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Ag-Catalyzed Stereoselective Cyclohexadienyl Transfer: A Novel Entry into Arylphenylmethanols

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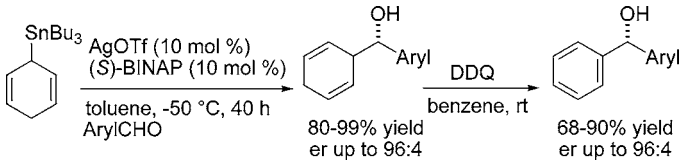
ABSTRACT



The letter describes a novel concept for the synthesis of biologically important arylphenylmethanols. Stereoselective cyclohexadienyl transfer from 1,4-cyclohexadienyltributyltin to various aromatic aldehydes using AgOTf/BINAP as a catalyst precursor provides 1,4-cyclohexadienylphenylmethanols that are readily oxidized to the corresponding arylphenylmethanols. Fifteen examples are presented.

Diarylmethanols are an important class of biologically active compounds.[1,2] An obvious approach to diarylmethanols is the stereoselective aryl transfer to aromatic aldehydes.[2,3] Recently, many papers on this particular reaction have appeared; however, as compared to the aryl transfer reaction, the stereoselective allyl transfer to aldehydes using allylmetal compounds is far more intensively investigated and better understood. In the allyl transfer, the reaction mostly occurs via a well-organized rigid 6-membered chair transition state.[4] As a new concept for aryl transfer to aldehydes, we therefore suggest following a two-step protocol comprising a stereoselective cyclohexadienyl transfer, which might occur via a 6-membered chair transition state and a subsequent oxidation of the cyclohexadiene substituent (Scheme 1). We have recently shown that 1,3-cyclohexadienyl compounds **2** are readily prepared with high stereoselectivity either by using chiral cyclohexadienyl-Ti-complex **1**[5] or by using the achiral silylated cyclohexadienyl derivative **3** in combination with a chiral Cu(I) catalyst.[6] Unfortunately, we were not able to find a suitable oxidation protocol for the aromatization of diene **2** to the corresponding arene **6**. Therefore, we attempted to find a method for the stereoselective synthesis of 1,4-dienes of type **5**. We assumed that the 1,4-cyclohexadienes are readily oxidized to the corresponding arenes **6**.[7]

We have shown that the AgF or AgOTf-catalyzed reaction of diene **3** with aromatic aldehydes afforded substantial

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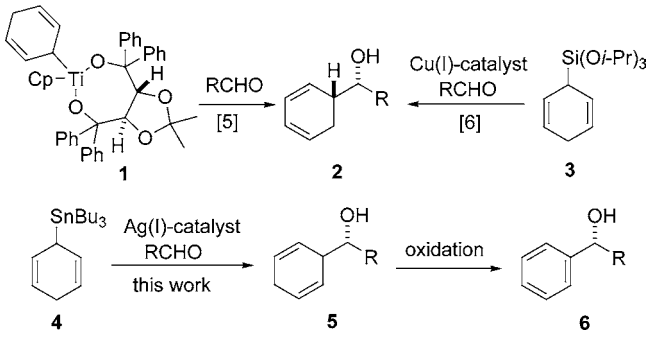
Scheme 1. Stereoselective Cyclohexadienyl Transfer and Subsequent Oxidation



amounts of the symmetrical diene **5** along with **2**.[6] Since Yamamoto successfully used allyltin derivatives as precursors for allyl-Ag-compounds,[8] we decided to investigate the stereoselective Ag-catalyzed cyclohexadienyl transfer from stannylated diene **4**[5b] to various aldehydes. Enantioselectivity and regiochemistry had to be controlled in this reaction. The challenge was to suppress the formation of the unwanted 1,3-diene **2**, which was obtained as the major or only product in our pervious studies.[5,6] Initial experiments were performed with AgOTf and para-fluorobenzaldehyde to give diene **5a** (R = 4-FC_6H_4). Reactions were conducted with 10 mol % of AgOTf in the presence of various chiral diphosphine ligands (10 mol %) in toluene at −30 °C for 16 h. A 2-fold excess of **4** was used and the selectivity was determined by gas chromatography (see Supporting Information). Some of the ligands used in this study are depicted in Figure 1, and the results are presented in Table 1.

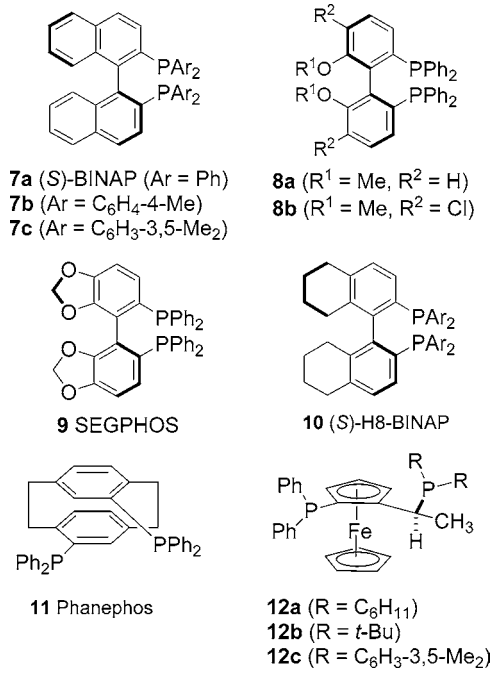


Figure 1. Chiral ligands **7**−**12** used in this study.

Table 1. Screening of Various Chiral Ligands (product **5a** with R = 4-FC_6H_4)

entry	ligand	er	yield [%][a]
1	**7a**	95:5	99
2	**7b**	94:6	99
3	**7c**	84:16	86
4	**8a**	78:22	51
5	**8b**	87.5:12.5	99
6	**9**	80:20	30
7	**10**	86:14	76
8	**11**	94.5:5.5	81
9	**12a**	41.5:58.5	25
10	**12b**	25.5:74.5	46
11	**12c**	34.5:65.5	66

[a] Isolated yield. The regioisomeric diene **2** was not formed.

A quantitative yield and a good selectivity were obtained with (*S*)-BINAP **7a**[9] (er = 95:5, entry 1). Pleasingly, the regioisomeric diene **2** and its anti isomer were not formed. tol-BINAP **7b** delivered a similar result whereas xyl-BINAP **7c** provided a lower selectivity and a slightly lower yield (entries 2 and 3). The reaction with MeO-BIPHEP[10] **8a** occurred with a lower yield and a lower selectivity (entry 4). Unreacted diene **4** remained. The yield increased with the more electrophilic Cl−MeO-BIPHEP[11] **8b**; however, as compared to BINAP, a lower selectivity was obtained (entry 5). SEGPHOS[12] **9** provided the worst result (entry 6). Hence, for the atropoisomeric chiral diphosphines, higher yields were obtained with more electrophilic ligands, and the dihedral angle of the biaryl backbone[13] was obviously important for the stereochemical outcome. A larger angle seemed to lead to higher selectivities. Therefore, H8-BINAP **10** was tested (entry 7). Disappointingly, selectivity was lower. A good result was achieved with Phanephos[14] **11** (entry 8). Josiphos type compounds[15] **12a**−**c** turned out to be not efficient ligands for this reaction (entries 9−11). Based on the initial

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screening, all the following experiments were conducted with (*S*)-BINAP.

The effects of the solvent and of the Ag counteranion were investigated next (Table 2). The influence of the solvent was studied with AgOTf as catalyst precursor. Reaction in THF went to completion; however, a lower selectivity was obtained as compared to the toluene experiment (entry 1). Halogenated arenes as solvents delivered **5a** in quantitative yield with acceptable selectivities (entries 2 and 3). Similar results were obtained in Et_2O, $MeOCH_2CH_2OMe$, and CH_2Cl_2 (entries 4, 5, and 9). Reaction in DMF and MeCN provided low yields (entries 6 and 7). Polar protic solvents were tolerated as reaction in MeOH occurred with excellent yield and good selectivity (entry 8). As a summary of the solvent screening, we could state that various solvents could be used, and the best result was obtained in toluene. Other Ag-salts than AgOTf such as $AgOCOCF_3$, $AgOCOCH_3$, and $AgSbF_6$ provided worse results, and no reaction occurred in the presence of $AgNO_3$ (entries 10−13). If 20 mol % of AgOTf was used, a lower yield and a lower selectivity were achieved (entry 14). An excess of BINAP with respect to AgOTf led to a slightly lower selectivity without affecting the yield (entry 15). The highest selectivity was obtained with AgOTf in toluene at −50 °C (er = 96:4, entry 16). However, to get a quantitative yield, the reaction time had to be increased to 40 h.

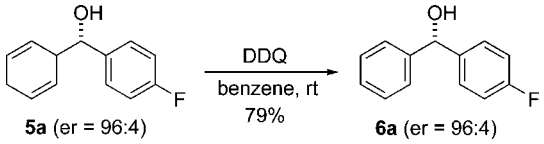
Table 2. Reaction of Diene **4** (2 Equiv) and 4-F−C_6H_4CHO in the Presence of an Ag(I)-salt (10 mol %) and (*S*)-BINAP (10 mol %) in Various Solvents at −30 °C for 16 h

entry	solvent	Ag-salt	er	yield [%][a]
1	THF	AgOTf	88:12	99
2	ClC_6H_5	AgOTf	92.5:7.5	99
3	FC_6H_5	AgOTf	93:7	99
4	Et_2O	AgOTf	92.5:7.5	99
5	$MeOCH_2CH_2OMe$	AgOTf	93:7	99
6	DMF	AgOTf	86.5:13.5	30
7	MeCN	AgOTf	93:7	10
8	MeOH	AgOTf	93:7	76
9	CH_2Cl_2	AgOTf	93.5:6.5	99
10	toluene	$AgOCOCF_3$	87.5:12.5	51
11	toluene	$AgOCOCH_3$	78:22	61
12	toluene	$AgNO_3$	–	–
13	toluene	$AgSbF_6$	89.5:10.5	15
14	toluene	AgOTf[b]	85.5:14.5	36
15	toluene	AgOTf[c]	90:10	99
16	toluene	AgOTf[d]	96:4	99

[a] Combined yield. The regioisomeric diene **2** was not formed. [b] Twenty mol % of AgOTf were used. [c] Ten mol % of AgOTf and 20 mol % of (*S*)-BINAP were used. [d] Reaction was conducted at −50 °C.

We were pleased to find that diene **5a** was stereospecifically oxidized with DDQ in benzene at room temperature to arylphenylmethanol **6a**, validating our concept (Scheme 2).[16]

Scheme 2. Oxidation of **5a**



5a (er = 96:4) **6a** (er = 96:4)

To test the substrate scope of the novel arlylphenylmethanol synthesis, various aromatic aldehydes were reacted with diene **4** under optimized conditions to give the corresponding alcohols **5b**−**o** which were further oxidized with DDQ to the arylphenylmethanols **6b**−**o** (Table 3). The enantioselectivity was determined on the oxidized products **6b**−**o**. The absolute stereochemistry (*S* enantiomer) was assigned by comparison of the optical rotations of **6b** and **6k** with those reported in the literature (see Supporting Information). The absolute configurations of all other compounds were assigned in analogy.

Table 3. Reaction of **4** in Toluene at −50 °C for 40 h with Various Aromatic Aldehydes in the Presence of AgOTf (10 mol %) and (*S*)-BINAP (10 mol %) and Subsequent Oxidation

entry	substituent R	yield [%][a] (compound)	yield [%][a] (compound)	er[b]
1	4-MeC_6H_4	90 (**5b**)	77 (**6b**)	88:12
2	4-*i*-PrC_6H_4	78 (**5c**)	88 (**6c**)	86:14
3	4-*t*-BuC_6H_4	96 (**5d**)	79 (**6d**)	88:12
4	4-ClC_6H_4	99 (**5e**)	81 (**6e**)	94:6
5	4-BrC_6H_4	89 (**5f**)	88 (**6f**)	93:7
6	4-IC_6H_4	84 (**5g**)	85 (**6g**)	92:8
7	4-$CF_3C_6H_4$	99 (**5h**)	89 (**6h**)	92:8
8	4-$MeOC_6H_4$	80 (**5i**)	78 (**6i**)	83:17
9	2-MeC_6H_4	84 (**5j**)	86 (**6j**)	94:6
10	2-$MeOC_6H_4$	92 (**5k**)	74 (**6k**)	78:22
11	3-MeC_6H_4	80 (**5l**)	72 (**6l**)	89:11
12	3-BrC_6H_4	96 (**5m**)	90 (**6m**)	91:9
13	3-$MeOC_6H_4$	86 (**5n**)	69 (**6n**)	90:10
14	2-naphthyl	91 (**5o**)	68 (**6o**)	95:5

[a] Isolated yield. [b] er determined by HPLC on compounds **6a**−**o**, see Supporting Information.

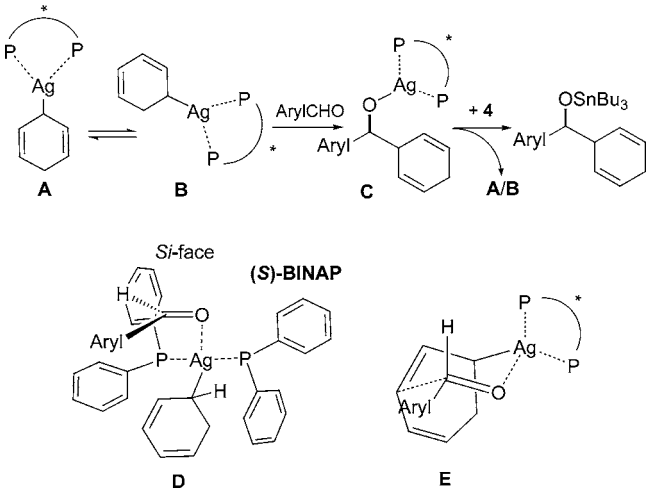
The less electrophilic para-alkyl- and para-alkoxy-substituted benzaldehyde derivatives provided slightly lower yields in the cyclohexadienyl transfer reaction. After oxidation, the phenylarylmethanols were isolated in moderate selectivity (entries 1−3, 8). A higher yield and a higher selectivity were obtained for the para-chloro derivative (entry 4), whereas slightly worse results were achieved with the corresponding Br- and I-congeners. Cyclohexadienyl transfer to the para-CF_3-substituted benzaldehyde occurred with high yield and moderate selectivity (entry 5). A good selectivity was obtained for the reaction with the ortho-methyl substituted benzaldehyde derivative (entry 9), but the ortho-OMe-compound delivered a lower selectivity. Acceptable yields and selectivities were achieved for the meta-substituted benzaldehyde derivatives (entries 11−13), and a good

(16) As a side product the corresponding ketone was formed in 19% yield.

selectivity was obtained for 2-naphthaldehyde (entry 14). For all substrates tested, the oxidation occurred in good yields (68−90%).

We believe that the reaction occurs via a cyclohexadienyl-Ag-complex of type **B** (see Scheme 3). Compound **B** can

Scheme 3. Possible Mechanism



be in equilibrium with complex **A**; however, considering a six-membered chair transition state (see **E**), the reacting complex is assumed to be **B**. The Ag-alcoholate **C** generated should then react with diene **4** to the corresponding Sn-alcoholate and the cyclohexadienyl-Ag-complexes **A**/**B**.[8] The stereochemistry can be explained using the quadrant-shielding model of BINAP-metal complexes introduced by Noyori.[17] To minimize the interactions of the aldehyde with the axial phenyl group at the P-atom in the (*S*)-BINAP-Ag(I)-complex, the aldehyde approaches the metal as suggested in model structure **D**. Intramolecular "allylation" using (*S*)-BINAP as a ligand should then occur from the *Si*-face as observed in the experiment. We do not consider an open transition state where a chiral Ag complex (probably cationic) acts as a Lewis acid because we could previously show that the Lewis acid mediated cyclohexadienyl transfer from **4** to benzaldehyde delivered *syn*-**2** (R = Ph) as major isomer. The syn isomer was not formed in the Ag-catalyzed process studied herein.[5b]

In summary, we presented a novel approach to arylphenylmethanols comprising an Ag-catalyzed stereoselective cyclohexadienyl transfer with subsequent oxidation. As previously shown,[6] cyclohexadienyl transfer from silylated diene **3** to aldehydes using Cu-catalysis provided 1,3-dienes **2** whereas the analogous Ag-catalyzed reaction with diene **4** afforded 1,4-dienes **5** exclusively. Hence, the two developed methods are complementary. Importantly, arylphenylmethanols are biologically interesting compounds.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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