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Asymmetric conjugate additions of TMSI promoted monoorganocuprate reagents, Li[RCuI], to various *N*-enoyl oxazolidinones†

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Abstract—Diastereoselective conjugate additions to different α,β-unsaturated *N*-acyl oxazolidinones using various monoorganocuprate reagents, Li[RCuI], are described. The TMSI activated conjugate addition reactions provided high yields (80–98%) and reversed major diastereomers (70–96% de) compared to the conventional copper(I)-promoted additions of Grignard reagents or the addition of Li[RCuI] to precomplexed $MgBr_2$/imides. © 2002 Elsevier Science Ltd. All rights reserved.

Organocopper compounds are among the most versatile reagents for C–C bond formations.[1] Additives have been used with organocopper chemistry for some time, one of the most notable reagents being chlorotrimethylsilane (TMSCl). This additive was originally employed to trap intermediate enolates,[2] but was soon discovered to increase the reactivity of cuprates in 1,4-addition reactions.[3] The discovery that TMSI is a better activator than TMSBr or TMSCl for monoorganocuprate reagents, RCu(LiI),[4] or more appropriately written as Li[RCuI],[5] has provided substantial evidence that this reagent is a powerful tool for conjugate additions to α,β-unsaturated carbonyl compounds.[6] Asymmetric conjugate additions of organocopper reagents to prochiral substrates using chiral heterocuprates[7] and chiral ligands[8] has expanded dramatically over the last decade. Chiral auxiliaries in conjugate additions of organocopper reagents have also been explored for some time, e.g. Oppolzer's camphor derivatives,[9] and Koga's γ-butyrolactam.[10] Evans' oxazolidinone has been used extensively due to the excellent levels of stereoselectivity in asymmetric aldol reactions.[11] Copper(I)-promoted asymmetric conjugate additions of Grignard reagents[12] and zirconium reagents[13] have been reported to add in a 1,4-fashion to *N*-enoyl derived oxazolidinones with high yields and stereoselectivities.

We now report conjugate additions of TMSI-promoted monoorganocuprate reagents Li[RCuI] to chiral *N*-enoyl derived oxazolidinones.[14] The opposite π-facial selectivity is obtained when employing the Li[RCuI]/TMSI reagent system than with the copper-promoted Grignard reagents, zirconium reagents, and TMSCl-promoted Gilman reagents to Koga's γ-butyrolactam.[6c] The yield of the products ranges from 80 to 98% (Tables 1–3) using the Li[RCuI]/TMSI system. The stereoselectivity (70–96% de) of the 1,4-products is highly dependent on the specific oxazolidinone and the copper reagent employed.

The diastereomeric ratio (de) was determined by ^{1}H NMR spectroscopy and further compared to the enantiomeric ratio (ee) obtained using optical rotation measurements of the known carboxylic acids[10] or the corresponding alcohols[15] after chemical removal of the chiral auxiliary. The highest stereoselectivities (96–92% de) were obtained using the *N*-enoyl phenylglycine-derived oxazolidinones **1** and **2** employing the Li[RCuI]/TMSI reagent (Table 1). Conjugate addition of PhMgCl/CuI (entry 5) to substrate **1** gave 90% de of **5b** as the major diastereomer. In contrast, the opposite major diastereomer **5a** was obtained in 92% de when applying the Li[PhCuI]/TMSI reagent to substrate **1** (entry 4). Conducting a copper reaction using cinnamate **3** or Li[MeCuI]/TMSI proved to be slightly less selective in the conjugate addition reactions (entry 10).

The diastereomeric ratio obtained using the copper-promoted Grignard reagent (or $MgBr_2$, entry 2) is most likely caused by the substrate reacting in the *syn-s-cis*

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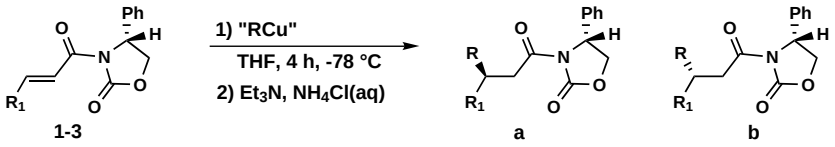
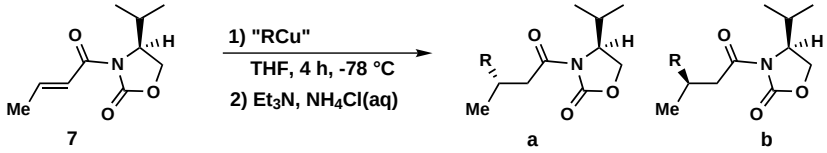
Table 1. Conjugate additions to phenylglycine-derived oxazolidinones **1–3**



Entry	Substrate	Reagent (RCu)	Product	Ratio (a:b)[b]	Yield (%)[a]
1	**1**; R_1 = Me	Li[*n*-BuCuI]/TMSI	**4**	98:2 (**4***S*:**4***R*)	83
2	**1**; R_1 = Me	Li[*n*-BuCuI]/$MgBr_2$	**4**	3:97 (**4***S*:**4***R*)	77[c]
3	**1**; R_1 = Me	Li[*n*-BuCuI]/$MgBr_2$/TMSI	**4**	98:2 (**4***S*:**4***R*)	80[d]
4	**1**; R_1 = Me	Li[PhCuI]/TMSI	**5**	96:4 (**5***R*:**5***S*)	83
5	**1**; R_1 = Me	PhMgCl/CuI	**5**	5:95 (**5***R*:**5***S*)	74[e]
6	**1**; R_1 = Me	PhMgCl/CuI/TMSI	**5**	5:95 (**5***R*:**5***S*)	51[e]
7	**2**; R_1 = *n*-Bu	Li[PhCuI]/TMSI	**6**	97:3 (**6***R*:**6***S*)	83
8	**2**; R_1 = *n*-Bu	Li[MeCuI]/TMSI	**4**	91:9 (**4***R*:**4***S*)	84
9	**3**; R_1 = Ph	Li[*n*-BuCuI]/TMSI	**6**	92:8 (**6***S*:**6***R*)	96
10	**3**; R_1 = Ph	Li[MeCuI]/TMSI	**5**	92:8 (**5***S*:**5***R*)	80

[a] Based on isolated and purified material (a+b).
[b] Ratio determined from the crude ^{1}H NMR spectrum.
[c] Precomplexed $MgBr_2OEt_2$ (1 equiv.) and imide **1** at +20°C.
[d] $MgBr_2OEt_2$ added to RCu at −78°C.
[e] CuI (1 equiv.) versus PhMgCl.

Table 2. Asymmetric conjugate addition to valine-derived oxazolidinone **7**



Entry	Reagent (RCu)	Product	Ratio (a:b)[b]	Yield (%)[a]
11	Li[*n*-BuCuI]/TMSI	**8**	95:5 (**8***R*:**8***S*)	88
12	*n*-BuMgBr/CuI	**8**	21:79 (**8***R*:**8***S*)	75[d]
13	Li[*t*-BuCuI]/TMSI	**9**	85:15 (**9***S*:**9***R*)[c]	92
14	Li[PhCuI]/TMSI	**10**	93:7 (**10***S*:**10***R*)	92

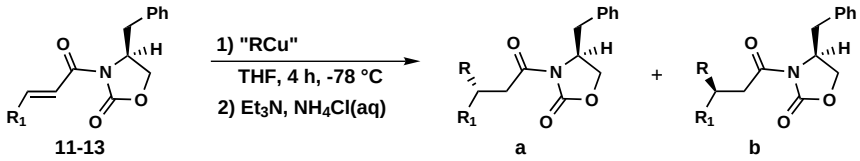
[a] Based on isolated and purified material (a+b).
[b] Ratio determined from the crude ^{1}H NMR spectrum.
[c] *R*/*S* assignment based on analogy.
[d] CuI (1 equiv.) versus BuMgBr.

conformation via chelation by RMgX to the carbonyl oxygens within the imide (Scheme 1).[12c]

A similar chelation model has been proposed for the copper-promoted conjugate addition of alkyl-zirconium reagents to *N*-acyl oxazolidinones.[13a] The TMSI-promoted additions of monoorganocuprates seem instead to undergo an initial copper-π complex formation followed by an alkyl transfer via the more stable non-chelated *anti-s-cis* conformation. A large difference in energy between the two conformations is most likely caused by the electrostatic repulsion between the carbonyl oxygen atoms in the non-chelated structure. Addition of scavenger chelating agents to the organocopper reagent such as magnesium bromide (entry 3) or lithium iodide (8 equiv.) did not appear to affect the de nor the yield for the TMSI activated additions of Li[RCuI]. On the other hand, the 'forced' complexation between $MgBr_2$ and imide **1** has a tremendous effect on the conjugate addition of Li[BuCuI] (entry 2). The precomplexed $MgBr_2$/imide and the Grignard reagents seem to react with the imide adopting the *syn-s-cis* conformation.

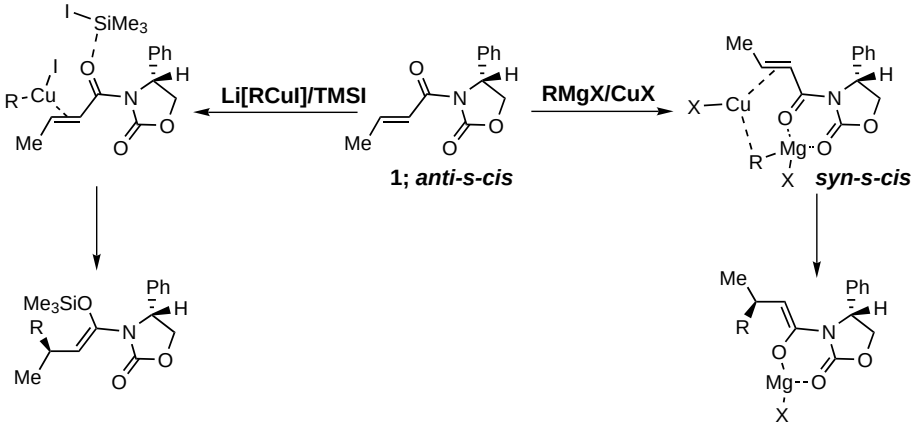
The copper-promoted Grignard reagent additions in THF were faster than the analogous additions using Li[RCuI]/TMSI in THF. Thus, quenching a Li[PhCuI]/TMSI reaction at −78°C after 2 h showed 50% consumption of substrate **1** while the addition of PhMgCl/CuI was complete within 2 h at −78°C. A relatively slow reaction at −78°C is most likely an important factor in obtaining a high de. In comparison, the additions of Li[MeCuI]/TMSI to substrates **2** or **3** gave 82–84% de of products **4** and **5**, while the corresponding MeMgBr/CuBr addition to the same cinnamate **3** has been reported to give only 48% de.[12d]

Table 3. Asymmetric conjugate addition to phenylalanine-derived oxazolidinones **11**–**13**



Entry	Substrate	Reagent (RCu)	Product	Ratio (a:b)[b]	Yield (%)[a]
15	**11**; R_1 = Me	Li[*n*-BuCuI]/TMSI	**14**	85:15 (**14***R*:**14***S*)	98
16	**11**; R_1 = Me	Li[*n*-BuCuI]/$MgBr_2$	**14**	50:50 (**14***R*:**14***S*)	71[c]
17	**11**; R_1 = Me	Li[PhCuI]/TMSI	**15**	87:13 (**15***S*:**15***R*)	86
18	**11**; R_1 = Me	Li[*t*-BuCuI]/TMSI	**16**	87:13 (**16***S*:**16***R*)[d]	85
19	**11**; R_1 = Me	PhMgCl/CuI	**15**	45:55 (**15***S*:**15***R*)	80[e]
20	**12**; R_1 = *n*-Bu	Li[PhCuI]/TMSI	**17**	88:12 (**17***S*:**17***R*)	87
21	**12**; R_1 = *n*-Bu	Li[MeCuI]/TMSI	**14**	82:18 (**14***S*:**14***R*)	86
22	**12**; R_1 = *n*-Bu	Li[MeCuI]/BF_3OEt_2	**14**	–	0[f]
23	**13**; R_1 = Ph	Li[*n*-BuCuI]/TMSI	**17**	90:10 (**17***R*:**17***S*)	91
24	**13**; R_1 = Ph	Li[MeCuI]/TMSI	**15**	86:14 (**15***R*:**15***S*)	83

[a] Based on isolated and purified material (a+b).
[b] Ratio determined from the crude ^{1}H NMR spectrum.
[c] Precomplexed $MgBr_2OEt_2$ (1 equiv.) and imide **11** at +20°C.
[d] *R*/*S* assignment based on X-ray structure of pure **16a**.
[e] CuI (1 equiv.) versus PhMgCl.
[f] 94% recovery of **12**.



Scheme 1.

Using TMSI as an additive is crucial for the successful addition of the noticeably more soluble Li[RCuI] reagent in THF at −78°C.[6] On the other hand, TMSI does not influence the stereoselectivity when applying the copper(I)-promoted PhMgCl to crotonate **1** (entry 6).

We were also interested in the substituent effects of the chiral auxiliary group on the stereoselectivity using the organocopper reagents. The capacity of the phenylglycine-derived auxiliary using the Li[RCu]I/TMSI was compared to the corresponding valine- and phenylalanine-derived oxazolidinones.

The valine-derived auxiliary **7** is slightly less efficient at blocking one π-face using the Li[RCuI]/TMSI reagent in conjugate addition reactions. Conjugate addition of Li[PhCuI]/TMSI to **7** (entry 14) gave **10a** in 86% de compared to the 92% de of **5a** obtained using the phenylglycine-derived oxazolidinone **1** (entry 4). As expected, excess of the opposite diastereomer (**8b**, 58% de) was obtained using copper-promoted addition of BuMgBr (entry 12), while the TMSI activated conjugate addition of Li[BuCuI] provided an excess of the other diastereomer (**8a**, 90% de).

We initially paid some attention to the phenylalanine-derived oxazolidinones **11**–**13**. Employing the TMSI-promoted organocopper reagents provided superior diastereomeric ratios compared to the copper-promoted Grignard reagent additions to the same substrates (Table 3). TMSI-promoted addition of Li[PhCuI] to **11** gave 74% de of **15** with **15a** as the major isomer (entry 17), while the corresponding copper-promoted addition of PhMgCl in the presence of 1 equiv. CuI showed a complete lack of π-facial selectivity (entry 19).[16] The

Li[MeCuI]/TMSI protocol was compared to Li[MeCuI]/BF_3OEt_2 under identical reaction conditions (entries 21–22). Thus, the TMSI-promoted reaction gave 86% of **14**, while the presence of BF_3OEt_2 did not give any conjugate addition product **14**. Li[BuCuI] underwent a smooth conjugate addition at −78°C to the precomplexed $MgBr_2$/imide **11** (entry 16) in 71%. This lack of stereoselectivity in the conjugate addition seems consistent using chelating reagents and the *N*-enoyl phenylalanine-derived oxazolidinone.

In conclusion, the Li[RCuI]/TMSI reagent is a very powerful tool in asymmetric conjugate additions to *N*-enoyl oxazolidinones. In particular, the phenylglycine-derived auxiliary is most efficient in blocking one π-face of the imide employing the Li[RCuI]/TMSI protocol. It is proposed that the Li[RCuI]/TMSI reagent reacts in the most favored *anti-s-cis* conformation, while $MgBr_2OEt_2$, or the more Lewis acidic RMgX/CuI reagent, favors the *syn-s-cis* conformation. We have also demonstrated that the valine-derived auxiliary is excellent in shielding one π-face of the imide in the conjugate additions using the Li[RCuI]/TMSI system. The phenylalanine-derived auxiliary provided moderate stereoselectivities (∼70% de) using the Li[RCuI]/TMSI protocol compared to the nearly complete lack of de's using copper-promoted conjugate additions of Grignard reagents. Taking advantage of $MgBr_2$ as a Lewis acid in asymmetric conjugate additions of organocopper reagents is currently under investigation in our laboratories.

Typical procedure: Methyllithium (1.4 M in diethyl ether, 1.83 mmol) was added under argon to a slurry of purified CuI[17] (2.15 mmol) in distilled THF (10 mL) at −40°C. After 20 min, the temperature of the orange heterogeneous methylcopper was lowered to −78°C and iodotrimethylsilane (1.83 mmol) was added via gas-tight syringe. Substrate **2** (0.732–1.46 mmol) dissolved in dry THF (7–10 mL) was added slowly via the cooled flask-wall. The resulting reaction mixture was stirred for 4 h at −78°C and freshly distilled Et_3N was added. Aqueous NH_4Cl/NH_3 (2–3 mL) was subsequently added at −78°C. The color of the excess orange methylcopper immediately collapses and the resulting heterogenous mixture was stirred for an additional hour at −78°C. The temperature of the mixture was allowed to reach ambient temperature, water (10 mL) and diethyl ether (20 mL) was added and the mixture stirred until the aqueous phase turned deep blue.[18] The organic layer was separated and the aqueous layer washed with ether (2×10 mL). Combined organic phases were dried with magnesium sulfate and the solvent removed under reduced pressure. The diastereomeric ratio was determined on the crude material (**4a**/**4b**; 82% de) on well resolved signals in the ^1H NMR spectrum. Product **4** was next purified using flash chromatography (30% diethyl ether in hexanes; R_f 0.40) to give 84% yield (based on substrate **2**).[19] The chiral auxiliary was subsequently removed using $LiBH_4$ in ether[15] to give (*R*)-3-methylheptanol[20] in 82% ee.

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