# 175. Enantioselective 1,4-Addition of Aliphatic *Grignard* Reagents to Enones Catalyzed by Readily Available Copper(I) Thiolates Derived from TADDOL

Preliminary Communication

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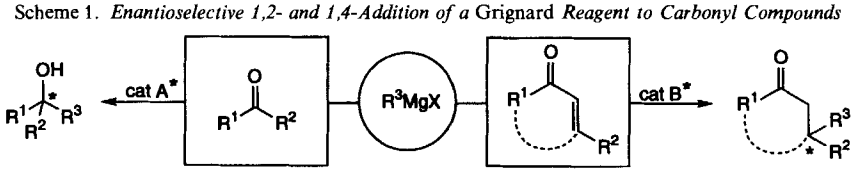
Two simple thiols derived from the parent TADDOL, α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol, are used to prepare $Cu^I$ complexes **C** and **D** to catalyze (0.05 equiv.) 1,4-additions of *Grignard* reagents RMgCl to cyclic enones with enantioselectivities which are comparable to or better than previously reported (enantiomer ratios up to 92:8).

The most readily available and common nucleophilic organometallic reagents are the *Grignard* compounds [1]. It remains to be a dream, among synthetic organic chemists, to be able to cause such (achiral) organomagnesium compounds to add, in a completely selective 1,2- or 1,4-mode, to the enantiotopic faces of an aldehyde or ketone, or of an α,β-unsaturated carbonyl derivative, under the influence of a *catalytic* amount of a chiral additive (*Scheme 1*)[3]). Use of *other* organometallic reagents (Zn, Cu, Cu/Li, Ce, Ti *etc.*, sometimes actually prepared from *Grignard* compounds) and application of *stoichiometric* or *excess* amounts of chiral additives in 1,2- and 1,4-additions is amply documented[4]) in the literature [2]. The 1,4-addition of *Grignard* compounds to α,β-unsaturated carbonyl compounds is induced by the addition of catalytic amounts of $Cu^I$ salts [5]. The groups of *Lippard*, *van Koten*, *Spescha*, and *Pfaltz* have employed catalytic amounts ($\leq 10\%$) of chiral $Cu^I$ complexes (derived from amino imines, amino thiols, mercapto sugars, and mercapto oxazolines) for enantioselective versions of this reaction (enantiomer ratios er up to 92:8) [6].

Scheme 1. *Enantioselective 1,2- and 1,4-Addition of a* Grignard *Reagent to Carbonyl Compounds*




[1]) Part of the Ph.D. thesis of *G.J.*, Diss. ETH No. 12300, 1997.

[2]) Part of the projected Ph.D. thesis of *A.P.*, ETH-Zürich.

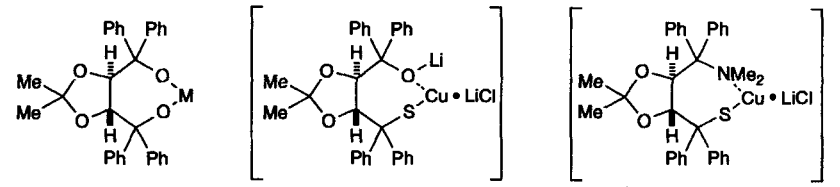
[3]) The situation is very similar when Li instead of Mg compounds are used [2].

[4]) For a recent review article on stereoselective synthesis involving Cu derivatives, see [3]. Practical aspects of 1,4-additions in organic synthesis are covered in *Perlmutter*'s monography [4].

Encouraged by previous successes with TADDOL-derived organometallic reagents [7], including those obtained from *Grignard* compounds [8–10] (*cf.* complexes **A** and **B**, *Scheme 2*), we have now tested the $Cu^I$ complexes **C** and **D** of thiols, prepared from the parent TADDOL **1**, for conjugate additions of *Grignard* compounds, with promising results to warrant this preliminary account.

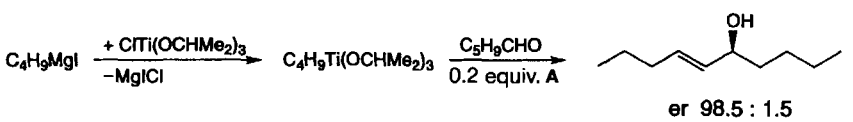
The TADDOL **1**[5]) is converted to the mercapto alcohol[6]) **3** through the chloro alcohol **2** which is also the intermediate on the way to the amino thiol **6** (*via* amino

Scheme 2. *TADDOL* (**1**) [11], *Products* **2**–**6** *of Substitutions* [13] [14], *Metal Complexes* **A**–**D**, *and Use in Enantioselective Nucleophilic Additions to an Aldehyde* [9] *and to a Ketone* [10]. For applications of the new Cu thiolates **C** and **D**, see *Scheme 3* and the *Table*.

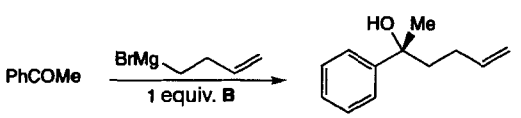



**A** M = $Ti(OCHMe_2)_2$ **C** **D**

**B** M = Mg




er 98.5 : 1.5

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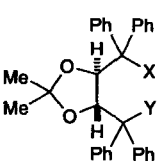


**1** X = Y = OH **4** X = OH, Y = $NMe_2$

**2** X = OH, Y = Cl **5** X = Cl, Y = $NMe_2$

**3** X = OH, Y = SH **6** X = SH, Y = $NMe_2$

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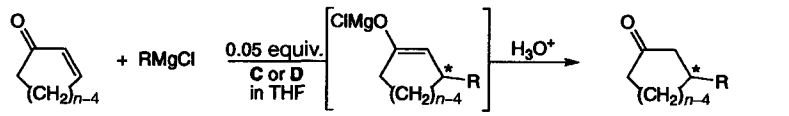
[5]) TADDOL **1** is commercially available from fine chemicals and reagents suppliers; **1** is obtained in one step [11] from the inexpensive tartrate acetonide.

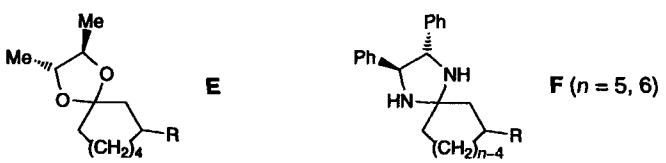
[6]) First obtained by *De Lucchi et al.* [12] from **1** and *Lawesson* reagent. We prepared **3** from the chloro alcohol **2** [13] (thiourea, then NaOH, *R. Wünsch*, hitherto unpublished results, ETH-Zürich, 1997); specific rotation, melting point, and other physical data of **3** are identical, within experimental error, with those reported in [12].

alcohol **4** and chloro amine **5**), as described recently [14][7]). The thiols **3** and **6** were converted to THF solutions (*ca.* $5 \cdot 10^{-3}$ M) of the $Cu^{I}$ complexes **C** (golden) and **D** (colorless) by treatment at $-75°$ with BuLi (2 and 1 equiv., resp.), addition to a $-75°$ cold suspension of CuCl[8]) in the same solvent, and warming to 0°. On a 1-mmolar scale, the neat cycloalk-2-enone was combined at $-75°$ with the solution of the Cu complex and 1.5 equiv. of *ca.* 0.5M RMgCl in THF was added within 2 h by syringe drive (workup after an additional 2 h). The enantiomer ratios (er) of the 3-substituted cycloalkanones thus obtained were determined by standard methods (*Scheme 3*). The results obtained with five-, six-, seven-, and eight-membered ring enones and with various *Grignard* reagents are collected in the *Table*.

Scheme 3. *Conjugate Additions of* Grignard *Reagents to Cyclic Enones in the Presence of the Cu-Thiolates* **C** *and* **D**. Commercial THF solutions of MeMgCl, i-PrMgCl, and BuMgCl were used. The commercial $Et_2O$ solution of PrMgCl was diluted with THF to the required 0.5M concentration. The enantiomer ratios were determined by gas chromatography *a*) with the β-substituted ketone directly (cycloheptanones, with a β-cyclodextrine column [15][16]), *b*) with the ketal **E** [16] (cyclooctanones, using the same β-CD column), or by $^{13}$C-NMR spectroscopy of the aminals **F** [6][17] (cyclopentanones and cyclohexanones).




(for specification of *n*, R, product configuration and er, see the *Table*)




The following comments are considered important:

*i*) We have no indication for formation of 1,2-adducts in the reactions catalyzed by **C** and **D**.

*ii*) The enantioselectivities observed are as good as the best ones reported in the literature [6]; with methyl *Grignard* reagent (→ **7**, $n = 7$, R = Me) our er value of *ca.* 9:1 (obtained with complex **D**) is actually the highest one reported.

*iii*) Although the ligands in complex **C** and **D** have the same configuration (*R*,*R*), the stereochemical course of the conjugate additions is opposite (*Si*-addition with **C** and *Re*-addition with **D**).

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[7]) Total yield of **3** and **6** from **1** *ca.* 30 and 25%, respectively. We find that it is extremely important to use pure samples of **3** and **6** in order to observe the selectivities reported herein.

[8]) A 1.3 equimolar excess of $Li_2$-**3** and Li-**6** over CuCl was used.

Table. *Results of the Enantioselective Conjugate Additions of Alkyl* Grignard *Reagents RMgCl to Cyclic Enones in the Presence of 0.05 Equiv. $Cu^I$ Complexes* **C** *and* **D**, *with Formation of Substituted Cycloalkanones* **7**. 1-mmol scale reactions, isolation of **7** by bulb-to-bulb distillation; determination of er by GC or NMR, as specified in *Scheme 3*. The absolute configurations are derived from optical comparison with literature values [6][18].

| Cycloalk-2-enon | Catalyst | R | *n* | Yield [%] | Product **7** enantiomer ratio er | (Sense of specific rotation) Abs. config. |
|---|---|---|---|---|---|---|
| Cyclopentenone | **C** | Bu | 5 | 23 | 40:60[a]) | |
| | **D**[b]) | Bu | 5 | 50 | 70:30[a])[b])[c]) | |
| Cyclohexenone | **C** | Bu | 6 | 77 | 18:82 | (−)-(*S*) |
| | **D** | Bu | 6 | 77 | 89:11 | (+)-(*R*) |
| Cycloheptenone | **C** | Bu | 7 | 81 | 13:87 | (−)-(*S*) |
| | **D** | Bu | 7 | 77 | 90:10 | (+)-(*R*) |
| | **D**[b]) | Bu | 7 | 80 | 91:9 | (+)-(*R*) |
| | **D** | Bu | 7 | 80 | 70:30[d]) | (+)-(*R*) |
| | **D**[b]) | Bu | 7 | 72 | 92:8[c]) | (+)-(*R*) |
| | **C** | Me | 7 | 68 | 18:82 | (−)-(*S*) |
| | **D** | Me | 7 | 58 | 89:11 | (+)-(*R*) |
| | **D** | Pr | 7 | 76 | 90:10 | (+) |
| | **D** | i-Pr | 7 | 65 | 75:25 | (+)-(*R*) |
| Cyclooctenone | **C** | Bu | 8 | 81 | 20:80 | (+) |
| | **D** | Bu | 8 | 78 | 76:24 | (−) |

[a]) Due to poor resolution in the $^{13}$C-NMR of **F** ($n = 5$), these values are not as accurate as for the cyclohexanone analogs. [b]) 0.1 Equiv. instead of 0.05 equiv. **D** used. [c]) Simultaneous addition of enone and BuMgCl to the catalyst solution at −75°. [d]) In this experiment the enone was added to a solution of BuMgCl and **D**.

*iv*) Common additives such as DBU, DMPU, HMPA, TMEDA, TBDPSiCl, TMSiCl, and 12-crown-4 (2 equiv. in all cases) did not improve the selectivities or yields in the reactions studied[9]).

*v*) Our results are in line with the generally observed increase of selectivity in conjugate additions when going from five- to six- to seven-membered ring enones [6].

Our ongoing investigations involve TADDOL-derived SH ligands in which the aryl groups and the substituents in 2-position of the dioxolane ring and on the amino N-atom are varied[10]). We are also studying conjugate additions to other α,β-unsaturated systems (enals, enoates, nitro olefines, alkenyl sulfones, and P derivatives), *in situ* trapping, by various electrophiles, of the carbanionoids formed, as well as other types of $Cu^I$ catalyzed reactions leading from achiral starting materials to chiral products. Finally, we try to obtain structural information about the complexes **C** and **D**, in order to elucidate the intriguing reversal of relative topicity.

We thank Dr. *R. Wünsch* for the preparation of a sample of thiol **3**, and *M. Brenner* for carrying out some experiments. Continous support of our group by *Novartis Pharma AG*, Basel, is gratefully acknowledged.

[9]) In almost all cases, the results with complex **D** were poorer in the presence of additives. Notable exceptions: **7** ($n = 7$, R = Bu) was formed with the same selectivity (er *ca.* 9:1) in the absence and presence of TMEDA or TBDPSiCl. Additives have not yet been tested with complex **C**.

[10]) There are more than 90 different $C_2$- and $C_1$-symmetrical TADDOLs and TADDOL analogs known [19].

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