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Synthesis of α,α–Disubstituted-α-Amino Acids by Double Nucleophilic Addition to Cyanohydrins

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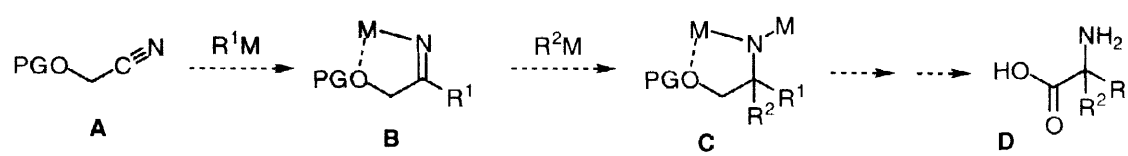
Abstract: The synthesis of tertiary carbinamines was achieved by the double nucleophilic addition of Grignard reagents to cyanohydrins. Titanium isopropoxide was found to promote the process. In a typical example, the rapid conversion of a carbinamine to the coresponding α,α-disubstituted-α-amino acid was also demonstrated. © 1998 Elsevier Science Ltd. All rights reserved.

Quaternary α-amino acids are an important class of compounds since they can induce physical and chemical changes in peptides.[1] Dramatic conformational effects are observed when the α-proton of a natural amino acid is replaced by a methyl group.[2] Typically, these compounds have been prepared by enolate alkylation of substituted glycine derivatives[3] or by the Strecker-type reactions.[4] An alternative approach to these amino acids involves the oxidation of α-hydroxy carbinamines which can be readily obtained by a double nucleophilic addition to protected cyanohydrins (Figure 1).[5] Unfortunately, very few cases of efficient double nucleophilic additions to nitriles have been reported. Moreover, this reaction usually gives low yields and the structural diversity of the nucleophiles used is usually very limited. A classical example of a double nucleophilic addition to CN triple bond involves the addition of allylmagnesium bromide on the iminate generated by the addition of a Grignard reagent.[6] Herein, we report that the nucleophilic addition to iminate **B**, obtained by the addition of a Grignard reagent to a protected α-cyanohydrin **A**, is greatly promoted by the addition of titanium isopropoxide.[7]

Figure 1



Initially, we studied the sequential nucleophilic addition to cyanohydrins **1** and **2** using alkyl- and allylmagnesium bromide reagents. Only the corresponding ketone **3** could be obtained in high yields when nitrile **1** or **2** was treated sequentially with two different alkylmagnesium bromide or organolithium reagents. Clearly, these conditions did not allow the second addition to occur (**B** to **C**, Figure 1). Conversely, the second

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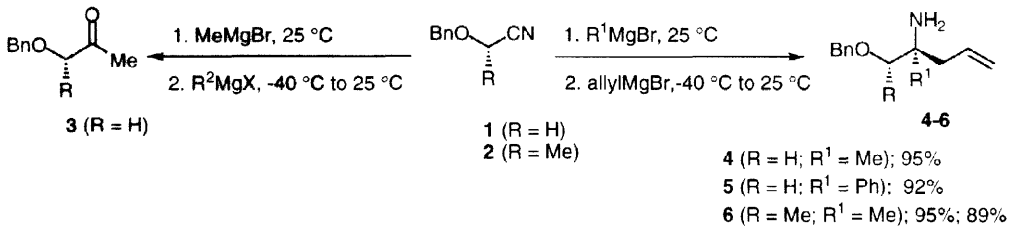
addition proceeded smoothly when allylmagnesium bromide was used as the second nucleophile. This higher reactivity of allylmagnesium bromide has been observed in the nucleophilic addition to imines.[8] Excellent yield and diastereoselectivity were observed with chiral α-substituted cyanohydrin **2** and the stereochemistry of the product is consistent with a chelation-controlled addition.[9] These derivatives are useful precursors to β-amino acids.[10]

Scheme 1



3 (R = H)

1 (R = H)
2 (R = Me)

4-6

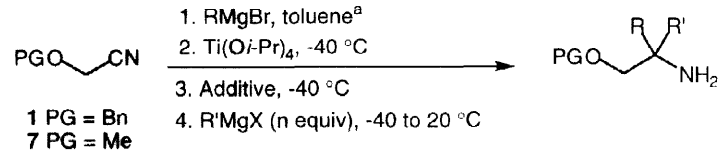
4 (R = H; R^1 = Me); 95%
5 (R = H; R^1 = Ph); 92%
6 (R = Me; R^1 = Me); 95%; 89% de

We then focused on the development of alternative conditions that allow sequential nucleophilic additions of two alkyl groups with the hope that this method should eventually be expandable to the synthesis of enantiomerically pure α,α-disubstituted-α-amino acid derivatives. We envisioned that the addition of a Lewis acid might increase the electrophilicity of the iminate resulting from the first nucleophilic addition and stabilize the product resulting from the double addition. Among several Lewis acids tested, Ti(O*i*-Pr)$_4$ was found to work the best. Moderate to good yields of the desired products were obtained when Ti(O*i*-Pr)$_4$ was added after the consumption of the cyanohydrin by the first nucleophile. The results of the titanium-promoted double nucleophilic additions on cyanohydrins **1** and **7** are shown in Table 1.

Entries 1 to 4 clearly demonstrate that the yield is low when ethylmagnesium bromide is used as the second nucleophile. Other experiments conducted in our laboratory have shown that Grignard reagents having protons in the β-position can undergo a β-hydride elimination side reaction.[11] However, addition of a chelating additive such as isopropanol (or the corresponding magnesium alkoxide) or pyridine slightly increased the conversion to the amine (entries 2 and 3). Conversely, triethylamine was not effective (entry 4). Symmetrical tertiary carbinamines can also be obtained by this method (entries 5 and 6). The yields are exceptionally high for the double addition of methylmagnesium bromide (entry 5) and satisfactory for the double addition of ethylmagnesium bromide (entry 6). The addition of methylmagnesium bromide to the iminate of the cyanohydrin **1**, obtained using EtMgBr as the first nucleophile, gave good yield of the corresponding carbinamine (entry 7). Unfortunately, the addition of isopropanol did not lead to a higher yield (entry 8). When the reaction was run with one equivalent of methylmagnesium bromide under reflux, a quantitative yield was obtained (entry 9). The choice of the first nucleophile is not limited to methyl- or ethylmagnesium bromide. For example, the addition of phenethylmagnesium bromide to cyanohydrin **1** or to the less hindered analog **7** proceeded smoothly to afford the desired amine in 50% yield or in 92% respectively (entries 10,11). Steric hindrance appears to be important since a 43% yield of the adduct was obtained when isopropylmagnesium

bromide was used as the first nucleophile (entry 12). When the second nucleophile is not prone to undergo β-hydride elimination, refluxing conditions can be used to produce reasonable yields of the amine (entry 13).

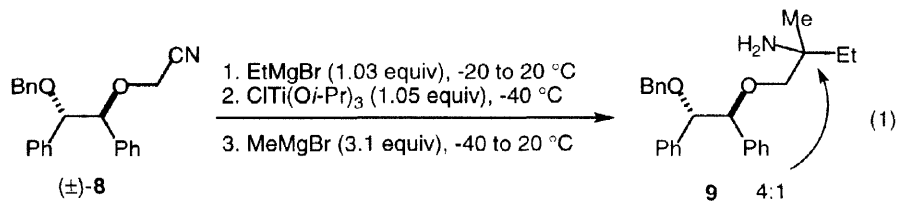
Table 1. Ti(O*i*-Pr)$_4$-promoted double nucleophilic addition to cyanohydrins[12]



Entry	R	Additive (equiv)	R'	n (equiv)	Yield (%)[b]
1[c]	Me	---	Et	3.05	15
2[c]	Me	*i*-PrOH (1)	Et	4.05	32
3[c]	Me	Pyridine (1)	Et	3.05	28
4[c]	Me	Et_3N (1)	Et	3.05	17
5[d]	Me	---	Me	---	96
6[e]	Et	---	Et	---	72
7	Et	---	Me	3.05	78
8	Et	*i*-PrOH (1)	Me	4.05	78
9[f]	Et	---	Me	1.05	100
10	$PhCH_2CH_2$	---	Me	3.05	50
11[g]	$PhCH_2CH_2$	---	Me	3.05	92
12	*i*-Pr	---	Me	3.05	43
13[f]	Me	---	Ph	1.05	60

[a]The reactions were done at 25 °C for benzyloxyacetonitrile or 0 °C for methoxyacetonitrile. [b]Isolated yields. [c]Conversion evaluated by ^{1}H NMR using phenanthrene as the internal standard. [d]Addition of 1 equiv of Ti(O*i*-Pr)$_4$ followed by 3 equiv of MeMgBr. [e]Addition on 3 equiv of EtMgBr followed by 1 equiv of Ti(O*i*-Pr)$_4$. [f]The solution is heated under reflux after the addition of the second Grignard reagent. [g]Methoxyacetonitrile was used as the starting material.

These conditions were also found to be quite effective for the addition of Grignard reagents to chiral, racemic nitrile **8**.[13] The sequential addition of ethyl- and methylmagnesium bromide produced the desired adducts in 62% yield as a 4:1 diastereomeric mixture.[14]

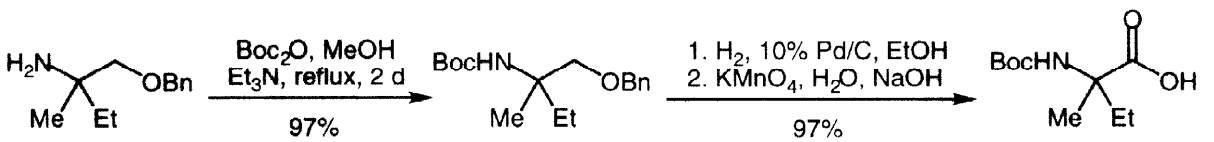


The formation of the racemic aminoacid **12** has been efficiently accomplished in 94% yield over three steps (Scheme 3). The amine was first protected as a Boc derivative and the alcohol was debenzylated and oxidized to the desired amino acid.

In summary, we have shown that the addition of allylmagnesium bromide to a cyanohydrin-derived chiral iminate can proceed with good selectivity *via* a chelate-type intermediate. We have also demonstrated that the Ti(O*i*-Pr)$_4$-promoted double nucleophilic addition to cyanohydrins proceeds relatively well. The method is very effective when the second nucleophile is an aryl or methylmagnesium bromide and the products

are efficiently converted into racemic α,α-disubstituted-α-amino acids. Research is currently underway in our laboratories to increase the scope of the method and to develop an enantioselective variation of this reaction.

Scheme 3



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12. To a stirred solution of the cyanohydrin in anhydrous toluene at 25 °C was added the first Grignard reagent. After disappearance of the starting material by tlc, the reaction was cooled to -40 °C and Ti(O*i*-Pr)$_4$ was added followed by the second Grignard reagent. The mixture was warmed to 25 °C and stirred overnight. A standard work-up afforded the crude amine which was purified by flash chromatography.
13. Obtained from stillbene diol: (a) PhCHO, TsOH, 96%; (b) DIBAL-H, 96%; (c) NaH, allyl bromide, 91%; (d) OsO_4, NMO; $NaIO_4$, >95%; (e) NH_2OH•HCl, AcONa; (f) DMAP, $SOCl_2$, >90%.
14. The stereochemistry of the product was not determined. Lower yields were obtained with Ti(O*i*-Pr)$_4$.