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Stable enols from Grignard addition to 1,2-diesters: serendipity rules

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Fondly dedicated to Professor Léon Ghosez in deep and sincere appreciation for his kindness and patience

Abstract—The temperature-dependent formation of a remarkably stable enol from the reaction of EtMgBr with a 1,2-diester was accidentally discovered. This compound was spectroscopically characterized (^{1}H and ^{13}C NMR, IR), and both methyl carbonate and trimethylsilyl ether derivatives were prepared. A mechanism for the selective formation of the stable enol ester and its corresponding keto form was suggested, and the kinetic stability of the enol was also documented. The generality of the observation of such a stable enol ester was demonstrated with the use of other Grignard reagents, and also other 1,2-diesters. The reaction of EtMgBr with a series of 1,2-amide esters also produced stable enol amides. The remarkable stability of the enol esters was attributed to the steric hindrance present in the aryl ester moiety of these compounds, and further studies will address the origin of this effect.

1. Introduction

Our current interest in stable enols originates from an accidental discovery that we made in the context of one of our research projects. Thousands of individuals have been blessed by serendipitous discoveries,[1] and they have often been eager to describe the accidental nature of their discovery.[2] In that respect, Louis Pasteur recognized the role that chance played in some of his discoveries, and expressed it succintly: “Dans les champs de l’observation, le hasard ne favorise que les esprits préparés”.[3] Our—unquestionably!—prepared minds are eager to report in this article the serendipitous discovery of a remarkably stable (isolable) enol obtained by Grignard addition to a 1,2-diester. The results of a series of studies that followed this observation, and directed toward the understanding of the remarkable stability of this enol, are also presented and discussed.

We were studying the photochemical electrocyclization of a series of substituted pyrimidin-2-ones for the preparation of bicyclic 1,3-diazetidin-2-ones,[4] which could be considered as aza analogues of β-lactam derivatives,[5] and we became interested in preparing and testing a carboxylic acid-substituted model compound (**1**, see Scheme 1). One of the early steps of the synthesis called for enolate chemistry on an α-ketoester, and the previously reported, sterically hindered α-ketoester **3b** was adopted (Scheme 1).[6] Steric blockage of the ester reactivity as the 2,6-di-*tert*-butyl-4-methoxyphenyl ester was necessary in order to avoid the formation of self-acylated products.[7] It was while preparing **3b** that we discovered the remarkable stability of its enol form.

Enols of carbonyl compounds are important intermediates in many chemical[8] and especially biochemical[9] processes. Remarkable progress in the synthesis and study of enols in recent years has been achieved by the groups of Capon, Kresge, and Rappoport, and several excellent reviews have appeared on this topic.[10] However, several decades ago, it is R. C. Fuson who first reported a beautiful and systematic study of a class of enols now known as Fuson’s sterically crowded stable simple enols.[11] ‘Stable simple enols’ describe isolable enols lacking functionality which give them special stability.[12] Herein, we report the remarkable

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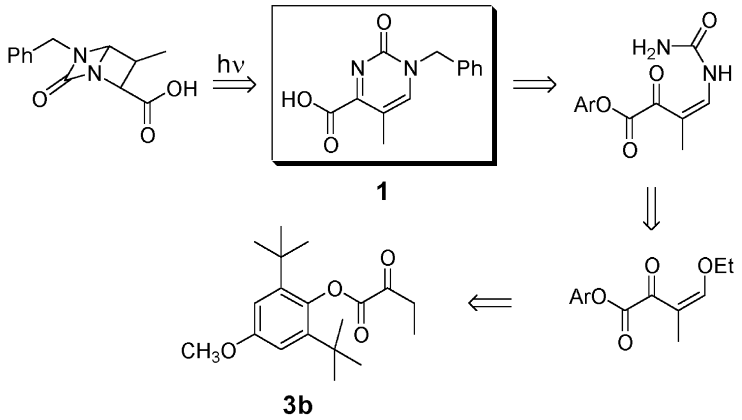


Scheme 1. Retrosynthetic analysis for the synthesis of carboxylic acid-substituted pyrimidin-2-one **1** and its corresponding bicyclic 1,3-diazetidin-2-one.

stability of an enol derived from an aliphatic 1,2-dicarbonyl compound, i.e. a stable (isolable) non-simple enol.

2. Results

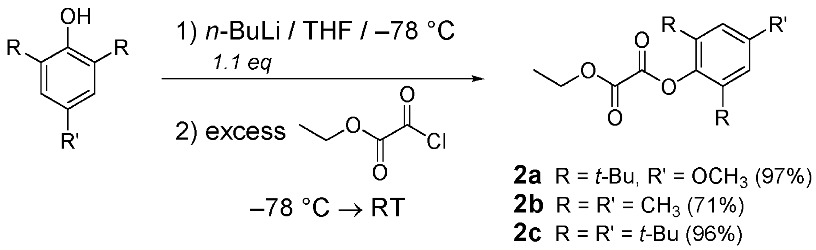
2.1. Generation, isolation, and characterization of enol ester 4b

The starting α-ketoester **3b** needed for the synthesis of pyrimidinone **1** was reported to be readily prepared by a simple two-step process as follows: esterification of ethyl oxalyl chloride with the lithium salt of 2,6-di-*tert*-butyl-4-methoxyphenol, followed by chemoselective nucleophilic addition of ethyl Grignard reagent to the unsymmetrical ethyl aryl oxalate at low temperatures (86–96% yield overall in two steps).[6a,d] First, 1,2-diester **2a** was indeed easily prepared in our hands in excellent yield on a large scale, and other 1,2-diesters were subsequently obtained in a similar fashion (Scheme 2).

For lack of a detailed experimental procedure in the reports of the synthesis of α-ketoester **3b**,[6a,d] one of us first treated a 0.02 M solution of 1,2-diester **2a** in diethyl ether (Et_2O) with a small excess (up to 1.2 equiv.) of a solution of ethylmagnesium bromide (EtMgBr) in Et_2O at low temperature (−78°C), and then continued stirring for 1.5 h while the reaction mixture warmed to room temperature (RT). While the appearance of the reaction mixture remained cloudy white at −78°C, the cloudiness dissipated when warming to RT, often leading to a clear, transparent solution. The addition of distilled water (H_2O) at RT produced a white reaction mixture, and the work-up procedure afforded the crude reaction product as a colorless, thick oil. The ^{1}H NMR analysis of this material first indicated the complete consumption of the starting 1,2-diester, and also confirmed the existence of the aryl moiety by the presence of the signals at 6.87, 3.80, and 1.30 ppm (Fig. 1, bottom). However, we were puzzled by the presence of signals in the olefinic region of the spectrum (6.03 and 5.73 ppm), and also by the presence of the doublet at 1.91 ppm. It was clear that the reaction had generated one product only, but certainly not the desired α-ketoester **3b**! With a rather limited number of possible structures for the reaction product given the reaction conditions, we came to consider the enol form (**4b**) of α-ketoester **3b** (Scheme 3). The solution (CCl_4) IR spectrum of the isolated material exhibited a sharp, non-hydrogen bonded OH stretch at 3501 cm^{-1}, thus reinforcing our hypothesis of the formation of enol ester **4b**.

With the structure of **4b** in hand, a detailed analysis of the spectral data that we initially collected (^{1}H NMR and IR) is as follows: the olefinic methyl group at 1.91 ppm (d, ^3J=7.2 Hz), the vinylic hydrogen at 6.03 ppm (dq, ^3J=7.2 Hz, ^4J=1.5 Hz), the hydroxyl hydrogen at 5.73 ppm (d, ^4J=1.5 Hz),[13] the OH stretch at 3501 cm^{-1}, and the conjugated ester carbonyl stretch at 1719 cm^{-1}. The expansion of the 5.70–6.10 ppm region is of great interest since it nicely demonstrates a case of allylic coupling (^4J=1.5 Hz), in this way further establishing the presence of enol ester **4b** (Fig. 1, bottom). Also, when the isolated material was placed in D_2O, the signal at 5.73 ppm disappeared, and the allylic coupling in the vinylic proton signal was not seen anymore, thus strongly supporting now the structure of enol ester **4b**. We later recorded the ^{13}C NMR spectrum of enol ester **4b**, and two additional signals were indeed observed in the C=C region of the spectrum (141.5 and 111.1 ppm).

Speculating on the mechanism of formation of this stable (isolable) enol, this intriguing observation was immediately



Scheme 2. Synthesis of 1,2-diesters **2a**–**c**.

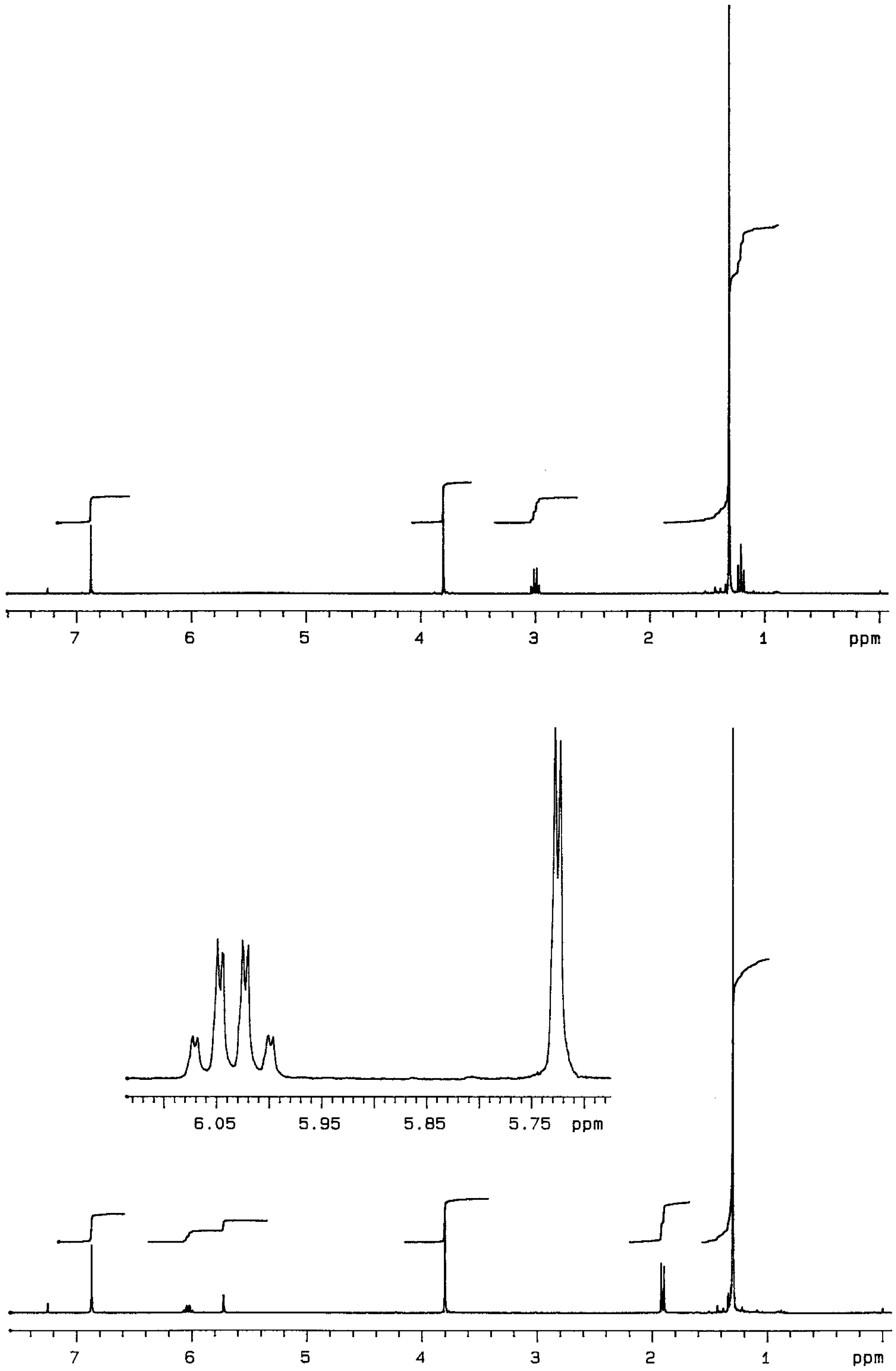
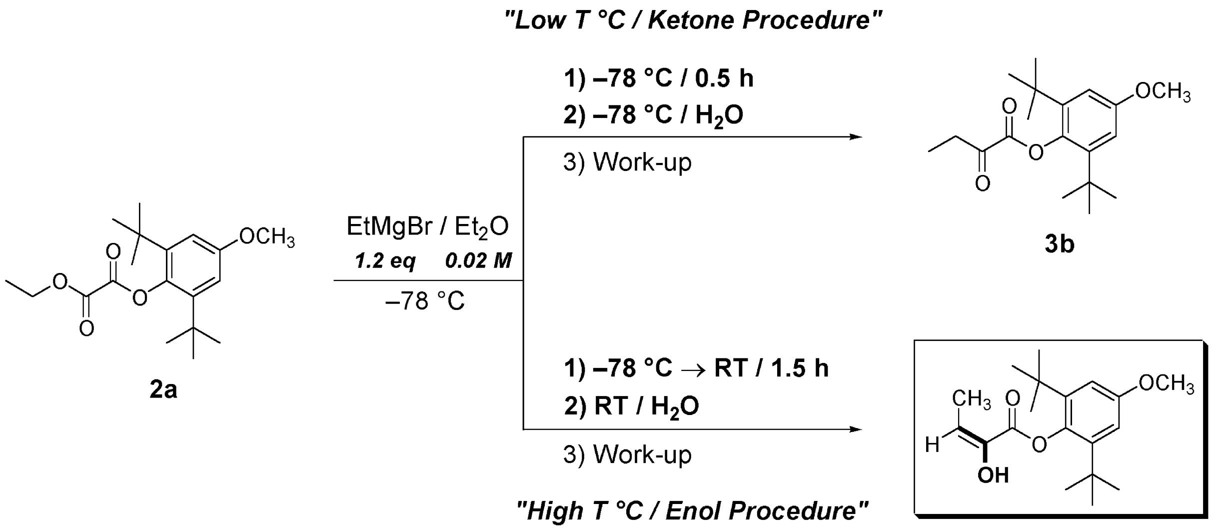


Figure 1. Bottom: ^{1}H NMR (300 MHz, $CDCl_3$-TMS) spectrum of enol ester **4b** with expansion of the vinylic proton signals and the alcohol proton signal. Top: ^{1}H NMR (300 MHz, $CDCl_3$-TMS) spectrum of α-ketoester **3b**.

followed by the reaction of **2a** with EtMgBr at −78°C for 0.5 h, and subsequent addition of H_2O at −78°C. The isolated material was also a thick oil, but its ^{1}H NMR analysis pointed out this time to the desired α-ketoester **3b** (Scheme 3) as the sole reaction product: a quartet at 3.0 ppm and a triplet at 1.21 ppm were the characteristic signals of **3b**, and the aryl moiety was represented by signals at 6.87, 3.80, and 1.31 ppm (Fig. 1, top). The solution (CCl_4) IR spectrum of the α-ketoester **3b** showed only one carbonyl stretch at 1739 cm^{-1}. The ^{13}C NMR spectrum of **3b** exhibited a—somewhat low—characteristic ketone carbonyl signal at 194.3 ppm, and the two signals indicating the presence of the ethyl group were seen at 32.8 and 6.9 ppm.

Each of these two procedures was repeated numerous times, and the ketone-free enol ester **4b** was always isolated in quantitative yield when the 'High *T*°C/Enol Procedure' was followed. It was also the case for the α-ketoester **3b** which



Scheme 3. Selective generation of α-ketoester **3b** and enol ester **4b**.

was always quantitatively obtained, free of its enol form, when the 'Low *T*°C/Ketone Procedure' was used (Scheme 3).[14] Only the incidental presence of a small amount of a strong base led to the partial formation of enol ester **4b** when the standard ketone procedure was used (vide infra).

Once convinced of the presence of a stable enol, we realized that each ^{1}H NMR signal characteristic of the enol moiety in **4b** actually existed as only one type of signal in each case. It was indeed legitimate to think that the two stereoisomeric enol esters would exhibit two distinct types of signal in each case, especially for the vinylic hydrogen. In other words, the generation of enol ester **4b** seemed to have been a completely stereoselective process. This assumption has been proven to be correct given a series of preliminary data obtained in the context of a systematic study that we have just initiated. Indeed, studying the effect of substituent size (R substituent, see Scheme 2) on the stability of the enol, the use of the 'High *T*°C/Enol Procedure' with 1,2-diester **2b** produced a ^{1}H NMR spectrum in which two types of signal were observed for the olefinic methyl group (1.87 and 1.77 ppm) and also for the vinylic hydrogen (6.10 and 5.75 ppm) of the enol ester derivative. The corresponding α-ketoester was also present, thus demonstrating the effect of substituent size on the stability and the stereoselective generation of the enol.[15] The exact geometry of the isomerically pure enol ester **4b** was proposed to be (*E*) on the basis of the following observation: when the chromato-

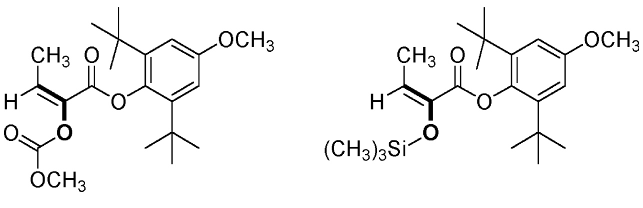


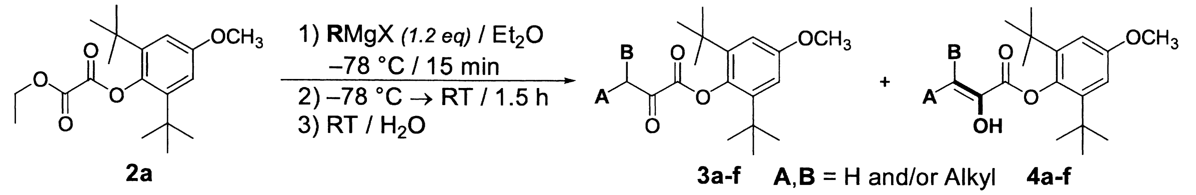
Figure 2. Methyl carbonate **5** and TMS ether **6** derived from (*E*)-enol ester **4b**.

graphically stable methyl carbonate derivative **5** of enol ester **4b** was prepared in order to further confirm the presence of the stable enol,[16] the vinylic hydrogen experienced a downfield shift of 0.91 ppm (q, ^3J=7.1 Hz); it was attributed to intramolecular hydrogen bonding between the vinylic hydrogen and the carbonate carbonyl oxygen in the (*E*) geometry of the enol methyl carbonate (Fig. 2).[17] The trimethylsilyl (TMS) ether derivative **6** was also prepared, but was more sensitive to silica gel chromatographic purification (67% isolated yield) (Fig. 2).[18] As expected, the TMS group was responsible for a significantly lower downfield shift, i.e. 0.36 ppm (q, ^3J=7.1 Hz).

2.2. Stability studies of enol ester 4b

Typically, when the 'High *T*°C/Enol Procedure' was carried out, crude enol ester **4b** was isolated as a colorless (or pale yellow), very thick oil (vide supra), and was kept under high vacuum in order to remove residual solvent (Et_2O). We first studied the kinetic stability of enol ester **4b** in pure liquid phase, and the enol–keto tautomerization of a series of samples was monitored daily by ^{1}H NMR analysis (C=C–C*H*$_3$ in **4b** vs O=C–C*H*$_2$CH$_3$ in **3b**). Only traces (<1%) of α-ketoester **3b** could be observed after standing on the bench at RT for 1 day. After 2 days, 1 week, 2 weeks, and 3 weeks of standing under similar conditions, **3b** was present in as much as 5, 45, 78, and 90%, respectively.[19] For a few samples, this study was hampered by the spontaneous crystallization of some of the oily material, and this event was shown to dramatically slow down the enol–keto equilibrium; after 3 weeks, the enol content of such samples was still greater than 95%. This observation led us to study the kinetic stability of **4b** in solid phase. A few solid samples of the enol ester were obtained when the corresponding oily material was stored in the freezer immediately after its isolation.[20] While kept at −10°C, or standing on the bench at RT for several months, in the solid state, **4b** did not undergo tautomerization at all! A very similar stability was also observed in solution phase. First, we recorded daily the ^{1}H NMR spectrum of a dilute solution of **4b** in $CDCl_3$ (a

Table 1. Selective generation of the enol ester: nucleophile dependence



Series	RMgX	3^a (%)	4^a (%)
a	MeMgBr	82	18
b	EtMgBr	0	100
c	*n*-PrMgCl	70	30
d	*i*-PrMgCl	68	32
e	*n*-BuMgCl	70	30
f	*sec*-BuMgCl	100	0

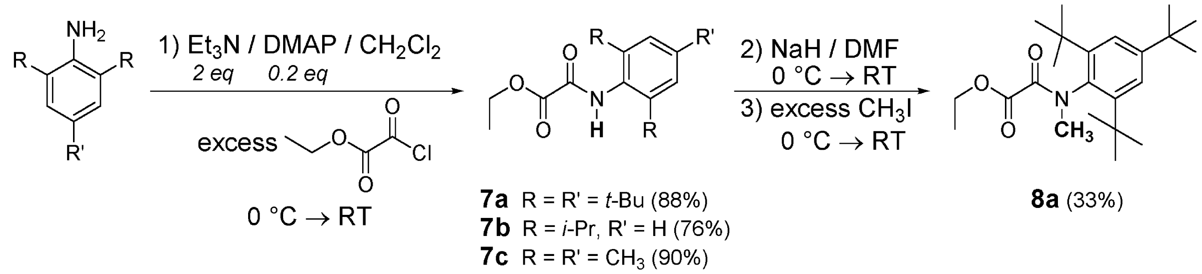
[a] Determined by 300 MHz ^{1}H NMR analysis of the isolated crude reaction mixture.

standard NMR sample), and after 1 month, α-ketoester **3b** was present in less than 5%. When a 0.02 M solution of **4b** in dry Et_2O was left stirring for 2 weeks at RT and under nitrogen, less than 6% of **3b** was observed. However, in the presence of an equimolar amount of triethylamine (Et_3N), **3b** was present in more than 85% after 1 day only; the enol–keto tautomerization was slower in the presence of *p*-toluenesulfonic acid (TsOH) since no more than 40% of **3b** could be observed after 1 day. Additional information regarding the tautomerization process was gained while purifying compounds **3b** and **4b**. For instance, silica gel column chromatography of enol-free, crude α-ketoester **3b** afforded a 86:14 ratio of **3b** and **4b**, and bulb-to-bulb distillation of ketone-free, crude enol ester **4b** afforded a 68:32 ratio of **4b** and **3b**.

2.3. Generality of the observation of a stable enol ester

To complete our series of studies following the discovery of stable enol **4b**, we decided to examine how general the observation of such a type of stable enol was. We first looked at the reaction of 1,2-diester **2a** with other alkyl Grignard reagents using the 'High *T*°C/Enol Procedure', and we observed that a stable (isolable) enol ester could be formed in many instances (Table 1).[21] Whereas the enol form (**4b**) of α-ketoester **3b** displayed this unique and intriguing stability, the degree of substitution of the alkene moiety did not seem to have a beneficial influence on the stability of the enol ester; indeed, the *i*-PrMgCl-derived enol **4d** (Table 1, **A**=**B**=Me) was present in only 32%, and the enol **4f** (Table 1, **A**=Me, **B**=Et, or **A**=Et, **B**=Me) was even not observed when *sec*-BuMgCl was used. Organolithium compounds, i.e. ethyllithium (EtLi)[22] and *n*-butyllithium (*n*-BuLi), were also tested with 1,2-diester **2a**, and both afforded, cleanly and quantitatively, the corresponding α-ketoester using the 'Low *T*°C/Ketone Procedure'. When the 'High *T*°C/Enol Procedure' was carried out, the reaction with EtLi afforded ketone-free enol ester **4b** and also a significant amount of the phenol derivative (DBHA), the formation of the latter indicating that nucleophilic addition to the carbonyl group of the aryl ester had also taken place; we had not observed yet this type of reactivity with Grignard reagents and 2,6-di-*tert*-butyl-substituted aryl alkyl 1,2-diesters. With *n*-BuLi, it is noteworthy that enol ester **4e** was isolated free of the corresponding α-ketoester **3e**, and only a small amount of DBHA was observed.

We finally considered using 1,2-amide esters in place of 1,2-diesters for the attempted generation of the corresponding enol amides from reaction with EtMgBr. Since the 4-*tert*-butyl substitution pattern present in target substrate **8a** (Scheme 4) had never been explored with 1,2-diesters, we first prepared 1,2-diester **2c** (Scheme 2), and not surprisingly, its reaction with EtMgBr produced the (*E*)-enol ester in quantitative yield. The synthesis of *N*-methyl amide ester **8a** then followed (Scheme 4),[23] but its reaction with EtMgBr according to the standard enol procedure did not produce the expected enol amide; the α-ketoamide was isolated in 65% yield, and a fair amount of unreacted **8a** was also recovered, thus indicating the lower reactivity of 1,2-amide esters. In a last attempt, we decided to also examine the behavior of unprotected 1,2-amide esters **7a–c**

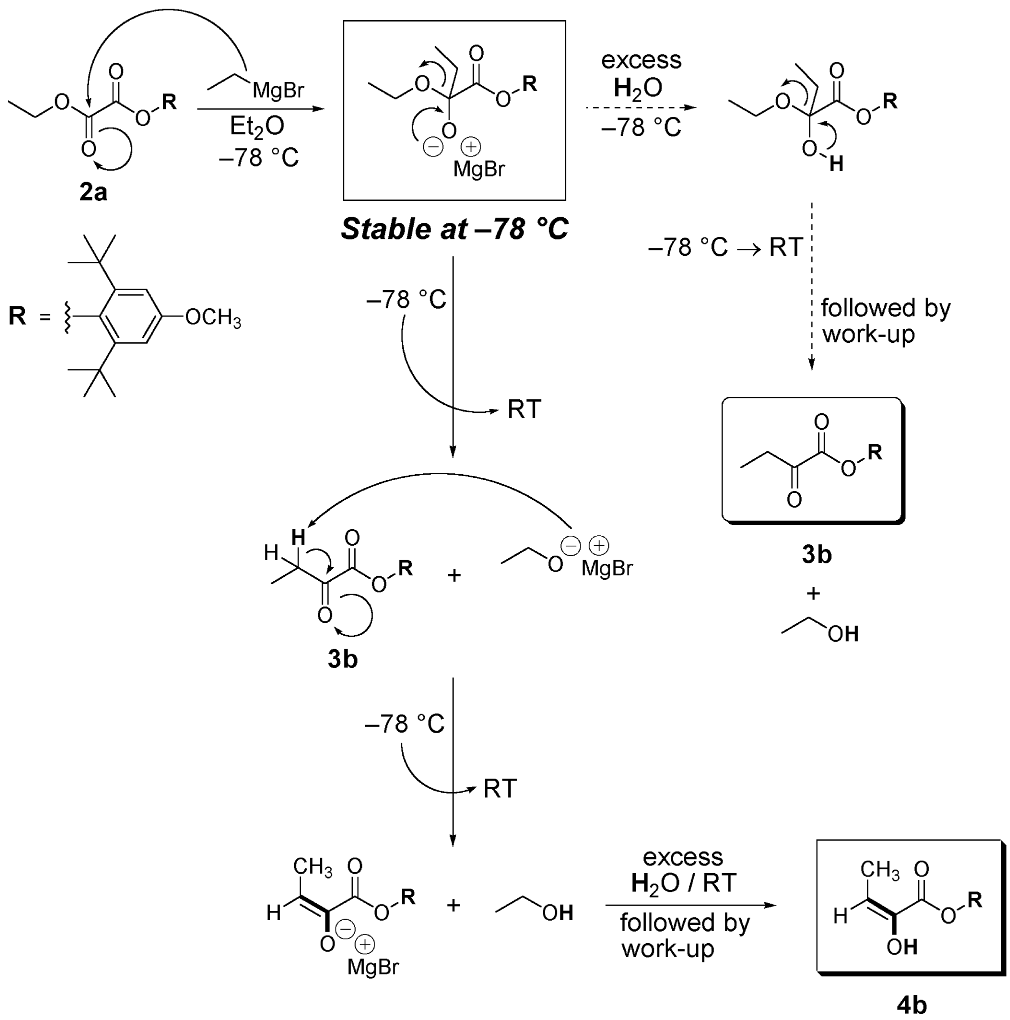


Scheme 4. Synthesis of 1,2-amide esters **7a–c** and **8a**.

(Scheme 4) in the presence of EtMgBr (2 equiv.), and to our delight, we could observe the formation of a stable (isolable) enol amide in each case;[24] the crude product isolated from each reaction also contained the corresponding α-keto-amide, and a fair amount of unreacted starting material. Clearly, the formation of a stable (isolable) enol derived from one of the sterically hindered 1,2-dicarbonyls seemed to be a rather general observation.

3. Discussion

It is quite early in our discovery that we realized the importance of a temperature change on the selective generation of α-ketoester **3b** and enol ester **4b**. In that respect, the observation of stable enol **4b** is a nice illustration of the temperature-dependent outcome of the tetrahedral intermediate. Scheme 5 shows the rationalization and proposed mechanism underlying the results presented above. In the first step, the tetrahedral intermediate that is formed by addition of EtMgBr to the least sterically hindered ester carbonyl group in **2a** is a quite stable species at −78°C.[25] Its stability is likely due to the formation of a strong chelate involving the magnesium alkoxide and the aryl ester carbonyl oxygen. The results obtained with the use of EtLi and *n*-BuLi also demonstrate the stability of a lithium-based tetrahedral intermediate at low temperature, quite likely for the same reason, i.e. the formation of a lithium alkoxide chelate. The reaction of this intermediate with excess H_2O at low temperature produces a hemiketal, which rapidly decomposes to the α-ketoester **3b**. To further illustrate the stability of the tetrahedral intermediate at low temperature, the reaction was also carried out with a large excess (3 equiv.) of EtMgBr, and ^{1}H NMR analysis of the crude reaction product showed again the clean and quantitative formation of **3b**. However, while warming to RT, the tetrahedral intermediate breaks down, and the α-ketoester **3b** is generated in situ along with bromomagnesium ethoxide (EtOMgBr); for this reason, only a small excess of EtMgBr is used to ensure completion of the reaction. An acid–base reaction then follows, and the magnesium enolate of **3b** is formed; its reaction with excess H_2O at RT selectively produces the corresponding enol ester **4b** endowed with remarkable kinetic stability. Interestingly, according to a somewhat similar set of reaction conditions (treatment of a ketone with excess base followed by an aqueous quench), the isolation of a highly substituted and hindered stable simple enol was reported some years ago; remarkably enough, the enol was shown to be thermodynamically more stable than its keto form.[26]



Scheme 5. Mechanistic rationale for the selective formation of α-ketoester **3b** and enol ester **4b**.

The occasional quench of the reaction mixtures with methanol (MeOH) instead of H_2O produced some experimental evidence of this proposed mechanism. For instance, when a large excess (1.5 equiv.) of *n*-BuLi was used with **2a** according to the 'Low *T*°C/Ketone Procedure', and excess MeOH was added for quench, a small amount of enol ester **4b** was also observed; under similar reaction conditions and an aqueous quench, α-ketoester **3b** was only observed. The excess *n*-BuLi is held responsible for the in situ generation of a significant amount of lithium methoxide (MeOLi), and strongly basic MeOLi enolizes some of the α-ketoester produced by decomposition of the hemiketal (vide supra). When 1,2-amide esters **7a–c** were used according to the standard ketone procedure, unreacted EtMgBr produced a significant amount of bromomagnesium methoxide (MeOMgBr) upon a MeOH quench, and a small amount of each of the enol amides was also observed; the α-ketoamides were the only products formed with an aqueous quench. Interestingly, with either procedure, the unreacted 1,2-amide ethyl esters **7a–c** and **8a** were recovered completely as their corresponding methyl esters, indicating their reaction with MeOMgBr.

Thus, the selective formation of stable (isolable) enols and their corresponding ketones from Grignard addition to 1,2-diesters and 1,2-amide esters can be rationalized. However, whereas the size of the substituents at the two *ortho* positions of the aryl moiety has clearly a strong effect on the stability of the enol tautomer, the origin of this effect is not well understood, yet. The systematic study of the effect of substituent size that we have just initiated, along with a single crystal X-ray structure determination of enol ester **4b** and computational studies, will seek to gain an understanding of the origin of this effect.

4. Conclusion

In summary, we have reported the serendipitous discovery of a remarkably stable enol derived from an aliphatic 1,2-dicarbonyl compound, and we have also demonstrated the generality of this observation. Whereas the existence of the enol tautomer of alicyclic 1,2-dicarbonyls, especially alicyclic 1,2-diketones, has been well documented, there has been only a scarcity of reports on stable enol forms of aliphatic 1,2-dicarbonyls.[27] In that sense, the observation just described is illustrative of a case of enol stability that we deem worthy of additional exploration, so efforts to gain further insight into the understanding of this remarkable stability are already underway. The results will be reported in due course.[28]

5. Experimental

5.1. General experimental

All reactions were performed in oven (150°C) and/or flame-dried glassware under an inert atmosphere of dry nitrogen. All the solvents used were reagent grade and distilled from the indicated drying agents: diethyl ether (Et_2O) and tetrahydrofuran (THF): Na, benzophenone; dichloromethane (CH_2Cl_2) and dimethylformamide (DMF): CaH_2; triethylamine (Et_3N) was used as reagent grade solvent. 'Brine' refers to a saturated aqueous solution of NaCl. Bulb-to-bulb distillations were performed on a Büchi Glass Oven B-580 and boiling points (bp) correspond to the uncorrected recorded air bath temperatures (ABT). Melting points (mp) were recorded in open glass capillaries on a MEL-TEMP® II (Laboratory Devices, Inc.) melting point apparatus and are uncorrected.

Column chromatography was performed using 230–400 mesh ASTM silica gel 60 purchased from EM Science. The solvents used for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane and dichloromethane (CH_2Cl_2): $CaCl_2$; ethyl acetate (EtOAc): K_2CO_3; diethyl ether (Et_2O) was used as reagent grade solvent.

^{1}H and ^{13}C NMR spectra were recorded on either a Varian Gemini-300 (300 MHz ^{1}H, 75.5 MHz ^{13}C) or a Varian Inova-500 (500 MHz ^{1}H, 126 MHz ^{13}C) FT spectrometer in deuteriochloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal reference for ^{1}H NMR (0.00 ppm, ^{1}H) or chloroform as an internal reference for ^{13}C NMR (77.0 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sext (sextet), sept (septet), m (multiplet), br (broad), and exch (D_2O exchangeable); coupling constants, *J*, are reported in Hertz (Hz); integration is provided and assignments are indicated. Infrared spectra (IR) were recorded on a Perkin–Elmer Paragon 1000 FT-IR Spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67–100%); m (medium, 34–66%); w (weak, 0–33%). Low resolution electron impact mass spectra (EI-MS) and accurate mass EI spectra (EI-HRMS) were recorded at the University of Missouri-St Louis Mass Spectrometry Facility.

5.2. General procedure for the preparation of 1,2-diesters (2a–c)

5.2.1. Preparation of 2,6-di-*tert*-butyl-4-methoxyphenyl ethyl oxalate (2a). A three-necked, 250 mL round-bottom flask with a magnetic stir bar and fitted with a gas inlet adapter and septa was filled with dry THF (80 mL), and a solution of 2,6-di-*tert*-butyl-4-methoxyphenol (3.273 g, 13.85 mmol, 1.0 equiv.) in dry THF (20 mL) was added via syringe. The resulting clear orange solution was allowed to stir at RT for a few minutes, and then was cooled to −78°C, and stirred for ca. 5 min. A 3.86 M solution of *n*-BuLi in hexanes was added slowly via syringe (4.0 mL, 15.44 mmol, 1.12 equiv.), and the resulting intense yellow solution was stirred for 30 min at −78°C. The intermediate lithium phenoxide was then treated (dropwise addition) with ethyl oxalyl chloride (2.10 mL, 18.80 mmol, 1.36 equiv.), and the reaction mixture was allowed to warm to RT and stir for 2 h. The reaction mixture was then poured into H_2O (50 mL), and was extracted with Et_2O (2×150 mL). The extracts were combined, washed with brine (70 mL), dried ($MgSO_4$) upon stirring, filtered, and concentrated in vacuo to afford the crude reaction product as a thick, light brown oil. This material was purified by silica gel column chromatography (hexane/ethyl acetate, 15:1), and further purification was accomplished by bulb-to-bulb distillation to afford 4.557 g (97% yield) of 1,2-diester **2a** as a thick, pale yellow oil: bp 185–190°C (0.4 mm Hg, ABT). ^{1}H NMR (300 MHz, $CDCl_3$): 6.88 (s, 2H, Ph), 4.46 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.79 (s, 3H, OCH_3), 1.42 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.34 (s, 18H, 2×C(CH_3)$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): 158.8, 158.0, 156.9, 143.3, 140.7, 111.8, 63.2, 55.2, 35.5, 31.3, 13.8. IR (CCl_4): 2968 (m), 1789 (m), 1751 (s), 1590 (m), 1448 (w), 1418 (m), 1367 (w), 1306 (m), 1182 (s), 1145 (s), 1066 (m), 1018 (w). EI-MS: 336 (M, 36), 303 (11), 281 (8), 235 (81), 221 (60), 205 (100), 193 (16), 175 (55), 164 (27), 149 (32), 135 (34), 119 (33), 105 (34), 91 (52), 77 (21), 57 (25). EI-HRMS: calcd for $C_{19}H_{28}O_5$ [M^+] 336.1936, found 336.1939.

5.2.2. Preparation of 2,4,6-trimethylphenyl ethyl oxalate (2b). From 2,4,6-trimethylphenol (2.007 g, 14.74 mmol, 1.0 equiv.), dry THF (100 mL), a 2.57 M solution of *n*-BuLi in hexanes (6.60 mL, 16.96 mmol, 1.15 equiv.), and ethyl oxalyl chloride (2.20 mL, 19.69 mmol, 1.34 equiv.). The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 15:1) to afford 2.455 g (71% yield) of 1,2-diester **2b** as a thick, pale yellow oil which solidified as an off-white solid at RT upon standing: mp 32–34°C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.84 (s, 2H, Ph), 4.38 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 2.22 (s, 3H, C$_6$H$_2$-*p*-CH_3), 2.12 (s, 6H, 2×C$_6$H$_2$-*o*-CH_3), 1.37 (t, J=7.2 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): 157.3, 155.8, 144.9, 135.8, 129.1, 128.8, 63.0, 20.3, 15.6, 13.5. IR (CCl_4): 2985 (m), 2926 (m), 2864 (w), 1781 (s), 1752 (s), 1608 (w), 1483 (m), 1371 (w), 1308 (m), 1190 (s), 1153 (s), 1017 (m). EI-MS: 236 (M, 30), 136 (100), 135 (60), 121 (39), 91 (51), 79 (10), 77 (10). EI-HRMS: calcd for $C_{13}H_{16}O_4$ [M^+] 236.1048, found 236.1043.

5.2.3. Preparation of 2,4,6-tri-*tert*-butylphenyl ethyl oxalate (2c). From 2,4,6-tri-*tert*-butylphenol (1.160 g, 4.42 mmol, 1.0 equiv.), dry THF (50 mL), a 2.60 M solution of *n*-BuLi in hexanes (1.90 mL, 4.94 mmol, 1.12 equiv.), and ethyl oxalyl chloride (0.70 mL, 6.27 mmol, 1.42 equiv.). The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 5:1) to afford 1.536 g (96% yield) of 1,2-diester **2c** as a white solid: mp 60–62°C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.34 (s, 2H, Ph), 4.47 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 1.43 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.35 (s, 18H, 2×C$_6$H$_2$-*o*-C(CH_3)$_3$), 1.32 (s, 9H, C$_6$H$_2$-*p*-C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 158.5, 157.9, 148.0, 144.6, 140.9, 123.5, 63.3, 35.5, 34.8, 31.5, 31.4, 13.9. IR (CCl_4): 2966 (s), 2910 (m), 2874 (m), 1782 (m), 1751 (s), 1594 (w), 1428 (m), 1365 (m), 1188 (s), 1157 (s), 1134 (s), 1102 (m), 1018 (w). EI-MS: 362 (M, 42), 347 (10), 329 (20), 275 (15), 262 (25), 247 (100), 231 (30), 219 (7), 205 (22), 177 (9), 149 (8), 57 (19). EI-HRMS: calcd for $C_{22}H_{34}O_4$ [M^+] 362.2457, found 362.2452.

5.3. General procedures for the generation of enol esters (or enol amides) and their corresponding α-ketoesters (or α-ketoamides)

5.3.1. Preparation of the α-ketoester from EtMgBr addition to 2,6-di-*tert*-butyl-4-methoxyphenyl ethyl oxalate (3b). A two-necked, 100 mL round-bottom flask with a magnetic stir bar and fitted with a gas inlet adapter and a septum was filled with dry Et_2O (36 mL), and a solution of **2a** (0.258 g, 0.77 mmol, 1.0 equiv.) in dry Et_2O (4 mL) was added via syringe. The resulting colorless solution was allowed to stir at RT for a few minutes, and then was cooled to −78°C, and stirred for ca. 5 min. A 2.35 M solution of EtMgBr in Et_2O was added slowly via syringe (0.36 mL, 0.85 mmol, 1.10 equiv.), and the resulting cloudy white solution was stirred for 30 min at −78°C. The reaction mixture was then treated with distilled H_2O (0.50 mL) at −78°C, and was allowed to warm to RT and stir for ca. 5 min. The reaction mixture was then poured into H_2O (10 mL), and was extracted with Et_2O (2×50 mL). The extracts were combined, dried ($MgSO_4$) upon stirring, filtered, concentrated in vacuo, and the resulting material was kept under high vacuum for 30 min to afford crude, enol-free, **3b** (quant) as a colorless, very thick oil. This material could be purified by bulb-to-bulb distillation to afford enol-free **3b** which occasionally solidified as a white solid after a prolonged time in the freezer: bp 150–155°C (0.1 mm Hg, ABT); mp 47–49°C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.87 (s, 2H, Ph), 3.80 (s, 3H, OCH_3), 3.0 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 1.31 (s, 18H, 2×C(CH_3)$_3$), 1.21 (t, J=7.2 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): 194.3 (*C*O), 162.1 (*C*O$_2$), 156.7, 143.1, 140.9, 111.7, 55.1, 35.5, 32.8 (*C*H$_2$CH$_3$), 31.3, 6.9 (CH$_2$*C*H$_3$). IR (CCl_4): 2967 (s), 1739 (s), 1590 (m), 1448 (m), 1418 (s), 1305 (m), 1253 (s), 1223 (m), 1174 (s), 1095 (s), 1066 (s), 1025 (m). EI-MS: 320 (M, 8), 237 (17), 236 (100), 221 (34), 205 (5), 179 (2), 91 (2), 57 (6). EI-HRMS: calcd for $C_{19}H_{28}O_4$ [M^+] 320.1987, found 320.1990.

5.3.2. Preparation of the enol ester from EtMgBr addition to 2,6-di-*tert*-butyl-4-methoxyphenyl ethyl oxalate (4b). A two-necked, 100 mL round-bottom flask with a magnetic stir bar and fitted with a gas inlet adapter and a septum was filled with dry Et_2O (36 mL), and a solution of **2a** (0.257 g, 0.76 mmol, 1.0 equiv.) in dry Et_2O (4 mL) was added via syringe. The resulting colorless solution was allowed to stir at RT for a few minutes, and then was cooled to −78°C, and stirred for ca. 5 min. A 2.35 M solution of EtMgBr in Et_2O was added slowly via syringe (0.36 mL, 0.85 mmol, 1.12 equiv.), and the resulting cloudy white solution was stirred for 15 min at −78°C. The reaction mixture was then allowed to warm to RT and stir for 1.5 h. The resulting clear, transparent solution was then treated with distilled H_2O (0.50 mL) at RT, and was immediately poured into H_2O (10 mL), and extracted with Et_2O (2×50 mL). The extracts were combined, dried ($MgSO_4$) upon stirring, filtered, concentrated in vacuo, and the resulting material was kept under high vacuum for 30 min to afford crude, ketone-free, **4b** (quant) as a colorless, thick oil. This material occasionally solidified as a white solid in the freezer: mp 70–73°C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.87 (s, 2H, Ph), 6.03 (dq, J=7.2 Hz, 1.5, 1H, *H*C=C), 5.73 (d, J=1.5 Hz, 1H, O*H*, exch), 3.80 (s, 3H, OCH_3), 1.91 (d, J=7.2 Hz, 3H, H_3CC=C), 1.30 (s, 18H, 2×C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 165.7 (*C*O$_2$), 156.3, 143.3, 141.5 (HO–*C*=C), 141.0, 111.4, 111.1 (HO–C=*C*), 54.8, 35.2, 31.0, 10.6 (H$_3$*C*–C=C). IR (CCl_4): 3501 (m), 2967 (s), 1719 (s), 1589 (m), 1419 (m), 1393 (m), 1365 (m), 1304 (m), 1241 (s), 1219 (s), 1175 (s), 1133 (m), 1104 (w), 1069 (s). EI-MS: 320 (M, 6), 236 (100), 221 (31), 205 (6), 179 (3), 91 (3), 85 (2), 57 (5). EI-HRMS: calcd for $C_{19}H_{28}O_4$ [M^+] 320.1987, found 320.1989.

5.4. General procedure for the preparation of enol ester derivatives (5 and 6)

5.4.1. Preparation of the enol ester methyl carbonate derivative (5). The crude, ketone-free (^{1}H NMR analysis of the isolated crude material) enol ester (**4b**) was first prepared according to the procedure described in Section 5.3.2; from **2a** (0.322 g, 0.96 mmol, 1.0 equiv.), dry Et_2O (52 mL), and a 2.78 M solution of EtMgBr in Et_2O (0.38 mL, 1.06 mmol, 1.10 equiv.). Dry CH_2Cl_2 (20 mL) was added to the flask containing crude enol ester **4b**, and the resulting colorless solution was cooled to 0°C, and stirred for ca. 5 min. It was then treated (dropwise addition) successively with methyl chloroformate (0.30 mL, 3.88 mmol, 4.04 equiv.) and Et_3N (0.20 mL, 1.43 mmol, 1.49 equiv.), and the reaction mixture was allowed to warm to RT and stir overnight. The reaction mixture was then poured into H_2O (10 mL), and was extracted with CH_2Cl_2 (2×50 mL). The extracts were combined, dried ($MgSO_4$) upon stirring, filtered, and concentrated in vacuo to afford a thick, pale yellow oil. This material was purified by silica gel column chromatography (hexane/ethyl acetate, 5:1) to afford 0.329 g (91% yield) of **5** as a very thick, colorless oil. Further purification was accomplished by bulb-to-bulb distillation: bp 210–215°C (0.1 mm Hg, ABT). ^{1}H NMR (300 MHz, $CDCl_3$): 6.94 (q, J=7.1 Hz, 1H, HC=C), 6.86 (s, 2H, Ph), 3.86 (s, 3H, (C=O)OCH_3), 3.79 (s, 3H, C_6H_2-p-OCH_3), 1.93 (d, J=7.1 Hz, 3H, H_3CC=C), 1.31 (s, 18H, 2×C(CH_3)$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): 161.8, 156.6, 152.9, 143.8, 141.1, 140.2, 129.6, 111.7, 55.5, 55.2, 35.5, 31.3, 11.7. IR (CCl_4): 2960 (m), 1773 (s), 1748 (m), 1673 (w), 1590 (w), 1442 (m), 1418 (w), 1366 (w), 1270 (s), 1249 (s), 1175 (m), 1128 (m), 1067 (m), 1031 (m). EI-MS: 378 (M, 18), 236 (76), 221 (33), 205 (22), 193 (4), 177 (10), 164 (7), 149 (5), 135 (7), 129 (5), 119 (7), 105 (7), 99 (46), 91 (9), 77 (4), 59 (17), 57 (6). EI-HRMS: calcd for $C_{21}H_{30}O_6$ [M^+] 378.2042, found 378.2036.

5.4.2. Preparation of the enol ester trimethylsilyl ether derivative (6). From **2a** (0.313 g, 0.93 mmol, 1.0 equiv.), dry Et_2O (47 mL), and a 2.78 M solution of EtMgBr in Et_2O (0.40 mL, 1.11 mmol, 1.19 equiv.); the crude, ketone-free (^{1}H NMR analysis of the isolated crude material) enol ester (**4b**) was obtained in quantitative yield. From crude enol ester **4b**, dry CH_2Cl_2 (10 mL), trimethylsilyl chloride (dropwise addition; 0.60 mL, 4.73 mmol, 5.09 equiv.), and Et_3N (0.20 mL, 1.43 mmol, 1.54 equiv.). The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 5:1) to afford 0.246 g (67% yield) of **6** as a white solid: mp 90–92°C. ^{1}H NMR (300 MHz, $CDCl_3$): 6.86 (s, 2H, Ph), 6.39 (q, J=7.1 Hz, 1H, HC=C), 3.78 (s, 3H, OCH_3), 1.85 (d, J=7.1 Hz, 3H, H_3CC=C), 1.31 (s, 18H, 2×C(CH_3)$_3$), 0.22 (s, 9H, Si(CH_3)$_3$). ^{13}C NMR (75.5 MHz, $CDCl_3$): 164.9, 156.4, 143.7, 142.7, 141.5, 119.5, 111.7, 55.1, 35.5, 31.4, 11.6, 0.8. IR (CCl_4): 2963 (s), 2913 (m), 2874 (m), 2834 (w), 1739 (s), 1646 (m), 1590 (m), 1419 (m), 1391 (m), 1344 (m), 1253 (s), 1224 (m), 1184 (s), 1131 (s), 1067 (s). EI-MS: 392 (M, 27), 377 (13), 236 (31), 221 (12), 205 (4), 181 (2), 157 (15), 129 (100), 121 (2), 91 (2), 73 (27), 57 (4). EI-HRMS: calcd for $C_{22}H_{36}O_4Si$ [M^+] 392.2382, found 392.2376.

5.5. General procedure for the preparation of unprotected 1,2-amide esters (7a–c)

5.5.1. Preparation of *N*-2,4,6-tri-*tert*-butylphenyl-substituted 1,2-amide ester (7a). A two-necked, 100 mL round-bottom flask with a magnetic stir bar was charged with 2,4,6-tri-*tert*-butylaniline (1.491 g, 5.70 mmol, 1.0 equiv.), and was fitted with a gas inlet adapter and a septum. The flask was then purged with nitrogen, dry CH_2Cl_2 (35 mL) was added, and the resulting solution was cooled to 0°C, and stirred for ca. 5 min. It was then treated successively with Et_3N (1.60 mL, 11.48 mmol, 2.01 equiv.), 4-(dimethylamino)pyridine (DMAP; 0.144 g, 1.18 mmol, 0.21 equiv.), and ethyl oxalyl chloride (dropwise addition; 1.30 mL, 11.64 mmol, 2.04 equiv.), and the yellow reaction mixture was allowed to warm to RT and stir overnight. The reaction mixture was then poured into H_2O (50 mL), and was extracted with CH_2Cl_2 (2×100 mL). The extracts were combined, dried ($MgSO_4$) upon stirring, filtered, and concentrated in vacuo to afford a pale yellow solid. This material was purified by silica gel column chromatography (CH_2Cl_2) to afford 1.805 g (88% yield) of **7a** as a white solid: mp 229–230°C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.51 (s, 1H, NH, br), 7.42 (s, 2H, Ph), 4.45 (q, J=7.2 Hz, 2H, CH_2CH_3), 1.44 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.38 (s, 18H, 2×C_6H_2-o-C(CH_3)$_3$), 1.32 (s, 9H, C_6H_2-p-C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 161.3, 157.0, 150.0, 147.8, 128.6, 123.2, 63.6, 36.1, 34.9, 31.9, 31.3, 13.9. IR (CH_2Cl_2): 3395 (m), 3053 (w), 2967 (s), 2873 (m), 1762 (m), 1711 (s), 1597 (w), 1507 (m), 1478 (m), 1395 (m), 1365 (m), 1295 (s), 1258 (m), 1180 (m), 1140 (w), 1016 (m). EI-MS: 361 (M, 3), 346 (2), 304 (100), 288 (3), 272 (8), 258 (14), 244 (3), 230 (12), 214 (4), 200 (3), 174 (3), 172 (3), 158 (3), 91 (1), 57 (5). EI-HRMS: calcd for $C_{22}H_{35}NO_3$ [M^+] 361.2616, found 361.2620.

5.5.2. Preparation of *N*-2,6-di-*iso*-propylphenyl-substituted 1,2-amide ester (7b). From 2,6-di-*iso*-propylaniline (3.104 g, 17.51 mmol, 1.0 equiv.), dry CH_2Cl_2 (100 mL), Et_3N (4.90 mL, 35.16 mmol, 2.01 equiv.), 4-(dimethylamino)pyridine (DMAP; 0.439 g, 3.59 mmol, 0.21 equiv.), and ethyl oxalyl chloride (2.40 mL, 21.48 mmol, 1.23 equiv.). The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 5:1) to afford 3.686 g (76% yield) of **7b** as a white solid: mp 131–133°C. ^{1}H NMR (300 MHz, $CDCl_3$): 8.40 (s, 1H, NH, br), 7.37–7.31 (m, 1H, p-Ph), 7.22–7.19 (m, 2H, m-Ph), 4.44 (q, J=7.2 Hz, 2H, CH_2CH_3), 3.01 (sept, J=6.9 Hz, 2H, CH(CH_3)$_2$), 1.45 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.20 (d, J=6.9 Hz, 12H, 2×CH(CH_3)$_2$). ^{13}C NMR (126 MHz, $CDCl_3$): 160.8, 155.7, 145.6, 129.2, 128.7, 123.5, 63.4, 28.6, 23.4, 13.7. IR (CCl_4): 3393 (m), 3069 (w), 2965 (s), 2930 (m), 2870 (m), 1719 (s), 1501 (s), 1474 (m), 1446 (w), 1370 (m), 1293 (s), 1205 (m), 1160 (m). EI-MS: 278 (M+1, 13), 277 (M, 7), 248 (7), 230 (3), 204 (100), 189 (16), 186 (24), 176 (12), 170 (8), 160 (19), 146 (38), 144 (28), 130 (21), 128 (18), 117 (18), 115 (17), 106 (11), 91 (17), 77 (7), 65 (2). EI-HRMS: calcd for $C_{16}H_{23}NO_3$ [M^+] 277.1677, found 277.1680.

5.5.3. Preparation of *N*-2,4,6-trimethylphenyl-substituted 1,2-amide ester (7c). From 2,4,6-trimethylaniline (1.012 g, 7.48 mmol, 1.0 equiv.), dry CH_2Cl_2 (35 mL), Et_3N (2.10 mL, 15.07 mmol, 2.01 equiv.), 4-(dimethylamino)-pyridine (DMAP; 0.194 g, 1.59 mmol, 0.21 equiv.), and ethyl oxalyl chloride (1.0 mL, 8.95 mmol, 1.20 equiv.). The crude material was purified by silica gel column chromatography (hexane/ethyl acetate, 1:1) to afford 1.577 g (90% yield) of **7c** as a white solid: mp 76–78°C. ^1H NMR (300 MHz, $CDCl_3$): 8.37 (s, 1H, NH, br), 6.90 (s, 2H, Ph), 4.41 (q, J=7.1 Hz, 2H, CH_2CH$_3$), 2.26 (s, 3H, C_6H_2-*p*-CH_3), 2.18 (s, 6H, 2×C_6H_2-*o*-CH_3), 1.43 (t, J=7.1 Hz, 3H, CH$_2$CH_3). ^{13}C NMR (126 MHz, $CDCl_3$): 160.6, 154.5, 137.3, 134.4, 129.3, 128.7, 63.1, 20.6, 17.9, 13.6. IR (CCl_4): 3392 (m), 2983 (m), 2922 (w), 1719 (s), 1549 (m), 1506 (s), 1444 (w), 1370 (m), 1293 (s), 1227 (m), 1182 (s), 1142 (m), 1020 (m). EI-MS: 235 (M, 14), 206 (5), 162 (86), 161 (66), 146 (11), 134 (100), 119 (31), 117 (10), 105 (9), 91 (29), 79 (8), 77 (10), 65 (3). EI-HRMS: calcd for $C_{13}H_{17}NO_3$ [M^+] 235.1208, found 235.1206.

5.6. Preparation of *N*,*N*′-methyl-2,4,6-tri-*tert*-butylphenyl-substituted 1,2-amide ester (8a)

A three-necked, 100 mL round-bottom flask with a magnetic stir bar was charged with NaH (60% dispersion in oil; 0.261 g, 6.53 mmol, 2.32 equiv.), and was fitted with a gas inlet adapter and septa. The flask was then purged with nitrogen, and NaH was washed with pentane (2×10 mL). Dry DMF (15 mL) was added, and the resulting suspension was cooled to 0°C, and stirred for ca. 5 min. A solution of **7a** (1.018 g, 2.82 mmol, 1.0 equiv.) in dry DMF (15 mL) was then added dropwise via syringe, and the resulting opaque yellow reaction mixture was stirred at 0°C for 1 h. It was then treated with methyl iodide (dropwise addition; 1.25 mL, 20.08 mmol, 7.12 equiv.), and the reaction mixture was allowed to warm to RT and stir overnight. The resulting clear yellow reaction mixture was cooled to 0°C, treated with satd aqueous NH_4Cl (dropwise addition; 10 mL), and then poured into H_2O (30 mL), and extracted with Et_2O (2×100 mL). The extracts were combined, dried ($MgSO_4$) upon stirring, filtered, and concentrated in vacuo to afford a yellow solid. This material was purified by silica gel column chromatography (hexane/ethyl acetate, 10:1, then 1:1) to afford 0.351 g (33% yield) of **8a** as a white solid: mp 150–152°C. ^1H NMR (300 MHz, $CDCl_3$): 7.48 (s, 2H, Ph), 4.38 (q, J=7.2 Hz, 2H, CH_2CH$_3$), 3.27 (s, 3H, NCH_3), 1.44 (s, 18H, 2×C_6H_2-*o*-C(CH_3)$_3$), 1.39 (t, J=7.2 Hz, 3H, CH$_2$CH_3), 1.30 (s, 9H, C_6H_2-*p*-C(CH_3)$_3$). ^{13}C NMR (126 MHz, $CDCl_3$): 163.3, 163.0, 149.4, 146.3, 133.7, 125.6, 61.8, 42.1, 37.5, 34.7, 33.1, 31.2, 13.9. IR (CH_2Cl_2): 2966 (s), 1737 (s), 1668 (s), 1598 (m), 1478 (m), 1397 (m), 1364 (m), 1241 (m), 1095 (s), 1012 (m). EI-MS: 360 (1), 318 (100), 302 (2), 290 (11), 274 (2), 246 (5), 244 (3), 230 (3), 214 (1), 188 (2), 172 (2), 146 (1), 57 (3). EI-HRMS: calcd for $C_{23}H_{38}NO_3$ [$(M+1)^+$] 376.2851, found 376.2851.

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References

1. Roberts, R. M. *Serendipity: Accidental Discoveries in Science*; Wiley: New York, 1989.
2. For a recent example of a serendipitous discovery in organic synthesis and its report, see: Nugent, W. A. *Org. Lett.* **2002**, *4*, 2133.
3. "In the fields of observation, chance favors only the prepared mind"; Louis Pasteur (1822–1895).
4. (a) Nishio, T.; Kato, A.; Kashima, C.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1980**, 607. (b) Nishio, T.; Nakajima, N.; Kashima, C.; Omote, Y. *Heterocycles* **1983**, *20*, 849.
5. (a) Nangia, A.; Chandrakala, P. S. *Tetrahedron Lett.* **1995**, *36*, 7771. (b) Chandrakala, P. S.; Katz, A. K.; Carrell, H. L.; Sailaja, P. R.; Podile, A. R.; Nangia, A.; Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2597. (c) Mougenot, P. PhD Thesis, Université Catholique de Louvain, 1994. (d) Ghosez, L.; Nicaise, O. J. -C. Université Catholique de Louvain, unpublished results.
6. (a) Enders, D.; Dyker, H.; Raabe, G. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 618. (b) Enders, D.; Dyker, H.; Raabe, G.; Runsink, J. *Synlett* **1992**, 901. (c) Enders, D.; Dyker, H.; Raabe, G. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 421. (d) Enders, D.; Dyker, H.; Leusink, F. R. *Chem. Eur.* **1998**, *4*, 311. (e) Enders, D.; Sun, H.; Leusink, F. R. *Tetrahedron* **1999**, *55*, 6129.
7. 2,6-Di-*tert*-butyl-4-methylphenyl or BHT (butylated hydroxytoluene) esters, and 2,6-di-*tert*-butyl-4-methoxyphenyl or DBHA (dibutylated hydroxyanisole) esters have been used (1) by Heathcock and co-workers for the stereoselective generation of ester lithium enolates and their subsequent use in aldol reactions: (a) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846. (b) Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087, and (2) by Seebach and co-workers for providing sterically protected, but electronically effective carbonyl groups, and also for the generation of tetrasubstituted ketone lithium enolates: (c) Hassel, T.; Seebach, D. *Helv. Chim. Acta* **1978**, *61*, 2237. (d) Häner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396.
8. For a recent and very elegant application of reactive enols in synthesis, see the work of Wood and co-workers: (a) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748. (b) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371. (c) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326. (d) Moniz, G. A.; Wood, J. L.

J. Am. Chem. Soc. **2001**, *123*, 5095. (e) Drutu, I.; Krygowski, E. S.; Wood, J. L. *J. Org. Chem.* **2001**, *66*, 7025.

9. In glycolysis, the high phosphate group transfer potential of phosphoenolpyruvate (PEP) arises from the large driving force of the subsequent enol→ketone conversion.
10. (a) Hart, H. *Chem. Rev.* **1979**, *79*, 515. (b) Hart, H.; Sasaoka, M. *J. Chem. Ed.* **1980**, *57*, 685. (c) Kresge, A. *J. CHEMTECH* **1986**, *16*, 250. (d) Capon, B.; Guo, B.; Kwok, F. C.; Siddhanta, A. K.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 135. (e) Rappoport, Z.; Biali, S. E. *Acc. Chem. Res.* **1988**, *21*, 442. (f) Kresge, A. J. *Acc. Chem. Res.* **1990**, *23*, 43. (g) *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990. (h) Kresge, A. J. *Chem. Soc. Rev.* **1996**, *25*, 275.
11. (a) Hart, H.; Rappoport, Z.; Biali, S. E. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; pp 528–541 Chapter 8. For well-characterized examples of Fuson's aryl-substituted enols, see: (b) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1007. (c) Kaftory, M.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701. (d) Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 3669.
12. Thus 1,3-dicarbonyl compounds, α-nitro, cyano, acyl and sulfonyl carbonyl compounds and phenols are excluded[10g].
13. This value (5.73 ppm) is in accordance with those reported for hydroxyl hydrogens in enols of alicyclic 1,2-dicarbonyl compounds; for example, see: Floris, B. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; pp 278–279 Chapter 4. We have also recorded the ^{1}H NMR spectrum of a commercial sample of 1,2-cyclohexanedione (Aldrich, 97%), and it exhibited a hydroxyl hydrogen signal at 6.02 ppm. This greater value seems to indicate that intramolecular hydrogen bonding in aliphatic enol ester **4b** is also unlikely.
14. The quenching (distilled H_2O) and isolation (Et_2O extraction) conditions being identical for both procedures, it is reasonable to claim that the enol form **4b** was not present because it was not detected by ^{1}H NMR analysis of the isolated crude material.
15. The results of this on-going study will be reported in the full account of our work on stable enols derived from sterically hindered α-ketoesters.
16. A control experiment consisting of reacting α-ketoester **3b** under similar reaction conditions ($ClCO_2CH_3/Et_3N/CH_2Cl_2/$ 0°C→RT/overnight) afforded trace amounts of the corresponding enol ester **4b** and its methyl carbonate **5** in addition to unreacted α-ketoester. An attempt to quench the reaction mixture generated from the 'High *T*°C/Enol Procedure' with methyl chloroformate did not produce any of the desired methyl carbonate derivative **5**.
17. It is noteworthy that BHT and DBHA esters developed by Heathcock and co-workers as reagents for *threo*-aldolization also produced selectively, upon treatment with LDA, the corresponding Li (*E*)-enolates to give predominantly *threo* aldols.[7b]
18. All attempts to prepare the TBDMS ether of enol ester **4b** using TBDMSCl failed, and the α-ketoester **3b** was recovered.
19. A similar study with the enol derivative obtained by reaction of 1,2-diester **2b** with EtMgBr has documented a more rapid enol–keto tautomerization, thus demonstrating again the effect of substituent size on the stability of the enol.
20. The oily enol ester **4b** did not systematically solidify in the freezer.
21. The 'Low *T*°C/Ketone Procedure' was also systematically carried out with each nucleophile, and the corresponding ketone was always isolated in quantitative yield, and also characterized by ^{1}H NMR analysis.
22. EtLi is a developmental product which is available from FMC Corporation.
23. The direct synthesis of **8a** from commercially available 2,4,6-tri-*tert*-butyl-*N*-methylaniline ($ClCOCO_2C_2H_5/Et_3N/DMAP/$ CH_2Cl_2/0°C→RT/overnight) failed, but a clean reaction occurred, affording, after purification by SiO_2 column chromatography, a fair amount of a white solid of yet unknown structure.
24. The hydroxyl hydrogen in the enol amides was more deshielded (ca. 6.40 ppm) than that in enol ester **4b** (5.73 ppm), and the vinylic hydrogen in the crude methyl carbonate derivatives of the enol amides also experienced a significant downfield shift (ca. 0.75 ppm).
25. For a recent example of remarkably stable tetrahedral intermediates, see: Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 3188.
26. Pratt, D. V.; Hopkins, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5553.
27. Toullec, J. In *The Chemistry of Enols*; Rappoport, Z., Ed.; Wiley: Chichester, 1990; pp 378–380 Chapter 6.
28. A colateral benefit of this discovery, thanks to the simplicity of the experimental procedure, has been the development of a microscale experiment for the undergraduate organic chemistry laboratory; see: Nicaise, O. J.-C., Ostrom, K. F., Dalke, B. J. Submitted for publication.