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## Stereoselective synthesis of $\beta^2$ -amino acids by Michael addition of diorgano zinc reagents to nitro acrylates

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Abstract—Phosphoramidite-derived copper(I) catalysts readily facilitate the enantioselective 1,4-addition of dialkyl zinc reagents to nitro acrylates. The resulting 2-substituted 3-nitro propionic acid esters can easily be transformed to  $\beta^2$ -amino acids. © 2003 Elsevier Science Ltd. All rights reserved.

The synthesis of rare and unnatural amino acids in their stereochemically pure form has been the subject of intense research for decades. Because of their relevance to many processes in living matter, β-amino acids continue to attract particular attention of many synthetic chemists.<sup>1-5</sup> While quite a number of synthetic approaches towards enantiopure  $\alpha$ - and  $\beta^3$ -amino acids are known,<sup>6–11</sup> facile synthesis routes to the 2-branched β-amino acids are rare and limited to single compounds.<sup>11–15</sup> This fact contrasts the importance of those compounds which were found to be essential sub-structures and building blocks in peptides and naturally occurring compounds. Some of these molecules show high cytostatic or anti-viral activity or exhibit other unusual properties.<sup>16–18</sup> The tumour suppressing cryptophycines from marine sponges are good examples.<sup>19-21</sup>

In our efforts to develop a synthesis route which allows an economically feasible production of  $\beta^2$ -amino acids, we tried to avoid a diastereoselective approach with its known drawbacks, especially for industrial applications.<sup>22,23</sup> Instead we favoured a catalytic strategy based on our and others experiences in the 1,4-addition of dialkylzinc reagents to Michael acceptors.<sup>24–29</sup> A retro synthetic analysis prompted us to investigate the reaction of dialkylzinc reagents with nitro acrylic acid esters as Michael acceptors. The resulting 2-substituted 3nitro acrylates should be ideal intermediates for the synthesis of the respective  $\beta^2$ -amino acids. The required zinc reagents are readily available. Many dialkylzinc reagents can be purchased in bulk quantities, others, especially those containing functional groups are accessible by the method of Knochel.<sup>30–32</sup> Nitro acrylates can be made by standard procedures.<sup>33–35</sup>

As far as the catalyst is concerned, we and others have shown the value and suitability of copper(I) based molecules for such 1,4-additions.<sup>24,36,37</sup> While nitro acrylates represent two-fold Michael acceptors, the nitro group is known to be the strongest Michael acceptor and hence should desirably direct the C–C coupling to the C-2 atom.<sup>28,38,39</sup>

In order to check the scope and limitations of the reaction between dialkylzinc reagents and nitro acrylates, we tested several known ligands for the copper ion, mainly phosphites and phorphoramidites.<sup>25,38,40,41</sup> We found that all catalysts employed regioselectively facilitate the reaction. Moderate enantioselectivities were observed with most catalysts.



Only the Feringa-type BINOL-based ligand 1 and its enantiomer turned out to transfer the stereochemical information efficiently. Enantiomeric excesses of up to 87% could be obtained.

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Using ligand 1, we started with diethylzinc and nitro acrylic acid methyl ester to investigate the influence of the solvent on the reaction. Then we varied the ester R' for the optimal solvent and finally other alkylzinc reagents were tested for the most appropriate substrate. Representative results, obtained with 0.5 mol% catalyst<sup>†</sup> at  $-78^{\circ}$ C are shown in Table 1.<sup>‡</sup>

In contrast to the enantiomeric excess, the yields are nearly independent from the reaction conditions employed. The reaction proceeds with high regioselectivity to give the desired product. As can be seen from the data, solvents without donor atoms only give rise to

Table 1. Yields and enantiomeric excesses of 2-substituted3-nitro propionic acid esters with respect to solvent(THF-tetrahydrofuran, DCM-dichlormethane, T-toluene,DEE-diethylether, TBME-tertiary butyl methyl ether),substrate and reagent

R	R′	Solvent	Yield (%)	ee (%)
Ethyl	Methyl	DCM	20	5
		Т	93	13
		THF	98	25
		DEE	96	86
		TBME	94	85
Ethyl	Methyl	TBME	94	85
	'Butyl		97	87
	Benzyl		92	85
Methyl <sup>a</sup>	Methyl	TBME	97	18
Ethyl			94	85
<sup>i</sup> Butyl			96	79

<sup>a</sup> 1 h -78°C, then -30°C (1 h)

low ee values. The probable coordination of solvent molecules to the active complex has been discussed earlier.<sup>42</sup> Dialkyl ethers are the solvents most appropriate with the cheap TBME being the solvent of choice. The nature of the ester (R') does not influence either the yield or the enantiomeric excess of the product. Aiming towards amino acids, the substrate should on the one hand easily be saponified, while on the other hand, it should boil at a low temperature, since a safe distillation of this potentially explosive substance is required for purification: the methyl ester meets these requirements best.

In our first experiments, we restricted ourselves to three dialkylzinc reagents. While both diethyl- and diisobutylzinc yield the respective products with an enantiomeric excess of about 80%, dimethylzinc only resulted in an enantiomeric excess of 18%. The reason for this poor performance is likely to be the elevated reaction temperature,<sup>§</sup> which was necessary because of the low reactivity of dimethylzinc in comparison to the other alkylzinc reagents.

Each of the three 2-substituted 3-nitro propionic acid esters can readily be transformed to the respective  $\beta^2$ -amino acid via catalytic hydrogenation and subsequent saponification.<sup>¶</sup> The overall yield is 60–65%, calculated for the nitro acrylates. No racemisation occurs during these following reactions, as can be proved by capillary zone electrophoresis using  $\gamma$ -cyclodextrins as geometric selectors. After one recrystallisation of the hydrochlorides, the compounds are enantiomerically pure (ee >98%).

Hence, the outlined reaction sequence is a promising approach towards enantiomerically pure 2-branched  $\beta$ -amino acids. Despite the required low temperatures, the process is economically feasible. The high catalytic efficiency, the cheap substrate and the availability of several organozinc reagents are not the only reasons for that finding. The tolerance of organozinc reagents to functional groups in the alkyl chains and the fact that one compound serves as a substrate for various products, increases the potential of this synthesis.

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<sup>§</sup> Changed experimental conditions for this kind of reaction, which were published recently, could result in higher ee values here as well.<sup>43</sup>

<sup>&</sup>lt;sup>†</sup> Ratio Cu(I)tfa:1=1:2; a reduction of the catalyst concentration from 2 to 0.1% had no distinct influence on the product purity; however, lower amounts negatively effect the enantioselectivity. The (R,S,S)-ligand yields the (S)-, the (S,R,R) ligand yields the (R)configuration. The copper(II) ion is being reduced to Cu(I) in situ by dialkyl zinc.

<sup>&</sup>lt;sup>‡</sup> Illustrative procedure: 40 mg copper(II) trifluormethane sulfonate and 125 mg 1 are stirred together in 40 ml dry TBME under an argon atmosphere for 1 h. After cooling to -78°C, 2.5 ml diethylzinc is added via syringe. Then, a solution of 2.5g nitro acrylic acid methyl ester in 10 ml dry TBME are added (ratio R<sub>2</sub>Zn:substrate= 1:1). The solution is stirred at -78°C for 10 min and quenched afterwards with 30 ml 2 M hydrochloric acid. After warming to rt, the organic layer is separated, washed twice with water, dried and evaporated.

<sup>&</sup>lt;sup>¶</sup> Pd/C (10%), 20 bar; hydrochloric acid, 3 N, 3 h.

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