectivity (entries 7 and 8). As compared to the Ag-catalyzed reactions, CuOTf catalysis gave lower yields but better selectivities. BINAP and **7** provided similar results (entries 9 and 11), and **6** turned out to be the best ligand (entry 10): *syn*-**2** was obtained with high enantioselectivity (er = 92:8) and good *syn*:*anti* selectivity, and regioisomer **4** was formed in only small amounts. Worse results were achieved using **8**, **9**, or **10** (entries 12−14). Replacing CuOTf with $Cu(OTf)_2$ provided similar enantioselectivities (entries 16−20). Probably, the Cu(II)salt is reduced by the phosphine ligands during the reaction.[13]

We next tried to improve the yield of the $Cu(OTf)_2$-catalyzed reaction. Increasing the amount of MeOH to 3 equiv provided a slightly higher yield without affecting the enantioselectivity (entry 21). Replacing MeOH with 1 equiv of CF_3CH_2OH afforded a higher yield (entry 22), which was further increased to 60% upon using 3 equiv of CF_3CH_2OH (entry 23) and to 83% if 3 equiv of **3** was used without diminishing the selectivity (entry 24). The er was improved upon switching to ligand **6** (entry 25). Reaction with CuOTf under the same conditions gave the same result, supporting the notion that a Cu(I) species is the active catalyst (entry 26).[13] Importantly, the reaction is not moisture-sensitive and can be performed using THF of lower quality (technical grade) without affecting the yield and selectivity.

Scheme 3. Suggested Mechanism (**A** and **B** Models for *R*-DIFLUORPHOS as a Ligand)



The suggested mechanism is depicted in Scheme 3. A similar mechanism was suggested by Shibasaki for the Cu-mediated allylation of aldehydes using trimethoxyallyl silane.[4a] TBAF-induced desilylation of **3** in the presence of **13**, which we assume to be the resting state of the catalyst, leads to the chiral Cu(I) complex **11**. Reaction with RCHO provides Cu-alcoholate **12**, which is eventually hydrolyzed with CF_3CH_2OH to give **2** and **13**. We believe that the geometry of the phenyl groups at the P-atom in the Cu(I) complex resembles the geometry of the phenyl groups in BINAP-Ru complexes.[14] The selectivities can be explained using the quadrant-shielding model of BINAP-metal complexes introduced by Noyori.[15] Indeed, this model has already been used to explain selectivities in Cu(I)-BINAP-catalyzed stereoselective reactions.[16] Therefore, we assume that in order to minimize the interactions of the aldehyde with the axial phenyl group at the P-atom in the (*R*)-DIFLUORPHOS-Cu(I) complex the aldehyde approaches the metal as suggested in model structure **A**. Hence, intramolecular “allylation” using (*R*)-DIFLUORPHOS as ligand occurs from the *re* face as observed in the experiment. The relative *syn* configuration obtained in the experiment can be understood assuming a six-membered chair transition state as suggested in model **B**.

Finally, various aldehydes were tested in the desymmetrization of **3** (Table 3). The regioisomer **4** was formed in

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[13] (a) Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837. (b) Pagenkopf, B. L.; Krüger, J.; Stojanovic, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3124. (c) Bazán-Tejeda, B.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem. Eur. J.* **2006**, *12*, 8358.

[14] Ohta, T.; Takaya, H.; Noyori, R. *Inorg. Chem.* **1988**, *27*, 566.

[15] Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649.

[16] (a) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128. (b) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082.

Table 3. Reaction of **3** with Various Aromatic Aldehydes RCHO^a

entry	R	dr (*syn*:*anti*)	er (*syn*)	yield (%)^b
1	4-MeC_6H_4	14.8:1	96.5:4.5	60
2	4-*i*-PrC_6H_4	14.1:1	96:4	78
3	4-*t*-BuC_6H_4	24.1:1	97:3	84
4	4-MeOC_6H_4	28.9:1	97:3	59
5	4-FC_6H_4	7.8:1	94:6	91
6	4-ClC_6H_4	4.1:1	95:5	82
7	4-BrC_6H_4	4.7:1	92.5:7.5	85
8	2-MeC_6H_4	9.8:1	91.5:8.5	83
9	2-MeOC_6H_4	17.5:1	95.5:4.5	68
10	3-MeC_6H_4	8.7:1	96:4	55
11	3-MeOC_6H_4	6.1:1	94:6	59
12	3-BrC_6H_4	7.0:1	94:6	62
13	2-furyl	2.6:1	94.5:5.5	71
14	5-Br-2-furyl	3.4:1	94:6^c	44
15	2-thienyl	10.8:1	96.5:3.5	63
16	5-Br-2-thienyl	2.5:1	95.5:4.5^c	44
17	2-naphthyl	6.4:1	93:7	79

^{a} Conditions: THF at −25 °C for 20 h using **3** (3 equiv), Cu(OTf)$_2$ (10 mol %), **6** (10 mol %), CF_3CH_2OH (3 equiv), TBAF (1 equiv). and RCHO (1 equiv). ^{b} Regioisomer **4** was formed in <2% yield. ^{c} Determined after debromination.

<2% in these reactions, and moderate to excellent yields were achieved (44−91%). The reactions with *para*-substituted aromatic aldehydes occurred with good enantioselectivities and moderate to excellent *syn*:*anti* selectivities (entries 1−7); *ortho*- and *meta*-substituted aromatic aldehydes and heteroaromatic aldehydes work equally well (entries 8−17).[17]

In conclusion, we report the catalytic desymmetrization of readily available silylated cyclohexadiene **3** using Cu(OTf)$_2$/DIFLUORPHOS as a catalyst system. In the catalytic desymmetrization reaction, three selectivity problems that are (1) regioselectivity, (2) diastereoselectivity, and (3) differentiation of the enantiotopic double bonds were solved. To our knowledge, this is the first report on a catalytic desymmetrization reaction in allylsilane chemistry.[9] The cyclohexadienes **2** obtained are highly useful building blocks for the synthesis of natural products.

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Supporting Information Available: General experimental procedures, GC and HPLC analysis methods, and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Aliphatic aldehydes delivered worse results. Reaction with cyclohexane carbaldehyde afforded **2** (R = C_6H_{11}) with a 3.7:1 *syn*:*anti* selectivity along with the 1,4-diene **4** (R = C_6H_{11}) (ratio **2** (R = C_6H_{11}):**4** (R = C_6H_{11}) = 2.5:1) in a low combined yield (19%). The ee of the *syn*,product was not determined. Pivalaldehyde did not react under the optimized conditions with the cyclohexadienyl Cu species.