

Highly Stereoselective Synthesis of α,β -Unsaturated Ketones by CeCl_3 Mediated Addition of Grignard Reagents to β -Enamino Ketones

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A stereoselective synthesis of α,β -unsaturated ketones by direct addition of Grignard reagents to β -enamino ketones, mediated by dry cerium(III) chloride, is described and a *trans* relationship between the introduced framework and the carbonyl group is predominantly observed.

The α,β -unsaturated carbonyl functionality is firmly established as one of the most important structural units, useful for the preparation of many synthetic targets.¹ Furthermore this bifunctional moiety is present in a large number of molecules of biological significance.

The direct aldol condensation, and related processes, still represent the most common route to the synthesis of enones.² The Horner–Emmons approach, with its many variations, is also a well established procedure to reach the same goal.³ The recent development of other interesting methods for the preparation of enones,⁴ testifies to the considerable interest toward this class of compounds.

In spite of the above cited methods, complete stereochemical control over the geometry of the enone double bond is still lacking. The preferential formation of alkenes of *E* configuration is nearly always observed, whereas *Z* α,β -unsaturated ketones can be exclusively prepared by coupling acyl chlorides with alkenyl copper reagents of suitable geometry.⁵

β -Enamino ketones are reported to react with organolithium reagents to afford α,β -unsaturated ketones through a formal substitution of the amino fragment with the organometallic residue.⁶ This procedure shows no stereoselectivity on

the double bond formation and is restricted to enamino ketones bearing a secondary amine framework.

Recently we reported that Grignard reagents can be directly added to 1,3-diketones, in the presence of dry CeCl_3 , affording β -hydroxy ketones in good yields.⁷ This discovery prompted us to investigate this procedure with other enolizable substrates such as β -enamino ketones, prepared by reaction of imine anions with esters.⁸ Adding β -enamino ketones **1** at -78°C to Grignard reagents **2** in the presence of dry CeCl_3 at -78°C , followed by acidic quenching, directly affords α,β -unsaturated ketones **3** in satisfactory yields (Table 1).†

This reaction also shows surprising stereoselectivity: a *trans* relationship between the introduced group and the carbonyl function is predominantly observed (an exception is represented by the example in entry **d** in which a methyl group is inserted). This feature should make possible the tunable synthesis of both the geometrical isomers of enones by a suitable choice of the substrate–reagent couple.

Since little is known about the structure of organocerium compounds,⁹ the stereochemical outcome of this reaction can be tentatively rationalized by invoking cerium atom chelation, that produces a cyclic locked structure as depicted in Scheme 1.‡ A stereofacial differentiation would be provided by the methyl substituent on the nitrogen that shields one face of the molecule and consequently forces the Grignard reagent to attack the carbonyl group from the opposite side. A subsequent elimination process, probably favoured by the quenching source, leads to the α,β -unsaturated ketone **3** via the imino derivative **4**. Other reaction pathways, especially those involving non-chelated intermediates¹⁰ cannot be presently ruled out, but they offer less reasonable explanations of our preliminary experimental observations.

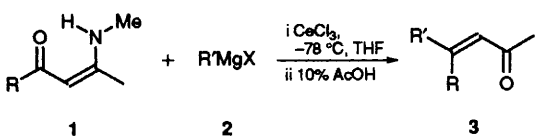
The presence of cerium chloride is essential for the success of this procedure since a rapid deprotonation of the nitrogen linked hydrogen, is normally observed in its absence leading, after quenching, to the unchanged starting material. Similar behaviour is shown by β -enamino ketones 'pre-chelated' with cerium chloride before the addition of the Grignard reagent.

The examples displayed in Table 1, although restricted to a series of ordinary Grignard reagents, effectively prove the peculiarity of this procedure in the preparation with unprecedented stereoselectivity, of α,β -unsaturated ketones.

This work was supported by the Ministero della Ricerca Scientifica e Tecnologica of Italy.

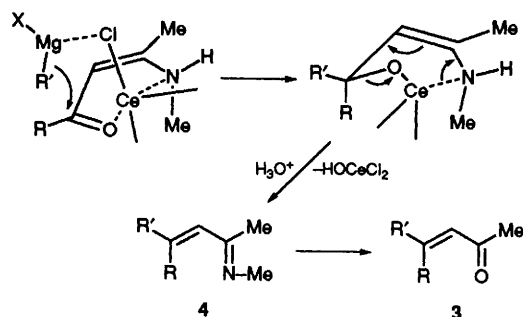
Received, 26th October 1993; Com. 3/06380A

Table 1 Reaction between β -enamino ketones **1** and Grignard reagents **2** in the presence of dry CeCl_3 in THF at -78°C then room temp. followed by quenching with 10% acetic acid



	R	R'MgX	Reaction time/h	Yield (%) ^a 3
a	Me	MeMgCl	1.5	81
b	Me	PhMgBr	3.0	85
c	Me	Bu ⁿ MgCl	1.5	75
d	Ph	MeMgCl	2.0	80 ^b
e	Ph	PhMgBr	4.0	78
f	Ph	Bu ⁿ MgCl	2.0	65
g	Bu ⁿ	Pr ⁿ MgCl	2.5	68

^a Isolated yields. All compounds prepared are known and their spectroscopical data (NMR, IR, mass spectra and elemental analyses) and are in full agreement with those reported in the literature. ^b A 85:15 *Z*–*E* mixture is recovered.



Scheme 1 Proposed mechanism for the formation of **3**

Footnotes

† Typical experimental procedure is as follows: Finely ground $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (2.6 g, 7.0 mmol) is dried by heating at 140°C , 0.1 Torr for 2 h. Dry THF (70 ml) is then added at 0°C and the milky suspension is stirred for 15 h under nitrogen at room temp. The Grignard reagent (7.0 mmol) is then added at -78°C and the mixture is stirred for 2 h at the same temperature. The appropriate β -enamino ketone (2 mmol), dissolved in dry THF (20 ml), is then added dropwise at -78°C , the mixture is stirred at this temperature for 1 h and then allowed to warm to room temp. Stirring is continued at room

temp. for the appropriate time (see Table 1) and the reaction mixture is quenched by addition of 10% aqueous acetic acid (90 ml). Usual work-up gives the crude product which is purified by column chromatography (hexane–ethyl acetate 8:2).

‡ This chelation would be of some importance for the reactivity of the system since with more cumbersome substituents on nitrogen (e.g. isopropyl) a lack of reactivity is generally observed.

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