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Diastereoselective Oxidative Coupling of Enolates of Chiral Carboxylic Acid Derivatives

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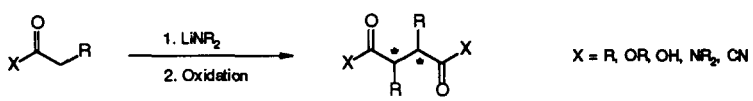
Abstract: *Enolates of chiral propionic acid amides were oxidatively dimerized with cupric salts or iodine with high simple as well as induced diastereoselectivity of up to 99:1. Intramolecular coupling of chiral dienolates of 1,7-heptanediamides led to a 1,2-disubstituted cyclopentane and a derivative of 1,2,6,7-cyclodecane tetracarboxylic acid.*

Oxidative coupling of stabilized carbanions such as dilithiated carboxylic acids[1] or enolates of carboxylic acid derivatives[2] and ketones[3] offers a convenient method for C-C bond formation and is reported to proceed both intermolecularly and intramolecularly in good yields[4] (Scheme 1). Furthermore, it provides an efficient synthetic approach to lignans[5], an important class of natural products displaying useful biological activities, e.g., as anti-cancer drugs. Recently we[6] and others[7] reported auxiliary controlled diastereoselective variants of this reaction. High levels of simple and induced diastereoselection were found. In this paper we report more detailed information and further investigations on this subject.

Scheme 1



With the exception of a few examples,[8] simple[9] diastereoselectivity in oxidative dimerization of achiral substrates seems to be low. In order to confirm this point, we deprotonated substrates **1a** and **1b** at -78 °C in THF following a procedure of Rathke[10] (Scheme 2). After addition of 0.5 eq. of I_2 or copper-(II)-pentanoate the reaction mixture was allowed to warm up to room temperature over night to give coupling products **3a** and **3b** in ratios of 57:43 and 48:52, respectively (Table 1)[11]. Thus, a significant degree of diastereoselection is not displayed in this reaction. However, dramatically improved results were obtained when the chiral amide **1c** or ester **1d** were subjected to the same reaction conditions. With these substrates we found high simple[8] as well as induced[8] diastereoselectivity in favour of (*S,S*)-**3** (entries 3-6, Table 1). These results are surprising because normally simple diastereoselectivity is little affected by an auxiliary. The steric course of this reaction can be generally rationalized as follows: if the primary oxidation products are achiral radical species, enantiotopic half spaces at the reacting C_α, described by descriptors *Re* and *Si*, combine non-selectively. This is obviously the case in the conversion of achiral substrates **1a** and **1b** to the coupling products **3a** and **3b.** All combinations (*Si/Si*, *Re/Re* and *Re/Si*, *Si/Re*) seem to be energetically equivalent. On the other hand, in enolates or radicals of chiral acyl derivatives **1c** and **1d** one of the diastereotopic half spaces of the reacting carbon is effectively sterically shielded. This can be assessed from alkylation experiments with enolates **2c** and **2d** which proceed with dia-

stereoselectivity of 98:2. So either (*Re/Re*) or (*Si/Si*), i.e., the *lk* combinations should be favoured provided that radical intermediates are configurationally stable.

The following points are of special interest: iodine or copper-(II)-pentanoate as oxidants yield the same products and the same high degree of diastereoselectivity. Acyl derivatives of auxiliary **5** have been shown to yield *syn*-enolates after deprotonation which are attacked by electrophiles at the C_α-*Re* face with selectivity of >95:<5[12]. Therefore, the exclusive *Re/Re* combination of *syn*-**2c**[13] is consistent with the (*S,S*)-configuration achieved in product **3c**. Surprisingly, products with the same relative configuration were obtained with acyl derivatives of **6** although *anti*-enolates are generated under essentially the same deprotonation conditions (LDA, -78 °C, THF). *Anti*-enolates of esters of **6** are known to react with electrophiles at the C_α-*Si* face. Thus, *anti* → *syn* isomerization of enolate or radical species must have occurred.

Scheme 2

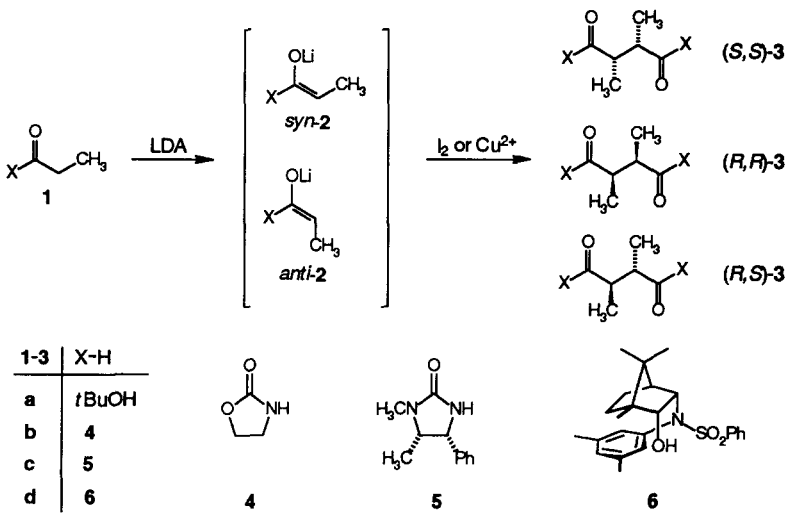


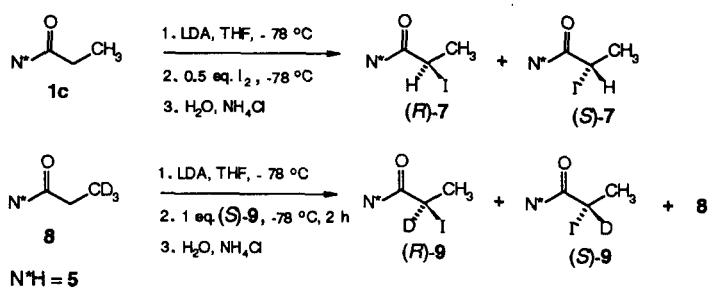
Table 1. Simple and Induced Diastereoselectivity in Oxidative Dimerizations of Enolates of Propionic Acid Derivatives (reaction conditions see Ref. 14)

Entry	Substrate	Oxidant	Diastereoselectivity	Yield [%]
1	**1a**	1.5 eq.Cu(II)	*rac*-**3a** : meso-**3a** = 57 : 43 [a]	25
2	**1b**	0.5 eq. I_2	*rac*-**3b** : meso-**3b** = 48 : 52 [b]	33
3	**1c**	0.7 eq. I_2	(*S,S*)-**3c** : (*R,R*)-**3c** : (*S,R*)-**3c** = >99 : <1 : <1 [b]	70
4	**1c**	1.1 eq. Cu(II)	(*S,S*)-**3c** : (*R,R*)-**3c** : (*S,R*)-**3c** = >99 : <1 : <1 [b]	66
5[c]	**1d**	0.5 eq. I_2	(*S,S*)-**3d** : (*R,R*)-**3d** : (*S,R*)-**3d** = 95 : 2.5 : 2.5 [b]	86
6	**1d**	1.0 eq. Cu(II)	(*S,S*)-**3d** : (*R,R*)-**3d** : (*S,R*)-**3d** = >99 : <1 : <1 [b]	36

[a] Determined by glc (capillary column, HP-1, crosslinked methyl silicone, 25 m x 0.2 mm x 0.33 μm).
[b] Determined by HPLC (silica, Merck Hibar Lichrosorb, 250 x 4 mm, Si 60, 5 mm, RI detection).
[c] Lithium cyclohexylisopropylamide was used instead of LDA.

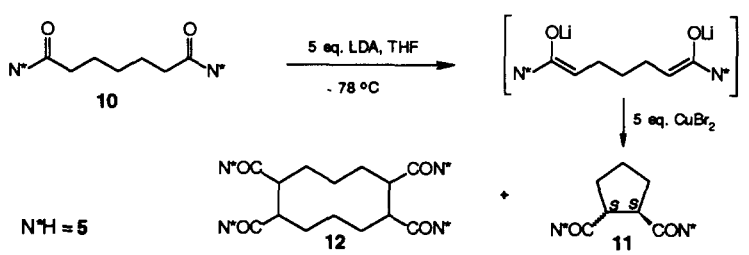
These results stimulated further experiments to gain insight into the mechanism of the reaction. When 0.5 eq. of I_2 was added to a solution of enolate *syn*-**2c** at -78 °C (coupling commences above -10 °C) the α-iodo derivatives **7** were formed non-selectively. On the other hand, when diastereomerically pure **9a** (**9b**)[15] was added in an analogous procedure to an enolate solution of **8** without warming up (Scheme 3), isomerization of **9a** (**9b**) occured and 43% **8**, 13% **9a** and 34% **9b** (41% **8**, 10% **9a** and 37% **9b**) were isolated. Control experiments proved that neither D- nor I-transfer occurred. We assume involvement of a SET mechanism which could explain the isomerization of enolate *anti*-**2d** as well as the isomerization of **9a** and **9b**. SET mechanisms have already been proposed for oxidative coupling of dilithiated carboxylic acids[1] with iodine.

Scheme 3

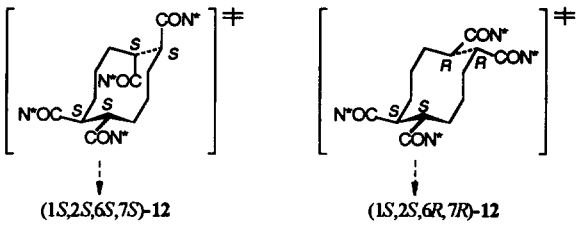


It was also of interest to investigate intramolecular oxidative coupling[16]. The acid diamide **10** (Scheme 4) was converted with 5 eq. of LDA into the corresponding dienolate which was oxidized with 5 eq. of $CuBr_2$. Surprisingly, the 1,2,6,7-cyclodecane tetraamide **12** was isolated (17 %) in addition to the anticipated 1,2-cyclopentane diamide **11** (23 %), both as pure stereoisomers (Scheme 4). The configuration of **11** was determined by saponification and esterification to (*S,S*)-dimethyl 1,2-cyclopentanedicarboxylate ($[\alpha]_D^{22} = +47.5$, c = 0.54, CCl_4; Ref.[17] $[\alpha]_D^{25} = +47.9$, c = 0.012, CCl_4).

Scheme 4



The cyclodecane derivative **12**, one of seven possible diastereomers[18], was not the expected (1*S*,2*S*,6*S*,7*S*)-isomer **12a** as proton NMR spectra displayed two sets of signals of the auxiliary group and the saponification product was optically inactive. Tentatively we assign the (*S,S,R,R*)-configuration (**12g**) by assuming that two stereogenic centres are formed under control of the auxiliary; auxiliary control of the other two centers in a transition state resembling the most stable BCB cyclodecane conformation[19] would require a diaxial disposition of amide groups. Therefore, we assume that the second bond forming step proceeds under substrate control, *i. e.*, with diequatorial disposition of the substituents as described below:



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9. Simple and induced diastereoselectivity are given by the ratio of diastereomers with different and the same configuration, respectively, of the new stereogenic centers; cf. Helmchen, G.: Nomenclature and Vocabulary of Organic Stereochemistry. In Houben-Weyl, *Methods of Organic Chemistry*, 4 th ed; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E.; Eds.; Thieme: Stuttgart, **1995**; Vol. E 21, p.55.
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11. All new compounds were characterized by spectroscopic data and gave correct elemental analyses.
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13. The following nomenclature for enolate stereoisomers is adopted throughout this paper: *syn-* and *anti-*enolates are defined by cis or trans position of the CH_3 group relative to the OLi group.
14. In a typical procedure 1.1 mmol of diisopropylamine in 1.1 ml of THF was treated at -10 °C with 1.1 mmol of nBuLi. The solution was cooled to -78 °C and dropwise treated with a solution of 1 mmol of substrate in 1.3 ml of THF and 0.25 ml of DMPU. After 30 min 0.5 mmol of I_2 in 1.5 ml of THF (or Cu-II-pentanoate neat) was added. The mixture was stirred and allowed to warm to room temperature over 4-6 h.
15. Diastereomers **9a/9b** of unknown configuration of the acyl group are identical to (*R*)-**9** or (*S*)-**9**.
16. On advice of one of us (G.H.) a similar intramolecular coupling with high selectivity was also achieved by Ito, Y.N.; Ariza, X.; Beck, A.K.; Bohác, A.; Ganter, C.; Gawley, R.E.; Kühnle, F.N.M.; Tuleja, J.; Wang, Y.N.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071 (cf. footnote 9 therein).
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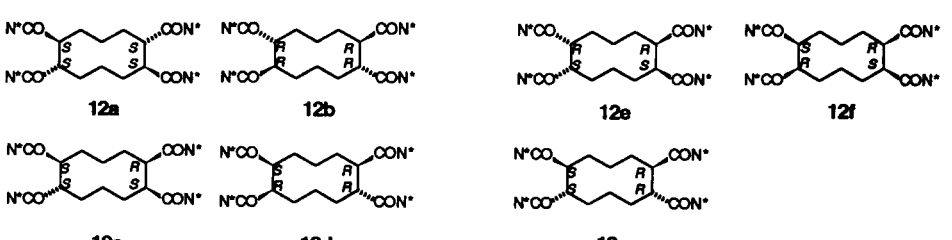
18. Possible stereoisomers of **12**:

Amides of Chiral Tetracarboxylic Acids — *Amides of Achiral Tetracarboxylic Acids*



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