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Stereoselective Hydrocoupling of [(1*R*)-*exo*]-3-*exo*-(Diphenylmethyl)bornyl Cinnamates by Electroreduction

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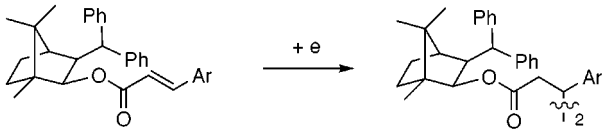
ABSTRACT

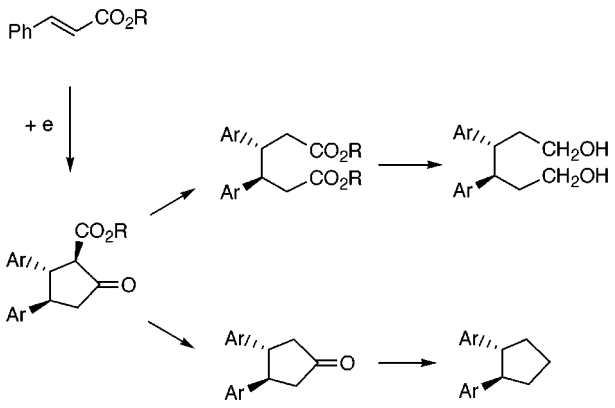


R,R-dimer 87-95% de

The chiral auxiliary [(1*R*)-*exo*]-3-*exo*-(diphenylmethyl)borneol, synthesized from (1*R*)-(+)-camphor in three steps, was highly effective for the stereoselective hydrocoupling of its cinnamates by electroreduction. From the resulting hydrodimers, (3*R*,4*R*)-3,4-diaryladipic acid esters and (3*R*,4*R*)-3,4-diarylhexane-1,6-diols were synthesized in 87−95% ee.

Electroreduction of α,β-unsaturated compounds in aqueous solution is a well-recognized method to obtain the corresponding hydrodimers.[1] In addition, the electroreduction of cinnamic acid esters in an aprotic solvent affords cyclized products of hydrodimers[2] as all-trans isomers stereospecifically (Scheme 1).[2a−c,e] These results prompted us to investigate enantioselective hydrocoupling of cinnamic acid derivatives, because the obtained hydrodimers can be converted into several C_2-symmetric compounds as shown in Scheme 1. We have started our study using readily available and well-known chiral auxiliaries such as optically active alcohols, oxazolines,[3] and oxazolidinones.[3b,4] We have already reported that (*S*)-4-isobutyloxazolidinone was the most effective chiral auxiliary among them.[5] The best selectivity for the *dl*-hydrodimer, however, was *R,R*/*S,S* = 85:15. Therefore, a more effective chiral auxiliary is desirable. Although the electroreduction of cinnamates derived

Scheme 1



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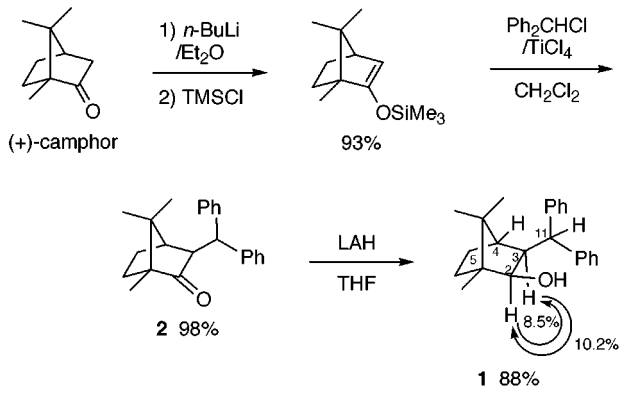
from (−)-menthol, (−)-8-phenylmenthol, and (−)-*endo*-borneol gave poor results,[5b] we investigated effective chiral auxiliaries based on a modification of (1*R*)-(+)-camphor, since it is readily available and inexpensive. We report herein that [(1*R*)-*exo*]-3-*exo*-(diphenylmethyl)borneol[6] (**1**) is a highly effective chiral auxiliary for the electroreductive hydrocoupling of its cinnamates.

The synthesis of **1** from (+)-camphor was carried out in three steps as shown in Scheme 2. To improve the total yield

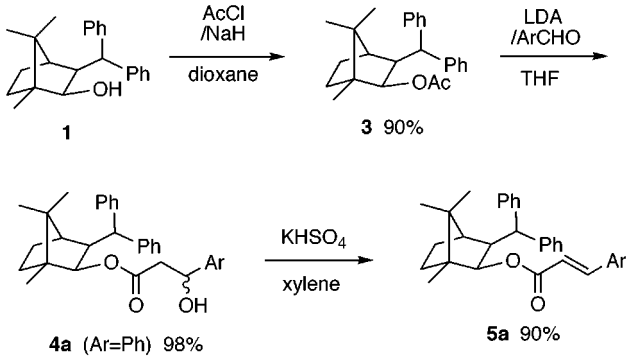
Scheme 2



of **1**, we modified the reported methods.[6,7] The trimethylsilyl enol ether of (+)-camphor was prepared in 93% yield by the successive treatment of (+)-camphor with *n*-BuLi and TMSCl in Et_2O. The reaction of the silyl enol ether with chlorodiphenylmethane in the presence of $TiCl_4$ at −50 °C for 1 h gave (1*R*)-3-*exo*-(diphenylmethyl)camphor (**2**) in 98% yield with a small amount of its stereoisomer. The 3-*exo*-ketone **2** was identified by its ^{1}H NMR spectrum, which showed the C3 endo proton as a doublet at δ 2.91 ppm coupled to the C11 proton (J = 12.1 Hz). If the C3 proton was exo, it should also couple to the C4 proton (J = 4−5 Hz) and C5 exo proton (J = 1−2 Hz).[8] The following LAH reduction of **2** in THF gave **1** with a small amount of its stereoisomer. Recrystallization of the crude product afforded isomerically pure [(1*R*)-*exo*]-3-*exo*-(diphenylmethyl)borneol (**1**) in 86% yield. The 2-*exo*-3-*exo* configuration of **1** has been suggested by Pearson[6b] and was also confirmed by its ^{1}H NMR analysis. Namely, the C2 endo proton (δ 3.83 ppm) gave a double doublet coupled to the C3 endo proton (J = 7.5 Hz) and the OH proton (J = 3.2 Hz), and the C3 endo proton gave a double doublet (δ 2.70 ppm) coupled to the C2 endo proton (J = 7.5 Hz) and the C11 proton (J = 13.0 Hz). In addition, NOE observed between the C2 and C3 protons shows that these protons are located on the same side (Scheme 2).

Unfortunately, all attempts for direct cinnamoylation of **1** failed. Pearson has reported that ester formation and hydrolysis of **1** was very difficult to accomplish because of steric hindrance.[6b] Consequently, the cinnamate of **1** was prepared in three steps (Scheme 3): acetylation of **1**, condensa-

Scheme 3



tion of the acetate **3** with benzaldehyde, and dehydration of the resulting hydroxy ester **4a** (Ar = Ph) gave *trans*-cinnamate **5a** in 79% overall yield. Several aryl-substituted *trans*-cinnamate **5b**−**h** were prepared similarly (Table 1).

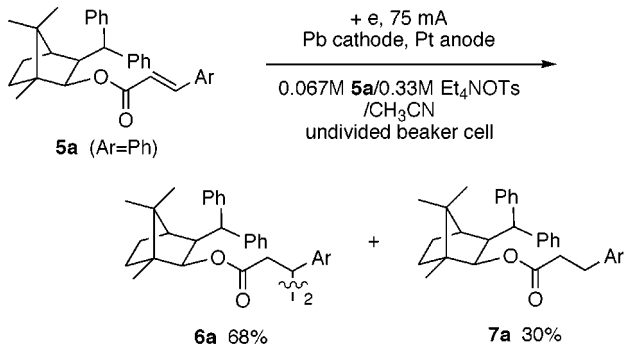
Table 1. Synthesis of *trans*-Cinnamates **5** from **1**

Ar	% yield of **4**[a]	% yield of **5**[a]
Ph	**4a** 98	**5a** 90
o-$MeOC_6H_4$	**4b** 81	**5b** 86
m-$MeOC_6H_4$	**4c** 82	**5c** 85
p-$MeOC_6H_4$	**4d** 98	**5d** 79
p-FC_6H_4	**4e** 95	**5e** 86
2-naphthyl	**4f** 83	**5f** 75
1-furyl	**4g** 98	**5g** 64
3,4-methylenedioxyphenyl	**4h** 87	**5h** 85

[a] Isolated yields.

Electroreduction of **5a** was carried out at a constant current of 75 mA in 0.33 M Et_4NOTs/acetonitrile using an undivided cell and a Pb cathode, according to the reported method.[5b] The noncyclized hydrodimer **6a** was obtained in 68% yield along with **7a** (Scheme 4). It is noted that the cyclized hy-

Scheme 4



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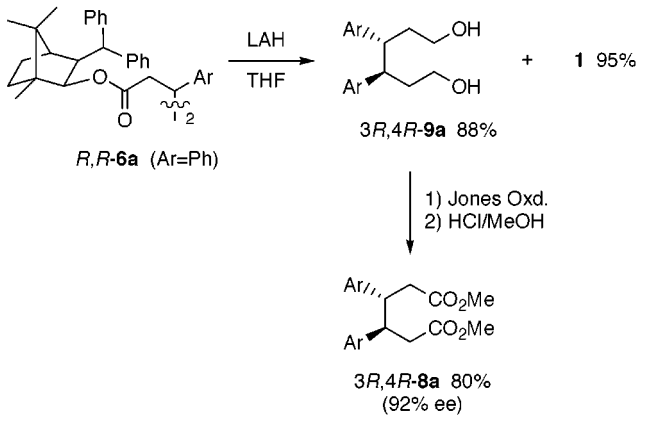
drodimer could not be detected, since Dieckmann condensation of **6a** is inhibited by the steric hindrance as mentioned above. The diastereomeric excess (de) of the hydrodimer **6a** seemed to be more than 90% by its ^{1}H NMR spectrum.[9]

To confirm the selectivity and stereochemistry, the dimer **6a** was transformed to known dimethyl ester **8a**[5] (Scheme 5). Hydrolysis of **6a** by normal methods failed owing to the steric hindrance. Alternatively, LAH reduction of **6a** afforded diol **9a** in 88% yield together with **1** in 95% yield. Oxidation of **9a** followed by esterification in methanol gave dimethyl ester **8a**, which consisted of only the *dl*-isomer; the *meso*-isomer was not detected by ^{1}H NMR analysis. The absolute stereochemistry and enantiomeric excess of **8a** were determined to be 3*R*,4*R* and 92% ee by ^{1}H NMR spectrum with Eu(hfc)$_3$ and chiral HPLC analysis.[5b] This result showed that the hydrodimer **6a** was obtained as a mixture of two stereoisomers, *R*,*R*-form (major) and *S*,*S*-form (minor), in 92% de.

Scheme 5



The electroreduction of aryl-substituted cinnamate **5b**−**h** and the subsequent transformation of the dimers **6c**−**h** were carried out by the same procedures as above, and the results are summarized in Tables 2 and 3. Although ortho substitution inhibited the electroreductive hydrocoupling significantly (Table 2, entry 2), para and meta substitution (entries 3−5, 7, and 8) did not hinder it except for the β-naphthyl group (entry 6). The enantioselectivities of diesters **8c**−**f** and the diacetates of diols **9g,h** were determined to be 87−95% ee by ^{1}H NMR spectra with Eu(hfc)$_3$. The 3*R*,4*R* configuration was confirmed for **8c**−**e** by ^{1}H NMR and chiral HPLC analyses[5b] and was assumed for **8f** and **9g,h** by ^{1}H NMR correlation of **6f**−**h** with **6a**.

Table 2. Electroreduction of *trans*-Cinnamates **5**

entry	Ar	% yield of **6**[a]	% yield of **7**[a]
1	Ph	**6a** 68	**7a** 30
2	*o*-MeOC6H4	**6b** 3	**7b** 77
3	*m*-MeOC6H4	**6c** 54	**7c** 28
4	*p*-MeOC6H4	**6d** 54	**7d** 35
5	*p*-FC6H4	**6e** 62	**7e** 24
6	2-naphthyl	**6f** 18	**7f** 57
7	1-furyl	**6g** 52	**7g** 31
8	3,4-methylenedioxyphenyl	**6h** 64	**7h** 22

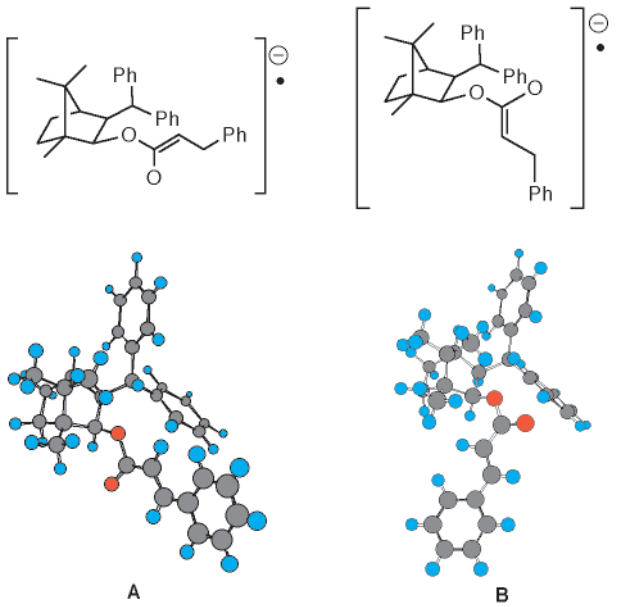
[a] Isolated yields.

Table 3. Transformation of **6** to **9** and **8**

Ar	% yield of **9**[a]	% yield of **8**[a] (% ee)[b]
Ph	**9a** 88	**8a** 80 (92)
m-MeOC$_6$H$_4$	**9c** 84	**8c** 75 (92)
p-MeOC$_6$H$_4$	**9d** 90	**8d** 78 (92)
p-FC$_6$H$_4$	**9e** 90	**8e** 80 (87)
2-naphthyl	**9f** 68	**8f** 52 (95)
1-furyl	**9g** 56 (87)[c]	
3,4-methylenedioxyphenyl	**9h** 70 (89)[c]	

[a] Isolated yields. [b] Determined by ^{1}H NMR analysis with Eu(hfc)$_3$. [c] Determined from the corresponding diacetate by ^{1}H NMR analysis with Eu(hfc)$_3$.

The reaction mechanism of the hydrocoupling of **5** can be speculated to be similar to that reported previously for cinnamic acid esters.[2a,b,10] An anion radical is produced by one-electron transfer to **5** and couples with another anion radical. Semiempirical (UHF/AM1) and DFT (UB3LYP 3-21G* and 6-31G*) calculations[11] of anion radical of **5a** gave two optimized structures **A** and **B** (Figure 1). From the results described above, it seems that the coupling occurs

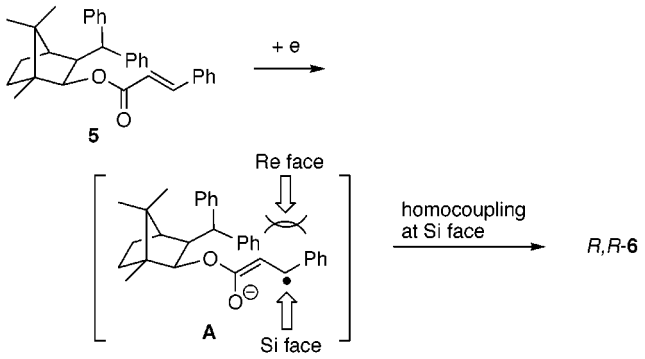


method	energy **A**-**B** (kcal/mol)
UHF/AM1	-3.12
UB3LYP/3-21G*	-5.48
UB3LYP/6-31G*	-5.99

Figure 1. Minimized structures of anion radical of **5a**.

from the more stable **A** at the less hindered Si face (β-side) and gives the *R*,*R*-dimer selectively (Scheme 6).

Scheme 6



At present [(1*R*)-*exo*]-3-*exo*-(diphenylmethyl)borneol (**1**) is the most effective chiral auxiliary for the electroreductive hydrocoupling of cinnamates. From the resulting hydrodimers **5**, the *R*,*R*-enantiomers of C_2-symmetric 3,4-diaryladipic acid diesters **8** and 3,4-diarylhexane-1,6-diols **9** were obtained in 87−95% ee. The utility of **1** as a chiral auxiliary in other reactions is now being investigated.

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

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(7) Full details of the modifications are in Supporting Information.

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(9) The ^{1}H NMR spectrum of **6a** showed major (>90%) three singlets for methyl protons at 0.19, 0.67, and 1.20 ppm with minor (<10%) three singlets at 0.11, 0.65, and 1.14 ppm.

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