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Asymmetric Michael Addition Reactions Using Ethyl (*S*)-4,4-Dimethylpyroglutamate as a Chiral Auxiliary

Jesús Ezquerra,*[a] Lourdes Prieto,[a] Carmen Avendaño[b], José Luis Martos[b] and Elena de la Cuesta[b]

a. *Centro de Investigación Lilly, S. A. Avda de la Industria, 30. 28108-Alcobenda. Madrid. Spain.*
b. *Departamento de Química Orgánica y Farmacéutica, Facultad de Farmacia, Universidad Complutense, 28040- Madrid. Sapin.*

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Abstract:

Ethyl 4,4-dimethylpyroglutamate has been used as a chiral auxiliary for α,β-unsaturated acids in Michael addition reactions. The conjugate addition of Grignard reagents to the amides in the presence of copper iodide, tetramethylene diamine (TMEDA) and trimethylsilyl chloride, proceeded with high yields and excellent stereoselectivities, yielding after hydrolysis enantiomerically pure β-substituted carboxylic acid derivatives.

Keywords: Asymmetric reactions, Michael addition, Carboxylic acids and derivatives, Stereoselection

The stereoselective conjugate addition of nucleophiles to α,β-unsaturated acyl derivatives containing a chiral auxiliary has became one of the most efficient methods to prepare optically pure β-substituted carbonyl derivatives. Following this methodology, several β-branched carboxylic acids have been synthesized *via* asymmetric Michael additions to chiral oxazolidinones[1-4], ester[5,6], amide[7,8] or imide[9-21] derivatives. Thus, Evans's oxazolidinones **1a,b**[9-14] and related chiral auxiliaries like **1c**[16], (4*R*,5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone (**2**)[17,18] or trityloxymethyl-γ-butyrolactam (**3**)[19,20], have been linked to α,β-unsaturated acids to allow asymmetric conjugate addition of several nucleophiles (Figure 1).

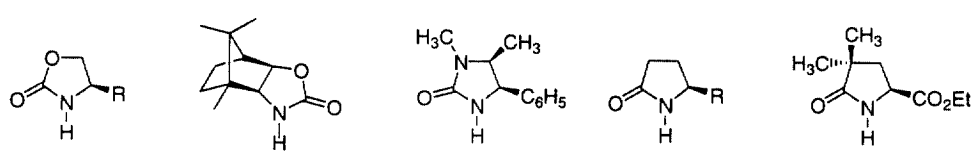

Figure 1

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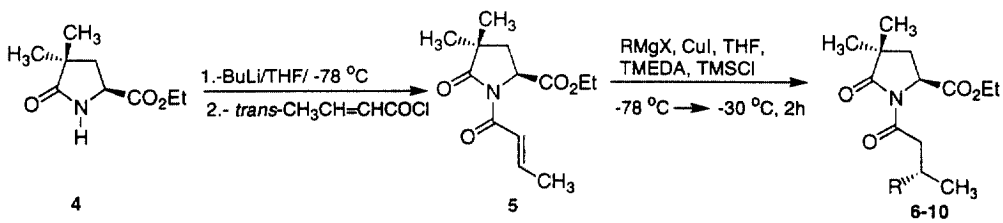
Recently, some of us have described the utility of ethyl (*S*)-4,4-dimethyl pyroglutamate (**4**) as a new "quat" chiral auxiliary in an aldol condensation[22], obtaining enantiopure (2*R*,3*R*)-3-hydroxy-2-methylpropionic acid in excellent yield and stereoselectivity. This chiral auxiliary is accessible from *N*-Boc-protected ethyl pyroglutamate by double alkylation of its lithium enolate with methyl iodide[23]. Remarkably, the potentially labile pyroglutamate C-2 stereogenic center, which is responsible for the asymmetric induction, was preserved during the aldol reaction and the chiral auxiliary was effectively recovered after the process. After these preliminary results, we report herein a further application of this chiral auxiliary in the conjugate addition reaction of Grignard derived organocopper reagents to α,β-unsaturated *N*-acyl fragments attached to **4**, as an effective means of preparing enantiopure β-substituted carboxylic acids.

Michael acceptor ethyl (*S*)-*N*-*trans*-2-butenoyl-4,4-dimethylpyroglutamate (**5**), was obtained from **4** by deprotonation with *n*-BuLi followed by treatment with crotonyl chloride in a 65% yield {$[\alpha]_D^{25}$ = -34.5 (c 0.31, CH_2Cl_2)} (Scheme 1).



Scheme 1

Table 1

Entry	Compound	RMgBr	Method[a]	Yield[b] (d.e.)[c]	$[\alpha]_D^{25}$
a	**6**	C_6H_5	A	35 (75)	
b	**6**	C_6H_5	B	80 (87)	
c	**6**	C_6H_5	A[d]	80 (>95)	
d	**6**	C_6H_5	C	81 (>95)	-21.7 (c 0.11, CH_2Cl_2)
e	**7**	C_2H_5	C	71 (>95)	-27.9 (c 0.19, CH_2Cl_2)
f	**8**	$CH(CH_3)_2$	C	70 (>95)	-36.0 (c 0.10, CH_2Cl_2)
g	**9**	c-C_6H_{11}	C	68 (>95)	-24.4 (c 0.11, CH_2Cl_2)
h	**10**	$CH{=}CH_2$	C	34 (>95)	-19.6 (c 0.28, CH_2Cl_2)

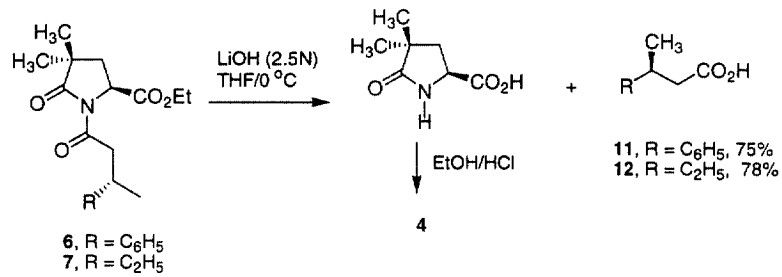
[a]**Method A**: THF-Me_2S/CuBr.Me_2S. **Method B**: THF-Me_2S/CuI.Me_2S. **Method C**: THF-TMEDA/TMSCl/CuI. [b]Isolated yield. [c]Determined by ^{1}H-NMR integration. Detection limit was determined by doping experiments. [d]TMEDA was used instead of Me_2S.

Attempts to perform the conjugate addition with phenylmagnesium bromide in the presence of catalytic amounts of CuBr.SMe_2 in THF[13] (Table 1, entry a) gave the Michael adduct **6** with a low yield (35%) and modest stereoselectivity (d.e. 75%). This poor reaction performance was improved by generating the Grignard derived organocopper reagent with copper iodide and using Me_2S as a reaction co-solvent[10] (entry b). The same chemical yield,

but a higher diastereomeric excess (d.e. > 95%), was obtained by replacing the Me_2S, by TMEDA (entry c). However, further extension of these reaction conditions to different Grignard reagents resulted in low yields and poor stereoselectivities.

We found that the best general reaction conditions, required the addition of TMSCl to generate the PhCu-TMEDA-TMSCl as an organocopper-Lewis acid reagent[24]. Good yields and excellent stereoselectivities were found using different aryl and alkyl Grignard reagents (entries d-g), except for the vinyl derivative **10** which was isolated in modest yield, probably due to a lower stability of the nucleophile. Notably the sterically undemanding ethylation, which is often difficult to control, proceeded with remarkable diastereoselectivity under these reaction conditions (entry e)

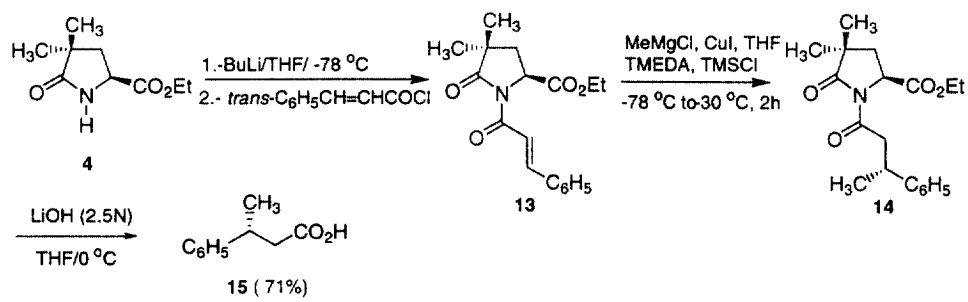
In order to confirm the *anti*-stereoselectivity of the Michael addition, adducts **6** and **7** were hydrolyzed under basic conditions[22], yielding a chromatography separable mixture of (*S*)-4,4-dimethylpyroglutamic acid (71% yield) and the corresponding β-branched carboxylic acids, (*S*)-3-phenylbutanoic acid (**11**) {75% yield, $[\alpha]_D^{25}$ = +46.0 (c 1, C_6H_6), lit [25] $[\alpha]_D^{22}$ = +52.0 (c 1.0, C_6H_6)} and (*R*)-3-methylpentanoic acid (**12**) {78% yield, $[\alpha]_D^{25}$ = -8.25 (c 1.0, $CHCl_3$), lit [26] $[\alpha]_D^{22}$ = -7.5 (c neat)}.



Scheme 2

Finally, the chiral auxiliary was quantitatively recovered by esterification of the (*S*)-4,4-dimethylpyroglutamic acid in EtOH/HCl(g), with no observable change in its chiral integrity[22].

A further application of **4** as a chiral auxiliary was in the synthesis of (*R*)-3-phenylbutanoic acid (**15**), the enantiomer of **11** (Scheme 3).



Scheme 3

The amide **13** was prepared by acylation of the chiral auxiliary with *trans*-cinnamoyl chloride {55% yield, $[\alpha]_D^{25}$ = -13.8 (c 0.06, CH_2Cl_2)}. Michael addition of the organocopper reagent derived from methylmagnesium chloride (method C) yielded the adduct **14** {78% yield, $[\alpha]_D^{25}$ = +20.9 (c 0.11, CH_2Cl_2), d.e. > 95%}, which upon basic hydrolysis gave rise to the corresponding (*R*)-3-phenylbutanoic acid (**15**) {71% yield, $[\alpha]_D^{25}$ = -49.4 (c 1, C_6H_6), lit [9] $[\alpha]_D^{22}$ = -54.2 (c 1.12, C_6H_6)}.

In conclusion, ethyl (*S*)-4,4-dimethylpyroglutamate (**4**) has been used as a chiral auxiliary for α,β-unsaturated acids in Michael conjugated additions with Grignard derived organocopper reagents. This new procedure gave good yields and excellent stereoselectivities, delivering enantiomerically pure β-branched carboxylic acids, after basic hydrolysis. Since the configurational stability at the C-2 stereogenic center was preserved, this new procedure complements the existing chiral auxiliary-based technologies and will be applied in other asymmetric transformations.

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