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Diastereoselectivity in Iodotrimethylsilane-promoted Conjugate Additions of Organocopper Reagents to Chiral α,β-Unsaturated Imides and Amides

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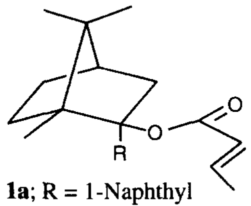
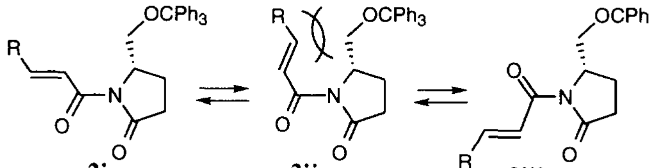
Abstract - *Conjugate additions of MeCu, PhCu and BuCu to the chiral enoylimides **2 a-c** in the presence of iodotrimethylsilane and lithium iodide in THF give the adducts, **4a-c** in yields above 90 % and diastereoselectivities from 80 to 93%. The dominating diastereomers are different from those formed with $LiR_2Cu/TMSCl$ or in copper(I)-mediated addition of Grignard reagents. Corresponding additions to enoylamides of* O-*tritylprolinol also give high yields of conjugate adducts, but lower diastereoselectivities, with dominating configuration in the acyl part opposite to those from the imides.*

There are now several chiral auxiliaries available for stereochemical control in conjugate additions with organocopper reagents,[1] and the field has been reviewed recently.[1,2] The combination of a monoorganocopper compound, lithium iodide and iodotrimethylsilane (TMSI) gives fast and efficient conjugate additions to α,β-unsaturated ketones and esters.[3] We have reported high asymmetric induction in the addition of butylcopper to the chiral bornyl crotonates **1** in the presence of TMSI and LiI,[4a] and that cuprate additions gave the other diastereomer.[4b] We interpreted this difference as reactions of the s-*trans* and s-*cis* conformers of the substrate, respectively.



1a; R = 1-Naphthyl
1b; R = Phenyl



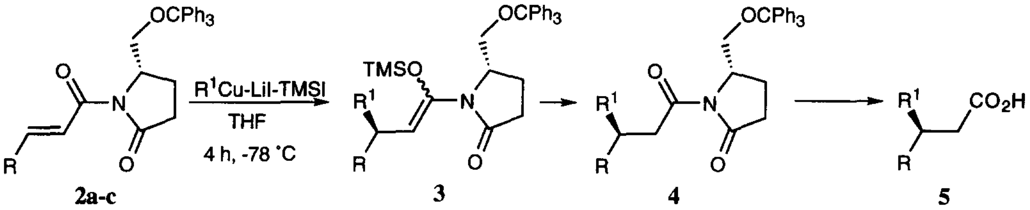
2i **2ii** **2iii**

2a; R = Ph
2b; R = Bu
2c; R = Me

We can now report that monoorganocopper reagents add to Koga's chiral glutamic acid-based imides, **2**,[1b] in the presence of TMSI and LiI in THF to give one strongly dominating diastereomer **4** in yields above 90%. Copper(I)-mediated additions of Grignard reagents[1b] and additions of silylcuprates in the presence of Mg[1c] to these substrates are known to give high excess of the other diastereomer, lower excess being obtained with LiR_2Cu, perhaps due to lower degree of chelation of the *syn*-s-*cis* conformer **2i.**[1b]

The additions of methyl-, butyl- and phenylcopper with TMSI and LiI were highly regio- and stereoselective and produced the configuration of the new acyl part as shown in formula **4/5.** The diastereoselectivity is highest (93 %) for the cinnamoylimide **2a**,[1c] and drops with decreasing size of the β-substituent to moderate for the heptenoylimide **2b**,[1b] and to 82 % for the crotonoyl imide **2c.**[1b] We measured the stereoselectivities by integrating well resolved ^1H-NMR signals of the crude imides and confirmed configuration and e.e. by optical rotation of the acids, **5**, easily obtained by hydrolysis.[1b]

An excess of RCu-LiI-TMSI proved important both for yield and for selectivity; we used 1.4 equiv. of RCu-LiI-TMSI with imides **2b** and **2c**, and 2 equiv. with imide **2a.**[3] With 1.4 equiv. of BuCu-LiI-TMSI with imide **2a**, yield and diastereoselectivity dropped to 59% and 83%, respectively. A proper work-up is important and direct hydrolytic work-up sometimes gave irreproducible results. Addition of pyridine at –78 °C after complete reaction but before the aqueous quenching provides high and reproducible yields and gives silyl ketene imides (**3**) as the primary products.

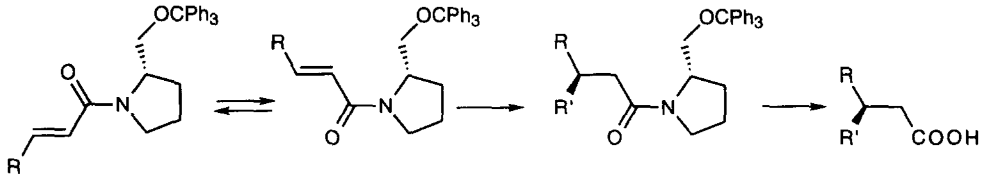


Unsaturated tertiary amides are known to prefer s-*cis* conformation.[5] Assuming planar conformations of the imides we rationalise the observed dominating configuration at the β-carbon by assuming attack on the less hindered side of the *anti*-s-*cis* conformer **2iii**, or on the crowded *syn*-s-*trans* conformer **2ii**. The latter would be in analogy with the bornyl crotonates.[4] The *syn*-s-*cis* form **2i**, suitable with chelating ligands,[1b] should give the other diastereomer. Planarity is not self-evident, however, and preliminary AM1 calculations indicate a non-planar conformation of the "enone" system with a low barrier for rotation.

The high selectivity could indicate a simultaneous activation of one carbonyl group and the olefinic double bond with TMSI and the organocopper reagent, perhaps with simultaneous co-ordination of TMSI to copper. The use of THF is important. In contrast to conjugate additions of lithium diorganocuprates the reactions with RCu-LiI-TMSI are faster in THF than in diethyl ether. This could partly be due to the higher solubility of the copper reagent and could also indicate that co-ordination of lithium to carbonyl groups is not so important in these reactions. In ether the reactions with BuCu-LiI-TMSI are slow and incomplete giving complex mixtures. In ether at –78 °C LiBu$_2$Cu/TMSCl opens the lactam ring of imide **2c** in 70% yield and gives only 25% of adduct **4c** as the *R*-diastereomer (70% d.e.). On the other hand we obtain 94% yield of the *S*-diastereomer (80% d.e.) from LiPh$_2$Cu-TMSCl (1.6 equiv.) and the crotonylimide **2c** in THF, in sharp contrast to the *R*-diastereomer obtained from addition of PhCu-LiI-TMSI to the same imide (entry 5). The "stereochemical switch" between RCu-LiI-TMSI and lithium organocuprate is analogous to what we observed for bornyl crotonates,[4b] to corresponding additions to methyl (*S*)-3-[2(1-dimethylaminoethyl)phenyl]-propenoate[6] and to those reported by Fleming[1c] and by Oppolzer.[1a]

Trimethylsilyl triflate, BuCu-LiI and **2a** gave the same yield (93%) as TMSI and a slightly lower d.e. (85%) of the same diastereomer. TMSBr[7] and TMSCN[8] gave complex mixtures and yields around 30 % of conjugate adducts when reacted with BuCu-LiI and **2a**. Enamides add lithium diorganocuprates in the presence of TMSCl.[9] The good results with the imides made us consider also enoylamides of *S*-*O*-tritylprolinol (**7**), obtained by acylations of prolinol with acid halides and pyridine followed by reaction with trityl chloride and triethylamine/DMAP. The amorphous amides (analysis, NMR and HRMS) gave NMR spectra showing the existence of rotamers (60:40) at room temperature, presumably syn and anti at the amide bonds. This contrasts to the enoylimides and to corresponding amides with pyrrolidine. Again we added methyl-, butyl- and phenylcopper, as well as LiI and TMSI to the cinnamoyl- and crotonylamides **7** at –78 °C and raised the temperature when necessary. The yields of the conjugate adducts **8** were in the range 90 to 96 %. As expected, the reactions were somewhat slower. The diastereoselectivities could not be evaluated from the NMR spectra for amides **8** and are judged from the rotation of the acids. They were lower than those for the imides and in the range 41 to 58 %, highest in the addition of butylcopper to the cinnamoylamide.

The dominating diastereomers consistently were "opposite to" those formed from the imides, and correspond to those in formula **8**. For planar starting amides and favoured s-*cis conformation* the dominating reaction should proceed from the *anti*-s-*cis* conformer **7ii**.



7i **7ii** **8** **9**

The low diastereoselectivity could be a consequence of the presence of rotamers in comparable amounts. The results with the amides of *O*-tritylprolinol also show the importance of the ring carbonyl in the Koga imides. It obviously gives improved diastereoselectivity, it should accelerate the conjugate addition and should give a lower barrier of rotation. In copper-promoted additions with magnesium present[1b,c] the favoured chelation in **2i** seems important. Both for the imides and the amides one could consider a chelation involving the trityloxy group and a carbonyl group.

Table 1. Conjugate Additions of R^1Cu–TMSI–LiI (1:1:1) to Imides **2** and to Amides **7** in THF at –78 °C. D.e. for amide adducts could not be measured accurately in the NMR spectra

Entry	Substr/R	R^1Cu	Adducts, **4** and **8**			Acids (or alcohols*), **5** and **9**		
				Yield %	d.e. %	e.e.	$[\alpha]_D^{20}$	
1	imide/Ph (**2a**)	Bu	**4a**	93	93	>95, *S*	+34.4[a]	*c*=1.43, PhH
2	imide/Ph (**2a**)	Me	**4b**	99	93	89, *S*	+50.8[b]	*c*=1.44, PhH
3	imide/Bu (**2b**)	Ph	**4a**	92	89	87, *R*	–32.2[a]	*c*=2.15, PhH
4	imide/Bu (**2b**)	Me	**4c**	91	89	92, *R**	+2.83[c]	*c*=0.85, CH_2Cl_2
5	imide/Me (**2c**)	Ph	**4b**	94	93[d]	91, *R*	–52.3[b]	*c*=1.16, PhH
6	imide/Me (**2c**)	Bu	**4c**	95	82	85, *S**	–2.60[c]	*c*=0.88, CH_2Cl_2
7	amide/Ph (**3a**)	Bu	**8a**	92	–	58 *R*	–20.1	*c*=2.60, PhH
8	amide/Ph (**3a**)	Me	**8b**	96	–	52, *R*	–29.5	*c*=0.85, PhH
9	amide/Me (**3c**)	Ph	**8b**	90	–	41, *S*	+23.6	*c*=1.70, PhH
10	amide/Me (**3c**)	Bu	**8c**	95	–	50, *R*	+2.1[e]	*c*=1.00, PhH

(a) Measured at 578 nm; Lit. 11: $[\alpha]_{578}$ +34.4 (*c* = 8, PhH) for (*S*)-3-phenylheptanoic acid. (b) Lit. 11: $[\alpha]_D$ +57.23 (*c* = 9, PhH) for (*S*)-3-phenylbutanoic acid. (c) Determined after reduction of the acid to the corresponding alcohol; Lit 12: $[\alpha]_D$ –3.07 for (*S*)-3-methylheptanol. (d) The diastereomers separate on silica gel. (e) Lit. 11 $[\alpha]_D$ 4.20 (neat) for (*R*)-3-methylheptanoic acid.

In conclusion the reaction between RCu-LiI-TMSI and the α,β-unsaturated imides **2** (presumably as *anti*-s-*cis* conformers **2ii**) in THF is highly diastereoselective. By proper choice of R and R^1 one can therefore easily obtain the desired diastereomer or acid. The lower selectivity with the corresponding amides **7** is mainly due to the presence of two stable rotamers, but still demonstrates an important role for the ring carbonyl in the Koga imides, even without chelation.

EXPERIMENTAL

Enoyl imides were prepared from (*S*)-5(trityloxymethyl)-2-pyrrolidone: $[\alpha]_D^{20}$ +14.6 (*c* = 1.48, $CHCl_3$), lit. 1b $[\alpha]_D^{20}$ +13.7 ($CHCl_3$). RCuLiI was prepared from titrated organolithium reagents (Aldrich) and purified CuI in THF.[10]

Typical procedure. Colourless iodotrimethylsilane (0.70 mmol, 0.1 mL) was added dropwise to a suspension of BuCuLiI (0.70 mmol) in dry THF (7 mL) under argon at –60 °C and the mixture stirred for 5 min. The temperature was then lowered to –78 °C and imide **2c** (0.50 mmol, 212 mg) in THF (7 mL) was slowly added during *ca.* 20 min. *via* the flask-wall. The resulting mixture was then stirred for 4 h. at –78 °C. Excess of dry pyridine (0.50 mL) was then added dropwise and the mixture stirred an additional hour at –78 °C. Aqueous NH_4Cl/NH_3 (3 mL) was then added slowly. The heterogeneous mixture was the stirred an additional 1 h. at –78 °C. The temperature was then raised to *ca.* +20 °C and water (3 mL) was added. The two resulting homogeneous phases was transferred to a separatory funnel and diluted with ether (30 mL) and water (30 mL). After separation the aqueous layer was extracted with ether (3 X 30 mL). The combined organic layers were washed with dilute aqueous copper(II) sulfate, dried over sodium sulfate and filtered through a 3 cm pad of Celite. Evaporation of solvent gave the crude silyl ketene imide **5** (>90% purity), which was hydrolysed. Chromatography on a flash column with silica gel (20-30 % ether in pentane, then gave 231 mg (95%) of **4** in 82% d.e. The diastereomeric fractions were carefully checked by ^{1}H-NMR spectroscopy.

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