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# Enantioselective Oxidative Coupling of the Titanium Enolate of 3-Phenylacetyl-2-oxazolidinone

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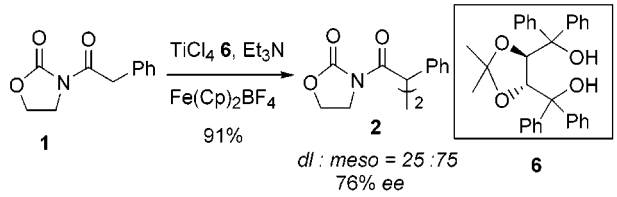
## ABSTRACT




**Enantioselective oxidative coupling of titanium and ytterbium enolates of 1 bound to chiral diol, e.g., TADDOL 6, and bisoxazoline ligands with ferrocenium cation as oxidant affords dimers 2 with moderate to good enantioselectivities.**

Diastereoselective radical coupling reactions can be achieved with thermally,[1] photochemically,[2] or electrochemically[3] generated radicals. Enolates linked to a chiral auxiliary are coupled stereoselectively by oxidation, probably via cation radicals[4] in some cases, preferentially to the (*S,S*)-, (*R,S*)-, or the (*R,R*)-homodimer depending on the oxidant and the metal atom in the enolate.[2,5] Enantioselective radical additions have been achieved recently by way of binding prostereogenic radicals or radical traps to a Lewis acid that is complexed by a chiral ligand.[6] However, to our knowledge no case of an enantioselective radical or cation radical coupling has been described yet.

We report here on the enantioselective, oxidative coupling of the titanium or ytterbium enolate of 3-phenylacetyl-2-oxazolidinone (**1**)[7] to the homodimer **2**, where the metal of the enolate is complexed to the chiral diols **3**−**6** or bisoxazoline ligands **7**−**9** (Scheme 1).[8] As oxidant the ferrocenium cation (**10**) was selected, which has been used before for the oxidative dimerization of enolates[9] and which should ensure oxidation by an outer sphere electron transfer, where the oxidant does not or only slightly interferes with the reaction of the intermediate. Oxidative coupling of the titanium enolate of **1** at 0 °C afforded 56% **2** (*dl*:*meso* =

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(8) Compounds **3**, **4**, and **5** were obtained from Fluka; **6** was prepared according to Beck, A. K.; Bastani, B.; Plattner, D. A.; Petter, W.; Seebach, D.; Braunschweiger, H.; Gysi, P.; La Vecchia, L. *Chimia* **1991**, *45*, 238−244; **7** was prepared according to Denmark, S. E.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem*. **1997**, *62*, 3375−3389; **8** according to Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc*. **1991**, *113*, 726−728; and **9** according to Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Soc. Chem*. **1991**, *113*, 728−729.

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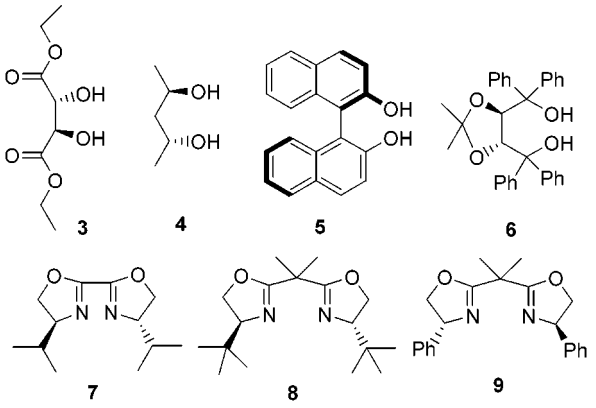
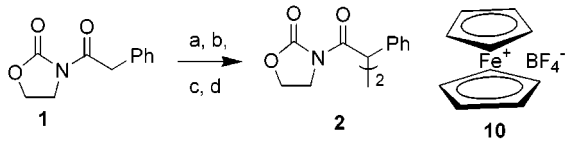
**Scheme 1.** Chiral Ligands **3**−**9** for Enantioselective Oxidative Coupling



40:60 (Scheme 2)); *dl*- and *meso*-**2** were assigned to the diastereomers of **2** from their crystal structures.

**Scheme 2.** Oxidative Coupling of Enolates from **1** to **2**[a]



[a] (a) (i) 1 equiv of $TiCl_4$, **1**, (ii) 1 equiv of $Et_3N$, (iii) 1.5 equiv of $FeCp_2BF_4$, (**10**), 0 °C; (b) (i) 1 equiv of $TiCl_4$, ligand, 2 equiv of $Et_3N$, (ii) **1**, 1 equiv of $Et_3N$, (iii) 1.5 equiv of **10**, 0 °C; (c) (i) 1 equiv of $TiCl_4$, ligand, (ii) **1**, 1 equiv of $Et_3N$, (iii) 1.5 equiv of **10**, 0 °C; (d) (i) 1 equiv of $Yb(OTf)_3$, ligand, 2 equiv of $Et_3N$, (ii) **1**, 1 equiv of $Et_3N$, (iii) 1.5 equiv of **10**, 0 °C.

For the enantioselective enolate coupling at first the chiral Lewis acid was prepared by adding 1 equiv of $TiCl_4$ to the chiral ligand in dichloromethane.[7a] Thereby it was essential to trap the evolving HCl with 2 equiv of triethylamine, and then 1 equiv of **1** and 1.5 equiv of **10** were added (Scheme 2b). The results are summarized in Table 1, which shows that with increasing size of the ligands **4**−**6** ,with the exception of **3**, the portion of the *dl*-diastereomer decreases, while the enantioselectivity increases.

**Table 1.** Enantioselective Titanium Enolate Coupling with Diols **3**−**6** and Bisoxazolines **7**−**9** as Ligands

| ligand | yield (%) | *dl*:*meso*[a] | ee (%)[b] |
|---|---|---|---|
| **3** | 67 | 54:46 | 39.2 (*R*,*R*) |
| **4** | 63 | 31:69 | 5.0 (*R*,*R*) |
| **5** | 52 | 24:76 | 15.6 (*R*,*R*) |
| **6** | 91 | 25:75 | 76.0 (*R*,*R*) |
| **7** | 59 | 35:65 | 5.8 (*S*,*S*) |
| **8** | 81 | 45:55 | 23.8 (*S*,*S*) |
| **9** | 58 | 48:52 | 46.4 (*S*,*S*) |

[a] Determined by RP-HPLC; [b] Determined by chiral HPLC.

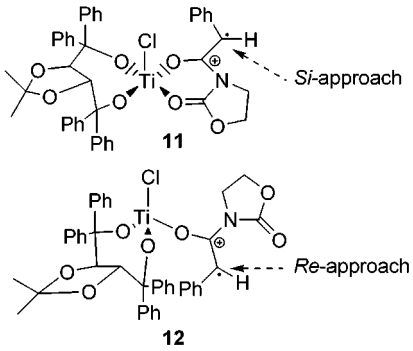
In the coupling with bisoxazolines as ligands the procedure was the same as with the diols, with the exception that only 1 equiv of triethylamine was needed as in the first step no HCl is formed (Scheme 2c, Table 1). The enantioselectivity increases with the substituent in the order $^i$propyl < $^t$bu < phenyl. It is noteworthy that with **9** the same major enantiomer was formed as with **7** and **8**, although **9** has the opposite configuration as **7** and **8** at the stereogenic centers.

With ytterbium triflate as Lewis acid and **1**, the corresponding ytterbium enolate was prepared (Scheme 2d). Oxidative homocoupling with TADDOL (**6**) as chiral ligand leads to 53% **2**, *dl*:*meso* = 54:46, 34% ee (without ligand **6**, 68% **2**, *dl*:*meso* = 78:22).

It appears reasonable to assume that the 1e-oxidation of the neutral enolate generates a cation radical that undergoes coupling.[4,5b−e] There are numerous coupling processes that are induced by 1e-transfer from olefins or aromatic compounds and afford dimers via intermediate cation radicals.[10]

It has been shown by crystal structure analysis that $TiCl_2$-TADDOL forms an octahedral complex with (*E*)-cinnamyl-2-oxazolidinone.[11] If a similar structure is assumed for the complex of **1** and $TiCl_2$-Taddol, one would obtain after deprotonation and chloride substitution a titanium enolate, whose 1e-oxidation would yield the cation radical **11** as a pentavalent complex (Scheme 3). There the *re* side of the

**Scheme 3.** Penta- and Tetracoordinated Ti Complexes **11** and **12**



cation radical would be shielded, and dimerization would occur from the *si* side. The same considerations would hold for the ligands **4** and **5**. Experimentally, however, the (*R*,*R*)-dimer is found in excess. This points to a tetrahedral complex **12**. There the metal bond to the oxygen with the weakest basicity is broken as a result of the decreased Lewis acidity of titanium after the enolate formation. This leads now to a shielding of the *si* side and the preferred formation of the (*R*,*R*)-dimer. This would also hold for the ligands **4** and **5**, whereas the results with ligand **3** would rather point to a reaction via the pentacoordinated complex **11**, possibly because of the lower basicity of the oxygens of the ligand,

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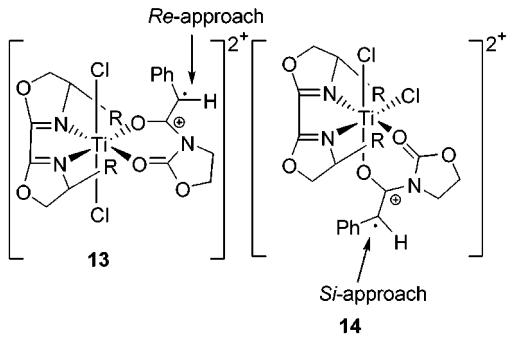
which would lead to a complex where the Lewis acidity of titanium is less decreased.

The use of bisoxazolines **7**−**9** as chiral ligands for zinc, magnesium, and copper in enantioselective metal-catalyzed reactions has been reviewed recently.[12] The combination of **8** with $TiCl_4$ in an enantioselective Baylis−Hillman reaction afforded the addition product with 6% ee.[13] As in the case of the diols as ligands the chiral $TiCl_4$−bisoxazoline complex would react with **1** to the titanium enolate, which would be oxidized with **10** to the dication radical complex **13**. However, if the bisoxazoline−titanium enolate complexes behave analogously as the zinc, magnesium, and copper complexes of bisoxazolines and acyloxazolidinones, in addition to the *trans*-octahedral configuration shown in **13** a *cis*-octahedral configuration **14** has also to be considered (Scheme 4).

**Scheme 4** *trans*-Octahedral and *cis*-Octahedral Ti Complexes **13** and **14**




The coupling via **13** should lead to (*R*,*R*)-**2** and by way of **14** to (*S*,*S*)-**2**. In the experiment with all three ligands **7**−**9** always the *S*,*S*-enantiomer was found. This means that with **7** and **8** the *cis*-octahedral complex appears reasonable while for **9**, where the stereogenic centers have the opposite configuration, the complex **13** is more plausible. Such an alteration of coordination with the change of the alkyl substituent to an aryl substituent at C-4 of the bisoxazoline has been assumed for other metal complexes in Diels−Alder,[14] hetero-Diels−Alder,[15] en-, [16] and radical reactions[6,17] to explain the enantioselectivity. This change of the complex configuration is also supported by the higher enantiomeric excess with **9**. Normally the *tert*-butyl-bisoxazoline affords the higher enantiomeric excess. In complex **13**, however, the substituent at the stereogenic center is much closer to the radical center than in complex **14**, which should lead to a better facial shielding and thus to a higher ee.

In the Diels−Alder reaction of cyclopentadiene with (*E*)-2-butenoyl-2-oxazolidinone in the presence of $Yb(OTf)_3$, binaphthol, and a tertiary amine, the cycloadduct could be obtained with 95% ee. On the basis of $^{13}C$ NMR and IR spectroscopy, a not-yet-complete model of the catalyst structure was developed.[18] It appears therefore premature to transfer this model to the complex between the ytterbium enolate cation radical of **1** and the ligand TADDOL.

The compound *meso*-**2** cannot be formed exclusively by statistical coupling of the intermediate cation radicals at the *re* or *si* side, because in this case, e.g., in the Table with ligand **6**, a *dl*:*meso* ratio of 60:40 would be expected. It appears reasonable that besides a transition state with a *syn*-staggered conformation favoring *R*,*R*- or *S*,*S* coupling (Table 1), another one with an *anti*-staggered conformation that favors the *meso* product competes, whereby the latter possibly sterically less crowded transition state could be favored. The possible role of dinuclear complexes on the stereoselectivity has not yet been investigated.

In conclusion, an enantioselective oxidative coupling of titanium and ytterbium enolates bound to chiral diol and bisoxazoline ligands has been found that affords moderate to good enantioselectivities. The results can be tentatively interpreted by using models, which have been applied to Diels−Alder, hetero-Diels−Alder, en-, and radical reactions with titanium complexes, whose structures have been deduced from crystal structures and spectroscopic studies.

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**Supporting Information Available:** Typical experimental procedure for the enantioselective oxidative enolate coupling. This material is available free of charge via the Internet at http://pubs.acs.org.

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