A Stereoselective Synthesis of (*E*)-α,β-Unsaturated Ketones Involving the Reactions of Organocerium Reagents with Secondary β-Enamino Ketones

Giuseppe Bartoli,* Enrico Marcantoni,* Marino Petrini and Letizia Sambri

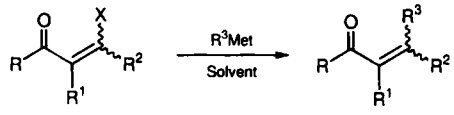
Abstract: Stereoselective construction of trisubstituted alkenes has wide applicability to the synthesis of many natural products. Specifically, β-disubstituted enones are important functionalized trisubstituted alkene targets. The reaction of organocerium reagents with secondary β-enamino ketones affords β-disubstituted α,β-unsaturated ketones in fairly good yields. This process shows considerable stereoselectivity, and α,β-unsaturated ketones of (*E*) configuration are predominantly observed. Organolithium-derived cerium reagents display better stereoselectivity than organomagnesium-based ones. The mechanism of the reaction varies with nitrogen substitution: *N*-phenyl groups give 1,2-addition products, whereas substitution products are observed with *N*-alkyl groups. When organocerium reagents were used with β-enamino ketones bearing secondary alkyl groups at the nitrogen atom, a lack of reactivity was observed.

Keywords
assymetric substitution · cerium reagents · enamino ketones · regioselectivity · synthetic methods

Introduction

The α,β-unsaturated carbonyl functionality is one of the most alluring structural units for synthetic organic chemists.[1] This bifunctional moiety is present in a large number of molecules that are particularly important owing to their versatility as synthetic intermediates and their widespread occurrence in biologically important compounds. Several synthetic methods for α,β-unsaturated ketones have been reported, and among them the direct aldol condensation and related processes still occupy a prominent position.[2] However, because of difficulty in directing the coupling, the conventional method has serious synthetic limitations. This is particularly noticeable when two different carbonyl compounds are used in a cross-coupling; the reaction is often accompanied by considerable side reactions such as self-condensation and polycondensation. The synthetic limitation arises because the reaction is reversible and cannot be driven to completion if the aldol is less stable than the parent carbonyl compounds. In addition, the reverse reaction in the presence of acid or base generates regioisomeric enols or enolates, which in turn attack the carbonyl compounds to yield a mixture of aldols. Furthermore, the resulting unsaturated carbonyl compounds may undergo a Michael addition between enolate anions to give a complex reaction mixture.

The striking efforts toward the drafting of new synthetic methods for the preparation of enones testify to the considerable importance of this class of compounds.[3] The reaction



Scheme 1. **1** **2**

(Scheme 1) of organocopper reagents with α,β-unsaturated carbonyl compounds containing a good leaving group at the β-carbon atom (i.e., halide,[4] acetate,[5] phosphate,[6] alkoxy,[7, 8e] alkylthio[8] and dialkylamino[9] substituents) affords β-alkyl-α,β-unsaturated carbonyl compounds in a chemoselective fashion.[10] In particular substitution reactions of (*E*) and (*Z*) vinylogous thiolesters with organocuprates[11] have been examined as a potential stereoselective synthetic route to α,β-enones, although bisconjugate addition to afford β,β-dialkyl carbonyl compounds may be competitive with the more reactive cuprates and substrates.[8] Thus, Mukaiyama[12] found that a variety of α,β-unsaturated ketones are conveniently synthesized from reaction of enamino ketones (X = NR_2 in **1**, Scheme 1) with organolithium compounds. The Mukaiyama method is limited to enamino ketones with no active hydrogens, and the reactivity is greatly influenced by the solvent used. The organolithium compounds react quite smoothly with enamino ketones in hydrocarbon solvents such as petroleum ether and *n*-hexane to give α,β-unsaturated ketones in fairly good yields.

We have, over the past several years, investigated the reactivity of organometallic reagents in the presence of dry cerium(III) chloride with enolizable substrates, leading to the development of new carbon–carbon bond-forming reactions.[13] During the course of this investigation, we discovered that the success of this strategy can be attributed to the known low basicity and higher nucleophilicity of organocerium reagents as opposed to organolithium and Grignard reagents, as pointed out by the

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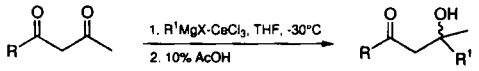
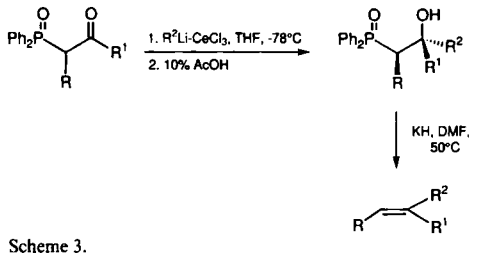
pioneering work of Imamoto et al.[14] These reagents can be used with substrates generally inert toward nucleophilic attack, such as 1,3-diketones and α-diphenylphosphinoyl ketones, affording β-hydroxy ketones[13a] and β-hydroxyalkylphosphine oxides,[13c,e] respectively, as depicted in Schemes 2 and 3. This



Scheme 2.



Scheme 3.

discovery prompted us to investigate this procedure with other enolisable substrates such as secondary β-enamino ketones.[15] We now report the results of an extensive study of this reaction as a function of substrate structure, and demonstrate that the use of cerium(III) chloride plays an important role in increasing the nucleophilicity and decreasing the basicity of organolithium and organomagnesium compounds, which can add to secondary β-enamino ketones to afford β-disubstituted α,β-unsaturated ketones in moderate to excellent yields. This process shows considerable stereoselectivity: α,β-unsaturated ketones of (*E*) configuration are predominantly observed, while the regioselectivity is affected by the nature of the substituent on the nitrogen atom (vide infra). The examples displayed in Tables 1 and 2 effectively demonstrate this peculiarity of the procedure in the preparation of β-disubstituted enones with unprecedented regioselectivity, which represent important functionalized trisubstituted olefins typically found in insect juvenile hormones and acyclic terpene precursors.[4f,5,6,8b-d]

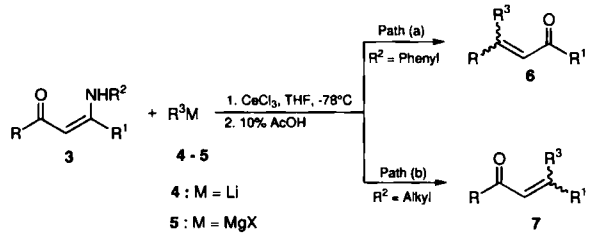
Abstract in Italian: *La sintesi stereoselettiva di alcheni trisostituiti è di fondamentale importanza nella preparazione di una notevole varietà di prodotti di origine naturale. In particolare gli enoni β-disostituiti rappresentano una interessante categoria di alcheni trisostituiti funzionalizzati. La reazione di reagenti di organocerio con β-enamino chetoni secondari produce chetoni α,β-insaturi β-sostituiti in buone rese. Questo procedimento mostra un considerevole grado di stereoselettività, infatti si osseva prevalentemente la formazione di chetoni α,β-insaturi di configurazione (E). I reattivi di organocerio generati a partire dai corrispondenti litio derivati determinano un grado di stereoselettività più elevato rispetto ai corrispondenti derivati del magnesio. Il meccanismo della reazione dipende dalla natura del sostituente presente sull'atomo di azoto nel substrato. Gruppi N-arilici provocano una reazione di addizione 1,2 mentre sostituenti N-alchilici danno prodotti di sostituzione. La presenza di gruppi alchilici secondari sull'atomo di azoto dei β-enamino chetoni determina una completa inibizione della reattività verso i reagenti di organocerio.*

Results and Discussion

β-Enamino ketones of type **3** can be efficiently prepared by reaction of imine anions with esters.[16] This reaction works well with aliphatic and aromatic esters and provides a mild and general method for the synthesis of asymmetrical enamino ketones, which are reported to be obtained from direct condensation of amines and diketones only when the reactivity of the two carbonyl groups differs markedly (i.e., aromatic vs. aliphatic carbonyls).[17,18] Furthermore, recently we have reported[19] a method for the almost exclusive regiocontrol of alkylation in the two positions (α′ and γ) of acyclic 1,3-diketone derivatives, and this allows preparation of β-enamino ketones of type **3** with a chain lengthening at C1 or C3 starting from easily available β-enamino ketones.

Adding β-enamino ketones (**3**) at −78 °C to organolithium (**4**) or Grignard reagents (**5**) in presence of dry cerium(III) chloride, followed by acidic quenching, directly affords α,β-unsaturated ketones **6** or **7** in satisfactory yields and with exclusive (*E*) configuration (Scheme 4, Tables 1 and 2).

Regioselectivity: The most relevant feature of this mild procedure to obtain β-disubstituted α,β-enones is that β-*N*-monophenylamino and β-*N*-monoalkylamino α,β-unsaturated ketones underwent nucleophilic 1,2-addition (path a, Scheme 4) and substitution (path b, Scheme 4), by reaction with the cerium



Scheme 4.

Table 1. Reaction of β-enamino ketones (**3**) with organolithium reagents (**4**) in the presence of dry $CeCl_3$.

Entry	R	R¹	R²	R³	Enamino ketone	Organolithium	Overall yield (%)	Enone (%) [a] 6	7
1	Me	Me	Me	Me	**3a**	**4a**	87.9	–	**7aa** (100)
2	Me	Me	Me	*n*Bu	**3a**	**4b**	80.6	–	**7ab** (100)
3	Me	Me	Me	*s*Bu	**3a**	**4c**	85.6	–	**7ac** (100)
4	Me	Me	Me	Ph	**3a**	**4d**	81.0	–	**7ad** (100)
5	Me	Me	*n*Bu	*n*Bu	**3b**	**4b**	79.6	–	**7bb** (100)
6	Me	Me	Ph	*n*Bu	**3c**	**4b**	82.1	**6cb** (100)	–
7	Me	Me	Ph	Ph	**3c**	**4d**	79.4	**6cd** (100)	–
8	Me	Me	*i*Pr	*n*Bu	**3d**	**4b**	n.r. [b]		
9	Me	Me	*i*Pr	Ph	**3d**	**4d**	n.r.		
10	*n*Pr	Me	Me	*n*Bu	**3e**	**4b**	72.9	–	**7eb** (100)
11	*n*Bu	Me	Me	Me	**3f**	**4a**	74.6	–	**7fa** (100)
12	*n*Bu	Me	*n*Bu	Me	**3g**	**4a**	75.6	–	**7ga** (100)
13	*n*Bu	Me	Ph	Me	**3h**	**4a**	79.4	**6ha** (100)	–
14	Ph	Me	Me	Me	**3i**	**4a**	76.4	**6ia** (11)	**7ia** (89)
15	Ph	Me	Me	*n*Bu	**3i**	**4b**	80.2	**6ib** (17)	**7ib** (83)
16	Ph	Me	Me	*s*Bu	**3i**	**4c**	79.8	**6ic** (46) [c]	**7ic** (54) [d]
17	Ph	Me	Ph	Me	**3j**	**4a**	76.5	**6ja** (100)	–
18	Ph	Me	Ph	*n*Bu	**3j**	**4b**	74.6	**6jb** (91)	**7jb** (9) [e]
19	Me	Et	Me	Me	**3k**	**4a**	n.r.		
20	Me	Et	Me	*n*Bu	**3k**	**4b**	n.r.		
21	Me	Et	Ph	Me	**3l**	**4a**	n.r.		
22	Me	*n*Bu	Ph	Me	**3m**	**4a**	n.r.		
23	Me	*n*Bu	*n*Bu	Me	**3n**	**4a**	n.r.		

[a] The mixture of enones **6** and **7** did not separate. [b] n.r. = No reaction, starting material was recovered. [c] A 72:18 mixture of (*E*):(*Z*) isomers. [d] An 88:12 mixture of (*E*):(*Z*) isomers. [e] An 85:15 mixture of (*E*):(*Z*) isomers.

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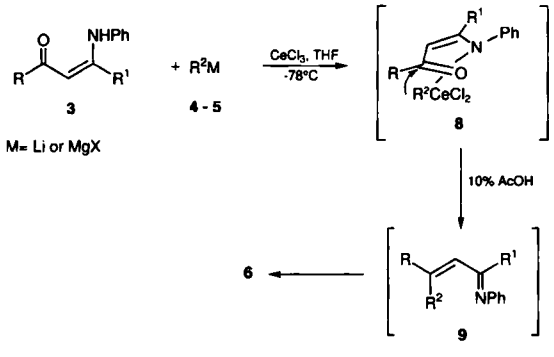
Table 2. Reaction of β-enamino ketones (3) with organomagnesium reagents (5) in the presence of dry $CeCl_3$.

Entry	R	R^1	R^2	R^3	Enamino ketone	Organo magnesium	Overall yield (%)	Enone (%) [a] 6	7
1	Me	Me	Me	Me	**3a**	**5a**	80.6	-	**7aa** (100)
2	Me	Me	Me	*n*Bu	**3a**	**5b**	75.0	-	**7ab** (100)
3	Me	Me	Me	Ph	**3a**	**5d**	84.5	-	**7ad** (100)
4	Me	Me	Me	Allyl	**3a**	**5e**	78.9	-	**7ae** (100)
6	Me	Me	Me	Bz	**3a**	**5h**	74.2	-	**7ah** (100)
7	Me	Me	Me	Diox [b]	**3a**	**5i**	68.9	-	**7ai** (100)
8	Me	Me	Me	*i*Pr	**3a**	**5j**	n.r. [c]		
9	Me	Me	Ph	*n*Bu	**3c**	**5b**	78.5	**6cb** (100)	-
10	Me	Me	Ph	Ph	**3c**	**5d**	89.6	**6cd** (100) [d]	-
11	Me	Me	Ph	Allyl	**3c**	**5e**	82.6	**6ce** (100)	-
12	Me	Me	*i*Pr	*n*Bu	**3d**	**5b**	n.r.		
13	*n*Bu	Me	Me	Me	**3f**	**5a**	69.5	-	**7fa** (100)
14	*n*Bu	Me	Me	*n*Pr	**3f**	**5g**	74.2	-	**7fg** (100)
15	*n*Bu	Me	Ph	Me	**3h**	**5a**	72.3	**6ha** (100)	-
16	Ph	Me	Me	Me	**3i**	**5a**	79.3	**6ia** (14)	**7ia** (86)
17	Ph	Me	Me	*n*Bu	**3i**	**5b**	74.5	**6ib** (20)	**7ib** (80)
18	Ph	Me	Me	Ph	**3i**	**5d**	77.4	**6id** (37)	**7id** (63)
19	Ph	Me	Me	Vinyl	**3i**	**5f**	76.3	**6if** (12)	**7if** (88)
20	Ph	Me	Ph	Me	**3j**	**5a**	71.6	**6ja** (100)	-
21	Ph	Me	Me	*n*Bu	**3j**	**5b**	92.0	**6jb** (100)	-
22	Me	Et	Me	*n*Bu	**3k**	**5b**	n.r.		
23	Me	Et	Me	Ph	**3k**	**5d**	n.r.		
24	Me	*n*Bu	Ph	Me	**3m**	**5a**	n.r.		
25	Me	*n*Bu	*n*Bu	Me	**3n**	**5a**	n.r.		
26	But [e]	Me	Me	Me	**3p**	**5a**	68.9	-	**7pa** (100)

[a] The mixture of enones **6** and **7** did not separate. [b] Diox = 1-ethyl-1,3-dioxolane. [c] n.r. = No reaction; starting material was recovered. [d] An 85:15 mixture of (*E*):(*Z*) isomers. [e] But-3-en-1-yl.

reagents in a highly stereocontrolled manner with preferential formation of alkenes of (*E*) configuration.

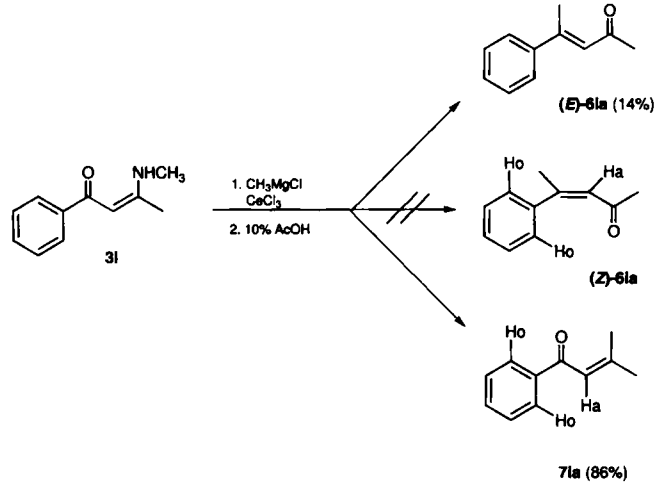
Little is known about the structure of organocerium compounds,[14:20] but the mechanism of nucleophilic 1,2-addition of organolithium or organomagnesium compounds to β-enamino ketones with an *N*-phenyl group in the presence of dry cerium(III) chloride can be tentatively rationalized by invoking the capacity of the aromatic nucleus to delocalize the nitrogen lone pair into the π electron system. This resonance interaction with the nitrogen-atom hybridized sp^2 favours the formation of the intermediate **8** (Scheme 5), thereby transferring the R^2 group



Scheme 5. Proposed mechanism for the formation of enones of type **6**.

easily in an intramolecular manner. A subsequent elimination process, probably favoured by the quenching source, results in the β-disubstituted α,β-unsaturated ketones **6** via the imino derivatives **9**. These imino derivatives have not been isolated, but are easily recognized by mass-spectral analysis of the crude reaction mixture after neutral work-up.

The same good yields of β-enones were obtained when the substituent on the nitrogen was changed from phenyl to methyl. The addition of CH_3MgCl–$CeCl_3$ to 3-(*N*-methylamino)-1-phenylbut-2-en-1-one (**3i**) gave, after acidic quenching, a mixture of two β-enones (Table 2, entry 16). In preliminary experimental observations[15] of the chemical shifts of the allylic protons we concluded that the product **7ia** had to be the (*Z*) isomer of compound **6ia** (Scheme 6). After examining the avail-



Scheme 6. Formation of β-enone **7ia** and structure obtained by ROESY analysis.

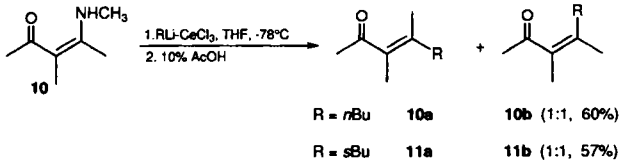
able literature data and evaluating the intramolecular NOE effect, we ruled out the hypothesis of a product having a (*Z*) configuration. Compound **7ia** was submitted to a ROESY analysis,[21] and remarkable cross-peaks were detected between the allylic protons and H_a, and between H_a and H_o in the aromatic ring. On the other hand, no interesting cross-peaks were detected at room temperature between the allylic protons of the methyl group and the protons of the aromatic ring. Therefore compound **7ia** must possess a completely different structure resulting from a substitution reaction of the reagent on substrate **3i**. This reaction of β-*N*-monoalkylamino α,β-unsaturated ketones with the cerium reagent derived from methylmagnesium chloride was observed with all organometallic-derived species (path b, Scheme 4; Tables 1 and 2), with preferential formation of (*E*)-α,β-unsaturated ketones.

Despite a decade of intensive interest in the chemistry of organocerium compounds and their application as reagents for organic synthesis, the solution structure of these reagents is not well understood.[22] Mechanistic investigations of the reaction of β-enamino ketones with organocerium compounds are hampered by the lack of information on the actual structure of the organometallic reagents, their state of aggregation in various solvents and the nature of intermediates involved in these very fast reactions. Nevertheless, recent studies have firmly established the preferential formation of the (*Z*) configuration in the β-*N*-monoalkylamino α,β-unsaturated ketone system with sp^3 hybridized nitrogen, and so we thought a strong coordination between the cerium reagent and nitrogen possible. This interaction suggested to us an addition–elimination pathway for nucleophilic vinylic substitution.[23] Finally, this substitution reaction exhibits high stereoselectivity with formation of α,β-enones with (*E*) configuration, depending upon the configurational stability of the products.

Stereoselectivity: The investigation of stereoselectivity in the reactions between organocerium reagents and β-enamino ke-

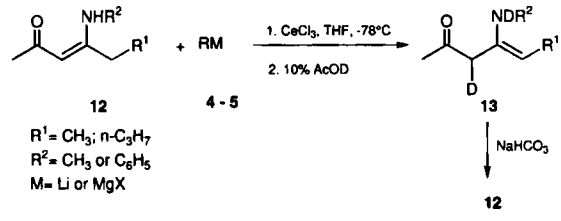
tones required a method for assigning olefin configuration in the product α,β-enones. Fortunately, it is well documented that a β-methyl substituent *syn* to a ketone in α,β-unsaturated carbonyl compounds resonates downfield relative to the *anti* methyl substituent in the NMR spectrum.[11a, 24] Consequently, the NMR chemical shifts of the β-methyl, β-methylene or γ-methine protons of β-secondary alkyl substituents provide a reliable guide for the assignment of olefin configuration. In most instances the (*E*)-α,β-enones were obtained as the major products, which facilitated purification of the individual (*E*) and (*Z*) isomers; otherwise isomer ratios were determined by NMR analysis of the crude reaction mixture. The olefin stereochemistry of (*E*)- and (*Z*)-4-phenylpent-3-en-2-one (**7ad**, Table 2) was assigned on the basis of the chemical shifts (*β-syn*, $\delta = 2.55$, (*E*) isomer; *β-anti*, $\delta = 2.31$, (*Z*) isomer) of the β-methyl absorptions. This is consistent with the assignment of the β-methyl absorptions in 1-phenyl-3-methylhept-2-en-1-one (**7jb**, Table 1) as *β-syn*, $\delta = 2.15$ and *β-anti*, $\delta = 1.95$, respectively. Finally the stereoselectivity showed by the reaction of organocerium reagents and β-enamino ketones is affected by the nature of the organometallic species involved. Generally organolithium-derived cerium reagents display a better stereoselectivity (Table 1, entries 4, 7) than the organomagnesium ones (Table 2, entries 3, 9), but the latter reagents are easily prepared and available in highly functionalized forms.

Reactivity: It is clear that linear alkyl substituents at the nitrogen of β-enamino ketones of type **3** have little or no influence on reactivity, since a change from methyl to *n*-butyl did not prejudice the high yield of the process. On the other hand, a branched chain at the nitrogen (Table 1, entries 8, 9; Table II, entry 2) produced a surprising lack of reactivity, and the starting material was recovered unchanged after acidic quenching. A more intriguing form of behaviour was displayed by C2 β-enamino ketone **10**, which reacted with organolithium-derived cerium reagents to give the expected products, but completely failed with organomagnesium–cerium(III) chloride species (Scheme 7). The additional observation that organomagnesium-derived secondary cerium reagents were unable to react with any β-enamino ketones tested (Table 2, entry 8) pinned the problem on the nature of the reagent used.[25] Organocerium reagents are indeed usually prepared by transmetallation reactions, and the utilization of organomagnesium reagents requires a temperature of 0 °C.[14] This process proceeds slowly at this temperature and at −78 °C it would be practically ineffective, so that a reactive species of type RMgX:$CeCl_3$ is postulated.[26] This RMgX:$CeCl_3$ complex still retains a consistent degree of basicity and also possesses a rather low reactivity compared with the organolithium-generated cerium reagent. The use of organocerium reagents prepared at 0 °C from secondary Grignard reagents and then cooled to −78 °C gave a rather complex mixture of products from which the α,β-unsaturated ketones were isolated in only 20–30% yield. The reagent stoichiometry also exerted a remarkable bias on the efficiency of organocerium addition. The best yields were obtained with a 3.5 molar excess of the reagent prepared from a 1:1 ratio of the organometallic reagent and dry $CeCl_3$. The presence of cerium(III) chloride is essential for the success of this procedure, since a rapid deprotonation is normally observed in its absence, leading, after quenching, to unchanged starting material.



Scheme 7.

Substituents at C1 on β-enamino ketones of type **3** had little or no influence on reactivity; changing from methyl to *n*-butyl or phenyl always resulted in a high-yielding process (Tables 1 and 2). Otherwise a chain lengthening at C3 produced a surprising lack of reactivity and the starting material was recovered unchanged after acidic quenching (Table 1, entries 19–23; Table 2, entries 21–24). Since treatment of β-enamino ketones of type **12** with organocerium reagents generated from different organometallic species did not generally give clear solutions, we excluded the use of direct NMR analysis to detect intermediate formation and used the method of deuterium incorporation (product **13** in Scheme 8) by NMR and MS techniques after quenching the reaction mixture with deuterated acetic acid. These deuteration experiments yielded products dideuterated at the *N*- and α-positions. This latter substitution is obtained presumably because the π-electron density is higher at the α-carbon than the γ-carbon;[27] indeed extended dienolates normally react with electrophile sources to produce α-deutero-β,γ-unsaturated β-enamino ketones. Upon washing of the deuterated product **13** with saturated aqueous $NaHCO_3$ a very fast shift of the β,γ double bond to the more stable α,β position was observed, together with a concomitant proton–deuterium exchange producing the starting material **12**. This result would support the preferential formation of a dianion, on the reaction of organocerium reagents with β-enamino ketones of type **12**, which regenerates the starting material upon hydrolysis.



Scheme 8.

Conclusions

We have investigated the unique reactivity of alkylcerium reagents derived from anhydrous $CeCl_3$ and an organolithium or organomagnesium compound. The cerium derivatives are less basic and have a higher affinity for Lewis-basic atoms, such as oxygen and nitrogen, than the precursor from which they are derived. In particular, organometallic compounds derived from cerium halides undergo chemoselective addition to substrates even with easily enolisable systems, such as β-*N*-monoalkylamino and β-*N*-monophenylamino α,β-unsaturated ketones. Moreover, we have reported a stereoselective synthesis of (*E*)-β-disubstituted α,β-unsaturated ketones by direct addition of organocerium reagents to secondary β-enamino ketones. Our results show that a method is now available for the almost exclusive regiocontrol of nucleophilic attack on the β-enamino ketone system. This attack can be on the carbonyl carbon or on the β-carbon of carbonyl group[28] depending on the nature of the *N*-substituent.

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A major drawback of this procedure lies in the lack of reactivity observed with substituents other than methyl in the C3 position on β-enamino ketones. Furthermore the impossibility of introducing secondary functionalized frameworks through the use of Grignard reagents represents a severe limitation of the present methodology.

In spite of these troubles and in view of the capriciousness of 1,2- vs. 1,4-addition of organometallic reagents to unsaturated carbonyl compounds,[29] the consistency of our results provides a useful route to substituted conjugate enones.

Experimental Procedure

Microanalyses were performed with a CHNS-O analyzer Model EA 1108 from Fisons Instruments; IR spectra were recorded with a Perkin–Elmer 1310 spectrophotometer. NMR spectra were recorded at 300 MHz on a Varian VXR 300. ^{1}H NMR shifts are given in parts per million from Me_4Si in $CDCl_3$. The ROESY experiment was run in a 10^{-2} M $CDCl_3$ solution. A time-shared spin-lock pulse was used [21]. Data points were collected into two matrices of 1024 × 1024; 256 increments were used with 16 transients each; mixing time 0.8 s; spectral window was 1733 Hz in both dimensions. Mass spectra were recorded on a Hewlett–Packard GC/MS 5970 by means of the EI technique (70 eV). Reaction progress was monitored by TLC or GLC on a Carlo Erba Fractovap 4160, with a capillary column of duran glass (0.32 mm × 25 m), stationary phase OV1 (film thickness 0.4–0.45 nm). Flash chromatography [30] was performed on Merck silica gel (0.040–0.063 mm) with hexane/ethyl acetate (8:2) as the eluent. All chemicals used were obtained commercially; literature methods were followed for the synthesis of β-enamino ketones (of type **3**, **10** and **12**) [15–18] and organometallic reagents. THF was dried by refluxing it over sodium wire until the blue colour of benzophenone ketyl persisted and distilling it into a receiver under a nitrogen atmosphere.

Reaction of β-Enamino Ketones 10 followed by Deuteration: Cerium(III) chloride ($CeCl_3 \cdot 7H_2O$) (0.19 g, 0.52 mmol) was placed in a 25 mL Schlenk flask with a stirrer bar. The flask was heated in vacuo in an oil bath to 140 °C/0.2 mmHg for 2 h. While the flask was still hot, argon was introduced. The flask was cooled in an ice bath and dry THF (3.8 mL) was introduced from a syringe. The suspension was stirred overnight at room temperature. The resulting white slurry was then cooled to −78 °C, and the organolithium or organomagnesium compound (0.52 mmol) was added dropwise from a syringe. After 1 h β-enamino ketone (0.19 mmol) in dry THF (0.8 mL) was added dropwise from a syringe and the suspension was stirred for a further 1 h at −78 °C before being allowed to warm to room temperature. A solution of CH_3COOD in D_2O (5%, 3 mL) was then added, and the organic layer was washed with D_2O, dried, evaporated under reduced pressure and submitted to NMR and GC-MS analyses. The deuterium incorporation in **13** was determined by observation of the NMR signals of hydrogen at $\delta = 2.35$ (d, $J_{HD} = 2.2$ Hz) and of vinylic hydrogen at $\delta = 6.30$ (t, $J = 7.45$ Hz) relative to tetramethylsilane. The mass spectrum showed also $M + 2$ ions. Samples washed with saturated aqueous $NaHCO_3$ and with water did not show deuterium incorporation.

Reaction between β-Enamino Ketones and Organocerium Reagents: A 100 mL three-neck flask fitted with septum and gas inlet was charged with $CeCl_3 \cdot 7H_2O$ (2.6 g, 7 mmol), which was dried by heating to 140 °C at 0.2 Torr for 2 h. The flask was allowed to cool to room temperature and vented to dry nitrogen, and THF (20 mL) was added from a syringe. This slurry was stirred overnight at room temperature and cooled to −78 °C. To this white suspension organolithium or organomagnesium compound (7 mmol) was added slowly from a syringe, and the reaction mixture was stirred for 1 h at −78 °C. A solution of β-enamino ketone (2 mmol) in THF (12 mL) was added slowly from a syringe, and the reaction mixture was stirred for 1 h at −78 °C. The reaction mixture was allowed to warm to room temperature over the course of 1 h and to react for 3 h at RT. The reaction mixture was quenched by addition of 10% aqueous acetic acid (45 mL) and extracted with Et_2O (3 × 100 mL). The extracts were washed with brine (1 × 50 mL), combined, dried ($MgSO_4$) and concentrated to afford an oil. Purification by flash chromatography on a silica gel column by a mixture of hexane–ethyl acetate (8:2) as eluent afforded β-disubstituted α,β-unsaturated ketone in good yield.

4-Methylpent-3-en-2-one (7aa): oil; IR (neat): 1685 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.84$ (d, $J = 1.28$ Hz, 3H), 2.18 (d, $J = 1.14$ Hz, 3H), 2.21 (s, 3H), 6.05 (s, 1H); MS: $m/z = 98$ (M^+), 83 (100), 55, 43, 39; $C_6H_{10}O$ (98.14): calcd C 75.43, H 10.27; found C 75.46, H 10.32.

(*E*)-4-Methyloct-3-en-2-one (7ab): oil; IR (neat): 1690 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.91$ (t, $J = 6.04$ Hz, 3H), 1.15–1.45 (m, 4H), 2.10 (d, $J = 1.10$ Hz, 3H), 2.15–2.23 (m, 2H), 2.17 (s, 3H), 6.08 (s, 1H); MS: $m/z = 140$ (M^+), 98, 83, 70, 69, 56, 43 (100); $C_9H_{16}O$ (140.22): calcd C 77.09, H 11.50; found C 77.05, H 11.52.

(*E*)-4,5-Dimethylhept-3-en-2-one (7ac): oil; IR (neat): 1670 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.80$ (t, $J = 7.02$ Hz, 3H), 1.05 (d, $J = 7.04$ Hz, 3H), 1.10–1.65 (m, 2H), 2.05 (d, $J = 1.0$ Hz, 3H), 2.17 (s, 3H), 1.90–2.28 (m, 1H), 6.03 (s, 1H); MS $m/z = 140$ (M^+), 125 (100), 112, 97, 83, 55, 43; $C_9H_{16}O$ (140.22); calcd C 77.09, H 11.50; found C 77.12, H 11.53.

(*E*)-4-Phenylpent-3-en-2-one (7ad): oil; IR (neat): 1670 (C=O), 1595 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 2.30$ (s, 3H), 2.55 (d, $J = 1.40$ Hz, 3H), 6.50 (d, $J = 0.95$ Hz, 1H), 7.35–7.55 (m, 5H); MS: $m/z = 160$ (M^+), 145, 115, 105, 91, 77, 65, 43 (100); $C_{11}H_{12}O$ (160.21): calcd C 82.46, H 7.55; found C 82.41, H 7.50.

(*E*)-4-Methylhepta-3,6-dien-2-one (7ae): oil; IR (neat): 1695 (C=O), 1620 (C=C), 1595 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 2.15$ (s, 3H), 2.18 (d, $J = 1.05$ Hz, 3H), 2.30–2.42 (m, 2H), 5.05–5.20 (m, 2H; CH_2=C), 5.85–6.05 (m, 1H; CH=C), 6.60 (s, 1H); MS: $m/z = 124$ (M^+), 109, 83, 57, 43 (100); $C_8H_{12}O$ (124.18): calcd C 77.37, H 9.74; found C 77.39, H 9.74.

(*E*)-4-Methyl-5-phenylpent-3-en-2-one (7ah): oil; IR (neat): 1680 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 2.08$ (s, 3H), 2.18 (s, 3H), 3.65 (d, $J = 0.92$ Hz, 2H), 6.05 (s, 1H), 7.15–7.30 (m, 5H); MS: $m/z = 174$ (M^+), 159, 131, 117, 104, 91, 77, 65, 43 (100); $C_{12}H_{14}O$ (174.24): calcd C 82.72, H 8.09; found C 82.65, H 8.12.

(*E*)-6-(1,3-Dioxolan-2-yl)-4-methylhex-3-en-2-one (7ai): oil; IR (neat): 1670 (C=O), 1590 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.45$ (t, $J = 6.70$ Hz, 2H), 1.60–1.70 (m, 2H), 2.15 (d, $J = 1.04$ Hz, 3H), 2.30 (s, 3H), 3.75–3.95 (m, 4H), 4.82 (t, $J = 7.04$ Hz, 1H), 6.82 (s, 1H); MS: $m/z = 184$ (M^+), 169, 141, 99, 73 (100), 45, 43; $C_{10}H_{16}O_3$ (184.23): calcd C 65.19, H 8.75; found C 65.12, H 8.71.

(*E*)-7-Methyldec-5-en-4-one (7eb): oil; IR (neat): 1685 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.85–0.95$ (m, 6H), 1.40–1.60 (m, 6H), 2.02–2.15 (m, 2H), 2.18 (d, $J = 1.40$ Hz, 3H), 2.25–2.35 (m, 2H), 6.08 (s, 1H); MS: $m/z = 168$ (M^+), 139, 126, 125, 98, 83 (100), 56, 43; $C_{11}H_{20}O$ (168.28): calcd C 78.51, H 11.98; found C 78.56, H 12.01.

2-Methyloct-2-en-4-one (7fa): oil; IR (neat): 1695 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.95$ (t, $J = 6.98$ Hz, 3H), 1.40–1.60 (m, 4H), 2.04 (d, $J = 1.28$ Hz, 3H), 2.15 (t, $J = 6.04$ Hz, 2H), 2.28 (d, $J = 1.14$ Hz, 3H), 6.05 (s, 1H); MS: $m/z = 140$ (M^+), 111, 96, 95, 68, 57, 43 (100); $C_9H_{16}O$ (140.22) calcd C 77.09, H 11.50; found C 77.05, H 11.50.

(*E*)-4-Methyldec-4-en-6-one (7fg): oil; IR (neat): 1685 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.85–0.95$ (m, 6H), 1.40–1.60 (m, 6H), 2.02–2.15 (m, 2H), 2.18 (d, $J = 1.40$ Hz, 3H), 2.25–2.35 (m, 2H), 6.08 (s, 1H); MS: $m/z = 168$ (M^+), 139, 126, 125, 98, 83 (100), 56, 43; $C_{11}H_{20}O$ (168.28): calcd C 78.51, H 11.98; found C 78.54, H 11.95.

3-Methyl-1-phenylbut-2-en-3-one (7ia): oil; IR (neat): 1660 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 2.04$ (d, $J = 1.28$ Hz, 3H), 2.23 (d, $J = 1.14$ Hz, 3H), 6.75–6.79 (m, 1H), 7.35–7.55 (m, 3H), 7.90–7.96 (m, 2H); MS: $m/z = 160$ (M^+), 159 (100), 145, 115, 105, 77, 65; $C_{11}H_{12}O$ (160.21): calcd C 82.46, H 7.55; found C 82.49, H 7.56.

(*E*)-4-Phenyloct-3-en-2-one (6ib): oil; IR (neat): 1680 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.90$ (t, $J = 7.10$ Hz, 3H), 1.35–1.50 (m, 4H), 2.30 (s, 3H), 3.05–3.10 (m, 2H), 6.40 (s, 1H), 7.35–7.50 (m, 5H); MS: $m/z = 202$ (M^+), 187, 159, 145, 77, 65, 51, 43 (100); $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97; found C 83.13, H 9.03.

(*E*)-3-Methyl-1-phenylhept-2-en-1-one (7ib): oil; IR (neat): 1660 (C=O), 1605 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 1.00$ (t, $J = 7.05$ Hz, 3H), 1.30–1.75 (m, 4H), 2.20 (d, $J = 1.00$ Hz, 3H), 2.22–2.30 (m, 2H), 6.70 (s, 1H), 7.30–7.55 (m, 3H), 7.85–7.95 (m, 2H); MS: $m/z = 202$ (M^+), 160, 159, 145 (100), 105, 77, 65, 43; $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97; found C 83.09, H 8.93.

(*E*)-5-Methyl-4-phenylhept-3-en-2-one (6ic): oil; IR (neat): 1675 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.88$ (t, $J = 6.98$ Hz, 3H), 1.10 (d, $J = 7.00$ Hz, 3H), 1.15–1.68 (m, 2H), 2.25 (s, 3H), 2.40–2.52 (m, 1H), 6.00 (s, 1H), 7.15–7.40 (m, 5H); MS: $m/z = 202$ (M^+), 187, 145, 117, 91, 77, 65, 43 (100); $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97, found C 83.10, H 8.92.

(*Z*)-5-Methyl-4-phenylhept-3-en-2-one (6ic): oil; IR (neat): 1675 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.95$ (t, $J = 7.15$ Hz, 3H), 1.05 (d, $J = 6.94$ Hz, 3H), 1.10–1.65 (m, 2H), 2.17 (s, 3H), 2.20–2.35 (m, 1H), 6.10 (s, 1H), 7.25–7.50 (m, 5H); MS: $m/z = 202$ (M^+), 187, 145, 117, 91, 77, 65, 43 (100); $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97; found C 83.16, H 8.99.

(*E*)-3,4-Dimethyl-1-phenylhex-2-en-1-one (7ic): oil; IR (neat): 1620 (C=O), 1600 (C=C) cm^{-1}; ^{1}H NMR: $\delta = 0.90$ (t, $J = 7.00$ Hz, 3H), 1.00 (d, $J = 6.04$ Hz, 3H), 1.20–1.50 (m, 2H), 2.20 (d, $J = 1.04$ Hz, 3H), 2.32–2.45 (m, 1H), 6.75 (s, 1H), 7.35–7.43 (m, 3H), 7.90–7.95 (m, 2H); MS: $m/z = 202$ (M^+), 187, 173, 159 (100), 145, 105, 77, 65, 51; $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97; found C 83.08, H 8.89.

(*Z*)-3,4-Dimethyl-1-phenylhex-2-en-1-one (7ic): oil; IR (neat): 1620 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.00$ (t, $J = 6.99$ Hz, 3H), 1.10 (d, $J = 6.15$ Hz, 3H), 1.45–1.60 (m, 2H), 1.88 (d, $J = 1.04$ Hz, 3H), 2.50–2.69 (m, 1H), 6.68 (s, 1H), 7.35–7.45 (m, 3H), 7.90–7.95 (m, 2H); MS: $m/z = 202$ (M^+), 187, 173, 159 (100), 145, 105, 77, 65, 51; $C_{14}H_{18}O$ (202.29): calcd C 83.12, H 8.97; found C 83.08, H 8.89.

(*E*)-1,3-Diphenylbut-2-en-1-one (7id): oil; IR (neat): 1630 (C=O), 1590 (C=C) cm^{-1}; ^1H NMR: $\delta = 2.10$ (d, $J = 1.00$ Hz, 3H), 6.80–7.40 (m, 11H); MS: $m/z = 222$ (M^+), 221 (100), 207, 178, 105, 77, 65, 51; $C_{16}H_{14}O$ (222.28): calcd C 86.45, H 6.34; found C 86.40, H 6.27.

(*E*)-4-Phenylhexa-3,5-dien-2-one (6if): oil; IR (neat): 1620 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR: $\delta = 2.30$ (s, 3H), 4.95–5.05 (m, 2H; CH_2=C), 5.95 (s, 1H), 6.25–7.45 (m, 6H); MS: $m/z = 172$ (M^+), 157, 129, 113, 77, 65, 51, 43 (100); $C_{12}H_{12}O$ (172.22): calcd C 83.69, H 7.02; found C 83.66, H 6.99.

(*E*)-3-Methyl-1-phenylpenta-2,4-dien-1-one (7if): oil; IR (neat): 1620 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR: $\delta = 2.20$ (d, $J = 1.0$ Hz, 3H), 4.60–4.80 (m, 2H; CH_2=C), 5.85–6.05 (m, 2H), 7.30–7.43 (m, 3H), 7.90–7.97 (m, 2H); MS: $m/z = 172$ (M^+), 157, 129, 113, 77, 65, 51, 43 (100); $C_{12}H_{12}O$ (172.22): calcd C 83.69, H 7.02; found C 83.68, H 7.00.

2-Methylocta-2,7-dien-4-one (7pa): oil; IR (neat): 1690 (C=O), 1610 (C=C) cm^{-1}; ^1H NMR: $\delta = 1.95$ (m, 2H), 2.02 (d, $J = 1.28$ Hz, 3H), 2.23 (d, $J = 1.14$ Hz, 3H), 2.85 (m, 2H), 5.10–5.15 (m, 2H; CH_2=C), 6.00–6.10 (m, 2H); MS: $m/z = 138$ (M^+), 125, 96, 95, 68, 57, 43 (100); $C_9H_{14}O$ (138.21): calcd C 77.36, H 9.62; found C 77.32, H 9.58.

(*E*)-3,4-Dimethyloct-3-en-2-one (10a): oil; IR (neat): 1680 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.95$ (t, $J = 7.0$ Hz, 3H), 1.20–1.40 (m, 4H), 1.80 (s, 3H), 1.85 (s, 3H), 2.15 (d, $J = 6.80$ Hz, 2H), 2.20 (s, 3H); MS: $m/z = 154$ (M^+), 139 (100), 125, 97, 69, 55, 43; $C_{10}H_{18}O$ (154.25): calcd C 77.87, H 11.76; found C 77.84, H 11.75.

(*Z*)-3,4-Dimethyloct-3-en-2-one (10b): oil; IR (neat): 1680 (C=O), 1600 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.90$ (t, $J = 7.15$ Hz, 3H), 1.30–1.55 (m, 4H), 1.72 (s, 3H), 1.85 (s, 3H), 2.15 (t, $J = 6.80$ Hz, 2H), 2.20 (s, 3H); MS: $m/z = 154$ (M^+), 139, 125, 112, 97, 69 (100), 55, 43; $C_{10}H_{18}O$ (154.25): calcd C 77.87, H 11.76; found C 77.90, H 11.73.

(*E*)-3,4,5-Trimethylhept-3-en-2-one (11a): oil; IR (neat): 1680 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.95$ (t, $J = 7.00$ Hz, 3H), 1.05 (d, $J = 6.9$ Hz, 3H), 1.10–1.65 (m, 2H), 1.80 (s, 3H), 1.85 (s, 3H), 2.18 (s, 3H), 2.20–2.65 (m, 1H); MS: $m/z = 154$ (M^+), 139 (100), 125, 111, 83, 69, 55, 43; $C_{10}H_{18}O$ (154.25): calcd C 77.87, H 11.76; found C 77.86, H 11.79.

(*Z*)-3,4,5-Trimethylhept-3-en-2-one (11b): oil; IR (neat): 1680 (C=O), 1605 (C=C) cm^{-1}; ^1H NMR: $\delta = 0.88$ (t, $J = 7.00$ Hz, 3H), 1.10 (d, $J = 7.00$ Hz, 3H), 1.15–1.68 (m, 2H), 1.74 (s, 3H), 1.85 (s, 3H), 2.20 (s, 3H), 2.40–2.52 (m, 1H); MS: $m/z = 154$ (M^+), 139 (100), 125, 111, 97, 83, 69, 55, 43; $C_{10}H_{18}O$ (154.25): calcd C 77.87, H 11.76; found C 77.90, H 11.78.

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