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Stereoselective Michael addition of trimethyl aluminium to nitro acrylates: a route to 2-methyl-3-amino propionic acid

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Dedicated to Professor Klaus Burger on the occasion of his 65th birthday

Abstract—The copper(I)-catalysed Michael addition of trimethyl aluminium to nitro acrylates yields 2-methyl-3-nitro propionic acid esters on a 200 g scale with enantiomeric excesses up to 92%.

Unnatural and rare amino acids as sub-units of complex molecules have been found to possess outstanding importance in terms of their biological activity and other relevant properties.[1,2] This applies to natural compounds such as cryptophycines and the antifungal cispentacin as well as to synthetic substances such as peptitic and non-peptidic lead structures for biological targets.[3–9] In spite of prior intense research on β-amino acids, synthesis and application, especially of this compound class, remains a compelling target of both chemists and biochemists.[10–12]

In this regard, the development of stereoselective and economically feasible synthesis routes towards 2-branched β-amino acids is a challenging task as it proved to be more complicated in comparison to their well investigated 3-substituted counterparts.[10,13–16] While quite a number of diastereoselective approaches are known, the atom efficient and more desirable enantioselective catalytic syntheses to β^2-amino acids are scarce.

Extensive research has been carried out on the copper-mediated catalytic Michael addition of organyls to appropriate acceptors.[17–19] Various chiral non-racemic ligands were found to facilitate distinct stereoinduction, among them Feringas' phosphoramidites and Alexakis' phosphites.[19–24] While the cheap aluminium organyls are known to act similarly, most research focuses on the 1,4-addition of organo zinc and organo magnesium compounds to α,β-unsaturated molecules.[17,25–28]

Continuing our and others' investigations on the synthesis of β^2-amino acids via Michael addition of organo metals to nitro acrylates and their derivatives, we extended this approach to aluminium organyls which are readily available as they are produced on an industrial scale.[26,29–32] Up to now, the reaction of aluminium organyls to α,β-unsaturated compounds has been mainly restricted to enones with emphasis on cyclic derivatives.[19,33,34] Attempts to add trimethyl aluminium to vinylic enones, to α,β-unsaturated esters and to nitro alkenes were reported to be unsuccessful.[33] Therefore, neither a regioselective nor even a stereoselective reaction with nitro acrylates, being a twofold Michael acceptor and bearing the reactive nitro group, could be expected.

We have succeeded in finding appropriate reaction conditions for this desired process, employing trialkyl aluminium R_3Al, which regioselectively yields the 2-substituted 3-nitro propionic acid esters. Chemical yields and stereoselective discrimination strongly depend upon the nature R, being optimum at R = methyl.

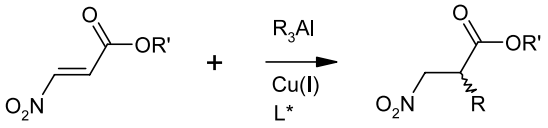

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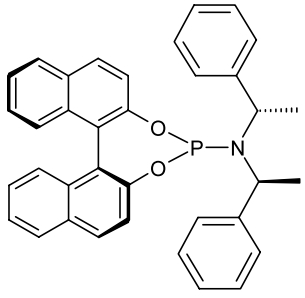
Table 1. Dependence of the yield and enantiomeric excesses of 2-substituted-3-nitro propionic acid methyl ester on reagent and solvent (THF, tetrahydrofuran; T, toluene; DCM, dichloromethane; DEE, diethylether; TBME, tertiary butyl methyl ether); isolated yields (ee/%)

R/Solvent	THF	T	DEE	TBME	DCM
Methyl[a]	15 (0)	40 (<5)	92 (92)	74 (85)	5 (0)
Ethyl[b]	18 (15)	0 (0)	69 (60)	60 (65)	–
Isobutyl[c]	20 (0)	3 (0)	71 (15)	67 (25)	–

[a] Temperatures: addition of R_3Al at −60°C, addition of the nitro acrylate and subsequent reaction at −50°C.
[b] Temperatures: addition of R_3Al at −78°C, addition of the nitro acrylate and subsequent reaction at −60°C.
[c] Temperatures: addition of R_3Al at −30°C, addition of the nitro acrylate and subsequent reaction at 0°C.

Regarding the chiral nonracemic ligand L*, we restricted ourselves to several of the well-investigated phosphites and phosphoramidites which have already shown their potential in the respective addition of dialkyl zinc compounds.[20,28,32]

Once more, Feringa's BINAP derived ligand **1** proved to be quite universal for this reaction type.



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Representative results, obtained with 1 mol% catalyst,[†] are shown in Tables 1 and 2.[‡]

While initial attempts to reproducibly add trialkyl aluminium compounds to nitro acrylates also failed in our laboratories, the prior reduction of the copper catalyst by a small amount of diethyl zinc proved to be the essential step to facilitate this reaction. Only by employing diethyl zinc first, did the characteristic orange colour indicated the forming of the copper(I)–**1** complex. Using this procedure, it was possible to synthesise the product on a 200 g scale with only 0.1 mol% catalyst.

Table 2. Dependence of the yields and enantiomeric excesses of 2-methyl 3-nitro propionic acid esters on substrate and solvent; isolated yield (ee/%) (R = Methyl)

Solvent	R′ = Methyl	R′ = Ethyl	R′ = *t*-Butyl	R′ = Benzyl
T	40 (<5)	18 (<5)	6 (0)	10 (0)
DEE	92 (92)	85 (92)	76 (88)	74 (84)
TBME	74 (85)	70 (85)	68 (82)	70 (75)

The temperatures stated in Table 1 were found to be the optimum in terms of reaction time and enantioselectivity. As can be seen from the data, many of the obtained results—concerning yields and enantiomeric excesses—are not too impressive. A clear exception is the conversion of trimethyl aluminium which gives the product in excellent chemical yields and good enantiomeric excesses. This dependence of comparable Michael additions on the nature of the aluminium organyl with the preference of the methyl derivative has already been observed by others and has been attributed to a AlR_3 dependent substrate binding pocket.[33]

Table 2 shows that the nature of R′ does not significantly effect the reaction, although the short alkyl esters give slightly better results. In contrast to these findings, the solvent dependence of the reaction is remarkable. As stated for similar reactions, ethers turned out to give the best ee values.[22,32,34] The poor performance of non coordinating solvents such as toluene and DCM prove the importance of donor atoms for the information transfer.[35]

With respect to scale-up and economic feasibility, the use of TBME as a cheap solvent and the nitro acrylic acid *methyl* ester as the substrate, which can easily be distilled and saponified, are preferred.

The good results for the reaction of trimethyl aluminium are in fact superior to those obtained with the slowly reacting dimethyl zinc in a comparable synthesis, hence offering an interesting alternative for the 2-methylated 3-nitro propionic esters.[32] While the ethyl-

[†] Molar ratio Cu(I)tfa / **1** = 1:2.
[‡] Representative procedure: 30 mg copper(II) trifluoromethane sulfonate and 94 mg **1** are stirred in 30 ml dry ether under an inert atmosphere. Then, 0.3 ml 1 m diethylzinc solution in hexan is added before stirring for 1 h. The orange solution is cooled to the stated temperature before the neat trialkyl aluminium is added via syringe. After 30 min stirring at this temperature, a clear yellow to brown solution has formed. Then, the nitro acrylic ester (0.0083 mol) in 10 ml ether is added at the temperature given in Table 1 and stirring at the respective temperature is continued for 60 min (ratio R_3Al:substrate = 1:1). The solution is quenched with 30 ml 2 M hydrochloric acid and allowed to warm to room temperature. The organic layer is separated, washed twice with water, dried and evaporated.

and isobutyl aluminium organyles do not appear comparatively useful, our first experiments, especially those carried out in diethyl ether, are promising starting points for further optimisations. Replacement of the catalyst salt by copper carboxylates has been advised as being advantageous in comparable reactions.[22]

As described earlier, the 2-substituted 3-nitro propionic acid esters can easily be transformed to the respective β^2 amino acids.[§] One recrystallisation of the hydrochlorides increases the stereochemical purity to >98%.

In summary, the use of trialkyl aluminium compounds for copper(I)-mediated Michael additions to nitro acrylates offers a promising alternative to the well established magnesium and zinc organyls each of them having specific advantages and drawbacks. While the atom efficiency of the trialkyl aluminium compounds with only one alkyl being transferred is comparatively low, the availability and low price of these compounds make up for this drawback.

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[§] 1. Catalytic hydrogenation: Pd/C (10%), 20 bar, hydrochloric acid, 3N, 3 h; 2. Saponification: 2N NaOH, rt, 12 h.