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Electroreductive Coupling of Optically Active α,β-Unsaturated Carbonyl Compounds with Diaryl Ketones: Asymmetric Synthesis of 4,5,5-Trisubstituted γ-Butyrolactones

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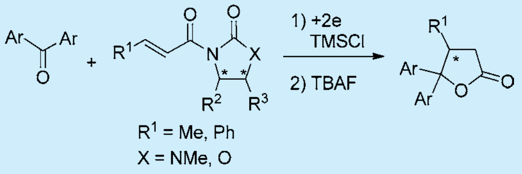
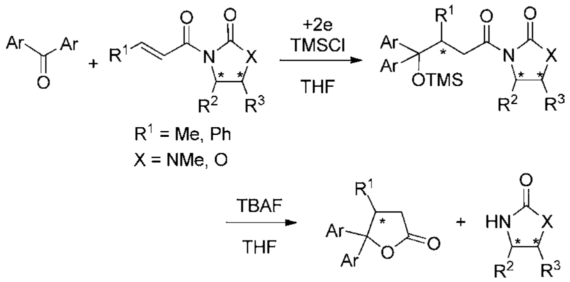
Ⓢ *Supporting Information*

ABSTRACT: The electroreductive coupling of optically active *N*-*E*-crotonoyl- and *N*-cinnamoylimidazolidin-2-ones and oxazolidin-2-ones with diaryl ketones in the presence of chlorotrimethylsilane gave adducts with high diastereoselectivity. The adducts were readily transformed to optically active 4,5,5-trisubstituted γ-butyrolactones by treatment with TBAF.



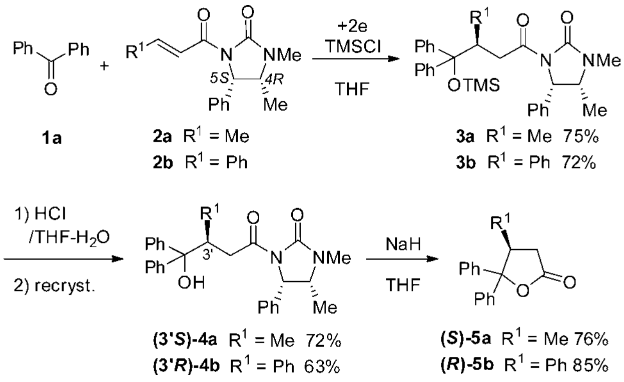
Reductive cross-coupling of α,β-unsaturated carboxylic acid derivatives with carbonyl compounds is a promising method for the synthesis of γ-hydroxy carboxylic acids and their derivatives, such as γ-butyrolactones, and has been realized using SmI_2[1] as a reducing agent and electroreduction.[2] To date, the enantio-[3] and diastereoselective[4] reductive couplings of α,β-unsaturated carbonyl compounds with ketones and aldehydes have been reported with SmI_2 to synthesize optically active di- and trisubstituted γ-butyrolactones. On the other hand, we have recently reported electroreductive cross-couplings between two different carbonyl compounds in the presence of chlorotrimethylsilane (TMSCl).[5] In this context, we report herein that the electroreductive coupling of optically active *N*-*E*-crotonoyl- (R^1 = Me) and *N*-cinnamoyl- (R^1 = Ph) imidazolidin-2-ones (X = NMe) and oxazolidin-2-ones (X = O) with diaryl ketones in the presence of TMSCl afforded coupled products with high diastereoselectivity, and the coupled products were transformed to optically active γ-butyrolactones by treatment with TBAF (Scheme 1). These reactions provide a useful method for the highly enantioselective synthesis of 4,5,5-trisubstituted γ-butyrolactones.[6] We also investigated the transition states of the electroreductive coupling by the DFT calculations to elucidate the high diastereoselectivity.

Scheme 1. Electroreductive Coupling of Optically Active α,β-Unsaturated Carbonyl Compounds with Diaryl Ketones and Transformation to 4,5,5-Trisubstituted Lactones



First, we attempted the electroreductive coupling of (4*R*,5*S*,*E*)-1-crotonoyl- (**2a**) and (4*R*,5*S*)-1-cinnamoyl-3,4-dimethyl-5-phenylimidazolidin-2-one (**2b**) with benzophenone (**1a**) (Scheme 2). According to the previously reported conditions,[2] the electroreduction was carried out in DMF solvent, and however, TMS-ether of benzhydrol was formed as the only product. Therefore, we examined other conditions for the electroreductive coupling and found that the electroreduction in THF solvent[5e,f] gave coupled products **3a** and **3b** in 75% and 72% yields, respectively. Although these products seemed to be obtained with high diastereoselectivity by ^{1}H NMR analysis (99% de for **3a** and 90% de for **3b**), they could not be further purified. For the purpose of

Scheme 2. Electroreductive Coupling of 2a,b with Benzophenone and Transformation to Enantiomerically Pure Lactones 5a,b



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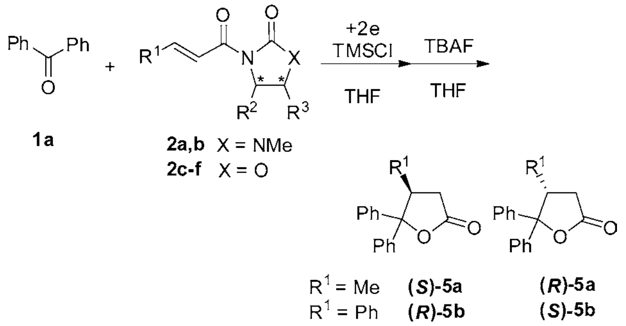
purification, the products **3a** and **3b** were desilylated in THF−H_2O in the presence of a catalytic amount of HCl at 0 °C to give **4a** and **4b**, which were recrystallized to afford diastereomerically pure major isomers (>99% de). Fortunately, the major isomer of **4a** was determined to be 3′*S* by X-ray crystallography (Supporting Information). Thus, the major isomer of **4b** was correlatively assumed to be 3′*R*. The major isomers of **4a** and **4b** could be converted into the corresponding enantiomerically pure *γ*-butyrolactones (*S*)-**5a** and (*R*)-**5b**, respectively, by treatment with a catalytic amount of NaH in THF at 25 °C.

Next, the electroreduction of imidazolidin-2-ones **2a,b** and oxazolidin-2-ones **2c−f** with **1a** was carried out under the same conditions, and the obtained coupled products were treated with TBAF in THF at 25 °C to give *γ*-butyrolactones **5a** and **5b** (Table 1). The sense of R^2- and R^3-substituents on the chiral auxiliaries in **2** apparently decides the sense of R^1-substituent on the products. That is, (*S*)-**5a** and (*R*)-**5b** were selectively produced from (5*S*)-phenyl-(4*R*)-methyl-substituted **2a,b** and (4*S*)-isopropyl-substituted **2e,f** (runs 1, 2, 5, and 6), whereas (*R*)-**5a** and (*S*)-**5b** were selectively formed from (4*R*)-phenyl-substituted **2c,d** (runs 3 and 4). The reactions of the *N*-*E*-crotonoyl substrates **2a,c,e** gave **5a** with good yields and high enantiomeric excesses (runs 1, 3, and 5). Among the *N*-cinnamoyl-substituted substrates **2b,d,f**, imidazolidin-2-one **2b** afforded **5b** with 60% yield and 93% ee (run 2), although oxazolin-2-ones **2d,f** gave **5b** in somewhat lower yields (runs 4 and 6).

Table 1. Electroreductive Coupling of 2a−f with Benzophenone and Transformation to Lactones 5a,b

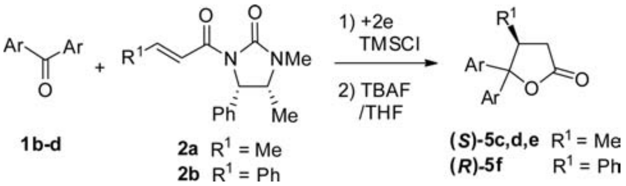


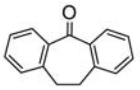
run	2	R^1	R^2	R^3	5	% yield[a]	% ee[b]
1	**2a**	Me	Ph (*S*)	Me (*R*)	(*S*)-**5a**	63	99
2	**2b**	Ph	Ph (*S*)	Me (*R*)	(*R*)-**5b**	60	93
3	**2c**	Me	Ph (*R*)	H	(*R*)-**5a**	68	95
4	**2d**	Ph	Ph (*R*)	H	(*S*)-**5b**	47	99
5	**2e**	Me	*i*-Pr (*S*)	H	(*S*)-**5a**	78	95
6	**2f**	Ph	*i*-Pr (*S*)	H	(*R*)-**5b**	40	59

[a] Isolated yield. [b] Determined by optical rotation.

4,4′-Difluorobenzophenone (**1b**), 4,4′-dimethoxybenzophenone (**1c**), and dibenzosuberone (**1d**) were employed as a diaryl ketone, and the results are summarized in Table 2. Optically active 4,5,5-trisubstituted lactones (*S*)-**5c,d,e** and (*R*)-**5f** were obtained by the electroreductive coupling of **2a,b** with **1b−d** and following desilylation with TBAF. Although the enantioselectivities of (*S*)-**5c** and (*S*)-**5e** could not be determined, those of (*S*)-**5d** and (*R*)-**5f** were ascertained to be 99% ee and 93 ee, respectively, by comparison of their optical rotations with those of enantiomerically pure samples. Enantiomerically pure samples of (*S*)-**5d** and (*R*)-**5f** were prepared from diastereomerically pure (>99% de) (3′*S*)-**4d** and (3′*R*)-**4f** according to the same procedure as described in Scheme 2 (Scheme 3). In addition, the stereostructures of (3′*R*)-**4f** and (*R*)-**5f** were confirmed by X-ray crystallography. Unfortunately, the electroreduction of **2a** with acetophenone or cyclohexanone gave no cross-coupled products under the same conditions.

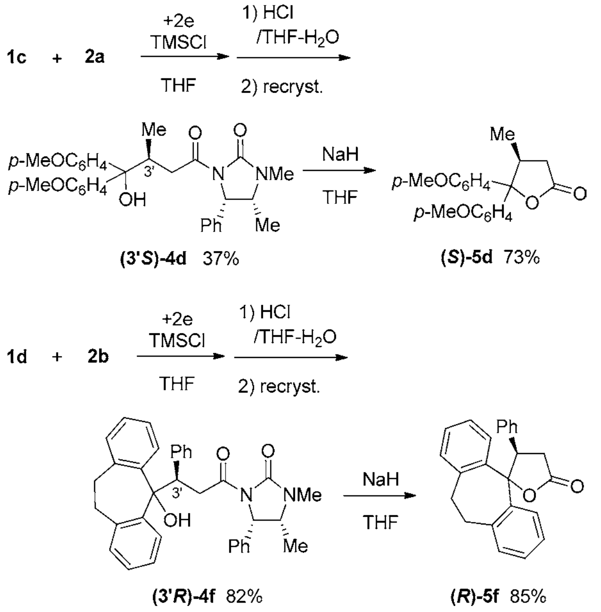
Table 2. Electroreductive Coupling of 2a,b with Diaryl Ketones 1b−d and Transformation to Lactones 5c-f



run	1	Ar_2CO	2	5	% yield[a]	% ee[b]
1	**1b**	Ar = *p*-FC_6H_4	**2a**	(*S*)-**5c**	23	ND[c]
2	**1c**	Ar = *p*-$MeOC_6H_4$	**2a**	(*S*)-**5d**	56	99
3	**1d**		**2a**	(*S*)-**5e**	55	ND[c]
4	**1d**		**2b**	(*R*)-**5f**	67	93

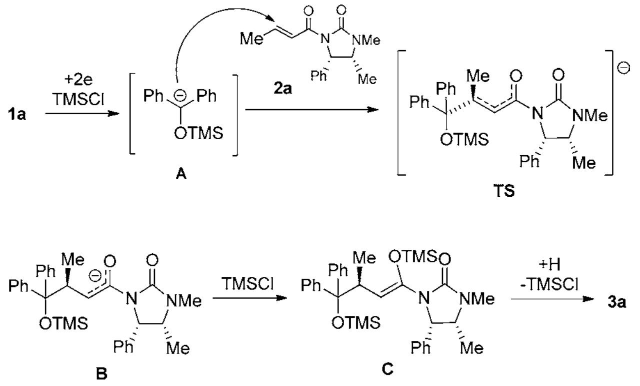
[a] Isolated yield. [b] Determined by optical rotation. [c] Not determined.

Scheme 3. Electroreductive Coupling of 2a,b with 1c,d and Transformation to Enantiomerically Pure Lactones (*S*)-5d and (*R*)-5f



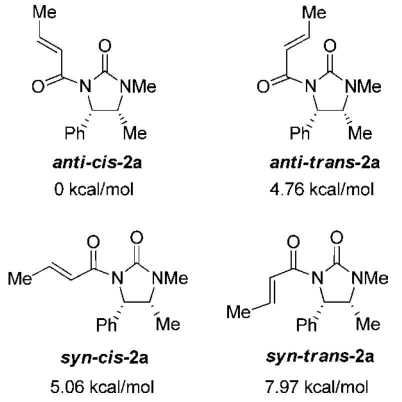
The presumed reaction mechanism of the electroreductive coupling of **2a** with **1a** is illustrated in Scheme 4. The cyclic voltamograms of **1a** in 0.03 M Bu_4NClO_4/DMF on a platinum cathode showed a first reduction peak at −1.87 V vs SCE, while those of **2a** under the same conditions revealed no reduction peak from 0 to −2.50 V vs SCE. These results suggest that **1a** is more reducible than **2a**. Therefore, the electroreductive coupling was supposed to be initiated by the reduction of **1a**. Carbanion **A** is formed by the two-electron transfer to **1a** and following *O*-silylation with TMSCl. The

Scheme 4. Presumed Reaction Mechanism of Electroreductive Coupling of 2a with 1a

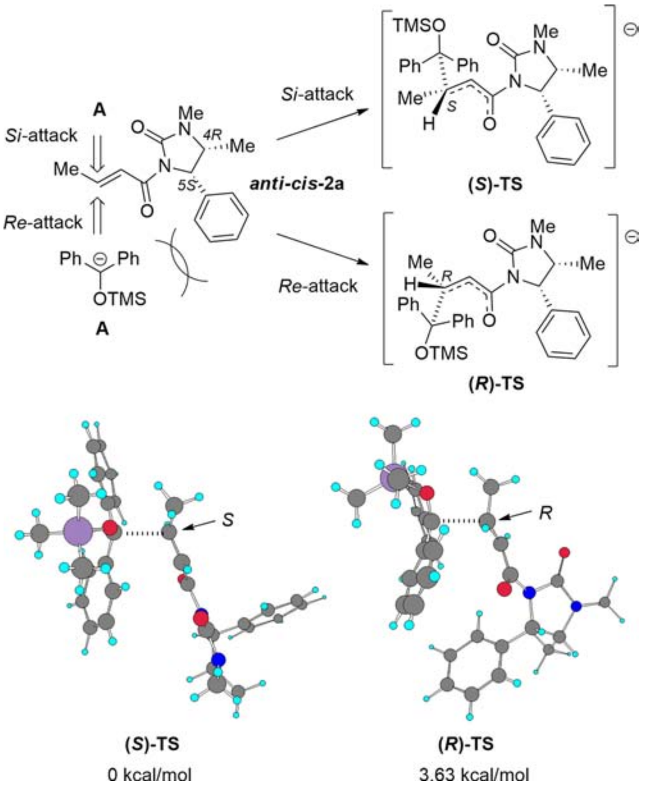


nucleophilic addition of **A** to the *β*-position of **2a** and subsequent *O*-silylation of resulting enolate anion **B** gives silyl enol ether **C**. The labile **C** is readily desilylated to **3a** during workup. The diastereoselectivity of **3a** is determined by the energy difference between transition states (**TS**) reading to the (*S*)- and (*R*)-**B**. Initially, the stable conformations of **2a** were calculated by the DFT method at the B3LYP/6-311+(2d,p) level using the IEFPCM model in THF (Supporting Information). As shown in Scheme 5, *anti-cis*-form is the most stable. Incidentally, the crystal structure of **2a** is also confirmed to be *anti-cis*. As depicted in Scheme 6, *Si*-attack of **A** to the *anti-cis*-form of **2a** seems to be more favorable than *Re*-attack, since *Re*-attack is blocked by 5*S*-phenyl group of **2a**. In fact, the DFT calculations for the transition states show that (*S*)-**TS** is much lower in energy than (*R*)-**TS** (3.63 kcal/mol corresponding to 99.6% ee); this energy difference is in good agreement with the experimental result (99% ee).

Scheme 5. Stable Conformations of 2a and Their Relative Energies Calculated at the B3LYP/6-311+(2d,p)/PCM(THF) Level



Scheme 6. Transition States for the Addition of A to *anti-cis*-2a and Their Relative Energies Calculated at the B3LYP/6-311+(2d,p)/PCM(THF) Level



In conclusion, the electroreduction of optically active *N*-*E*-crotonoyl- and *N*-cinnamoylimidazolidin-2-ones **2a,b** and oxazolidin-2-ones **2c−f** with benzophenone (**1a**) in the presence of TMSCl in THF gave intermolecularly coupled products **3** with high diastereoselectivity. The adducts **3** were readily transformed to optically active 4,5,5-trisubstituted *γ*-butyrolactones **5a,b** by treatment with TBAF in THF. Similarly, optically active 4,5,5-trisubstituted *γ*-butyrolactones **5c−f** were synthesized from **2a,b** and diaryl ketones **1b−d**. The high diastereoselectivity in the electroreductive coupling of **2a** with **1a** was in accordance with the DFT calculations of the transition states.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data for compounds, ^{1}H and ^{13}C NMR spectra of compounds, X-ray crystallographic data (ORTEP) of **2a**, (3′*S*)-**4a**, (3′*R*)-**4f**, and (*R*)-**5f**, and the results of DFT calculations for **2a** and **TS**. Crystallographic files for **2a**, (3′*S*)-**4a**, (3′*R*)-**4f**, and (*R*)-**5f** (CIF). 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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