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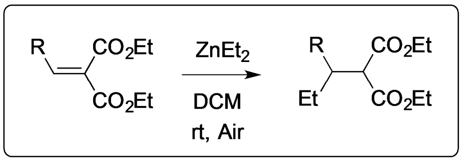

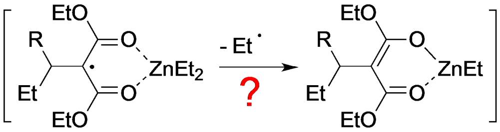

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Reactivity of benzylidene and alkylidenemalonates in radical addition mediated with dialkylzincs – An intriguing story

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ABSTRACT

Benzylidene- and alkylidenemalonates are extremely reactive radical acceptors in dialkylzinc-mediated radical additions. Theoretical investigations showed that the multi-step radical-polar crossover process should be highly exothermic. Not only the addition of the alkyl radical to the complexed substrate is enthalpically favored but what is more, the homolytic substitution at the metal leading to a zinc enolate should also be exothermic, even though it necessitates the cleavage of the C-Zn bond from the complexed α-alkoxycarbonyl radical intermediate. This work was undertaken to highlight the power of chelation in controlling the fate of this type of reaction. Much to our surprise, no unambiguous experimental evidence could be put forward to prove the formation of the expected zinc enolate intermediate. Additionally, benzylidenemalonates and their alkylidene analogues (although to a lesser extent) exhibit an intriguing behavior. The backward reaction (retro-addition) can be triggered at work-up depending upon experimental conditions.

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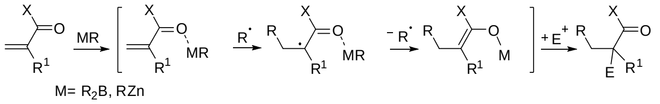
1. Introduction

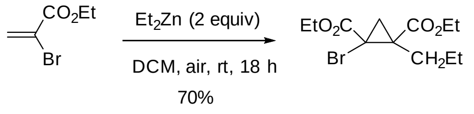
Radical-polar crossover processes involving homolytic substitution at boron[1] or zinc [2,3] by enoxyl radicals have become very popular. This step, that immediately follows the conjugate addition of an alkyl radical to α,β-unsaturated carbonyl compounds, is likely to be monomolecular. Boranes and dialkylzincs act as Lewis acids, they accelerate the initial addition step by coordinating to the oxygen atom of the substrate carbonyl group.[3,4] Enthalpic factors obviously control the rate of the subsequent group transfer step (Scheme 1). As the C-Zn bonds are weaker than C-B bonds,[5] the tandem reaction proceeds with a wider range of substrates in the case of dialkylzincs than in the case of boranes. The ease of the substitution at the metal or metalloid center was early correlated to the spin density delocalized at the oxygen atom in the radical adduct.[6] Whereas the cascade is strictly limited to enones in the case of boranes, it can be expanded to other activated alkenes in the case of dialkylzincs.



Scheme 1.

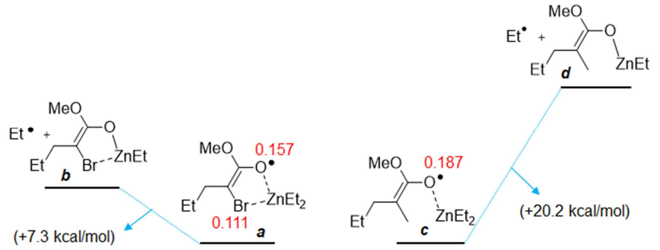
Dialkylzinc-mediated conjugate radical addition to α,β-unsaturated esters that leads to α-alkoxycarbonyl radicals fall into this category. The chain reaction is initiated by the reaction of R_2Zn with dioxygen that generates the alkyl radical $R^•$. This radical can either add directly to the activated double bond or act as a relay to promote the formation of another alkyl radical through iodine or hydrogen atom transfer. The addition step is followed by S_H2 at zinc and the process ends with the formation of zinc enolate, which is trapped by the electrophile.

A few exceptions have been reported in the literature where the intermediate radical evolves faster via inter-[7] or intramolecular addition to a double[8] or a triple bond[9] than it transfers the alkylzinc group. These reactions involve tertiary α-alkoxycarbonyl radicals. In fact, the criteria of trisubstitution of the carbon center in the α-alkoxycarbonyl radical does not by itself preclude S_H2 at zinc. Two complementary and indivisible factors, that is, the enthalpy gain in forming a zinc enolate stabilized by chelation and the spin density delocalized at the heteroatoms involved in the chelate, can counterbalance the influence of the radical branching. This was illustrated by Myabe *et al.*[10] reports on diethylzinc-mediated radical addition to dehydroaminoesters derivatives. These authors trapped the zinc enolates resulting from the tandem process by π-allyl palladium complex or acetic anhydride. Our group has recently shown that the formation of a five-membered chelate facilitated homolytic substitution at diethylzinc by the trisubstituted α-alkoxycarbonyl radicals resulting from the addition of alkyl radicals to ethyl α-bromomethacrylate. The addition of *i*-propyl radical and *t*-butyl radical were achieved in the presence of the corresponding iodides which unambiguously proved the radical nature of the mechanism. A strategy to prepare bromocyclopropanes followed from this work (Scheme 2).[7] It is worth being mentioned that this cascade reaction could neither be mediated with dimethylzinc nor with triethylborane.



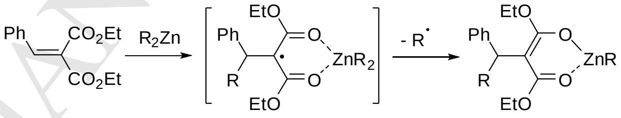
Scheme 2.

As detailed in Scheme 3, according to calculations performed at the M06-2X/aug-cc-pVTZ//M06-2X/aug-cc-pVDZ level of theory, the cleavage of the C-Zn bond from the intermediate complexed radical **a** necessitates only 7.3 kcal/mol (with an overall exothermicity of - 35.5 kcal/mol for the whole multi-step process[11]) whereas 20.2 kcal/mol are necessary to release ethyl radical from its tertiary analogue **c**. At the same time, the cumulated spin densities delocalized at oxygen and bromine in radical **a** exceed the spin density delocalized at the oxygen atom in radical **c**.



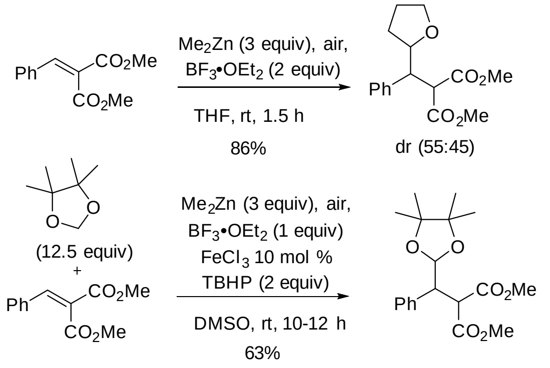
Scheme 3. Enthalpies of cleavage of the C-Zn bond and spin densities (in red) calculated at the M06-2X/aug-cc-pVTZ//M06-2X/aug-cc-pVDZ level of theory[7]

The propensity of benzylidenemalonates to form zinc enolates stabilized through the formation of six-membered chelates should similarly accelerate the homolytic substitution step in tandem reactions mediated with dialkylzincs (Scheme 4).



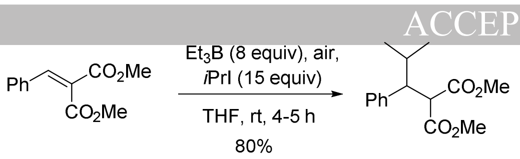
Scheme 4.

This reactivity has been elegantly exploited by Tomioka to add α-alkoxy radicals derived from THF and acetals under the mediation of dimethylzinc.[12,13,14] However, the fact that the reaction could not proceed in high yields in the absence of additive, notably $BF_3•Et_2O$ and *t*-butyl hydroperoxide as exemplified in Scheme 5, was quite puzzling. This led us to revisit the reactivity of diethyl benzylidenemalonate and look at the compared reactivity of diethyl butylidenemalonate in the presence of diethylzinc. This experimental study is disclosed herein. It was preceded by theoretical calculations.



Scheme 5.

Another intriguing feature of dimethyl benzylidenemalonate worth being noted. According to data reported by Liu et al., this substrate would be the only α,β-unsaturated ester that leads to α-alkoxycarbonyl radicals able to undergo homolytic substitution at triethylborane (Scheme 6).[15]



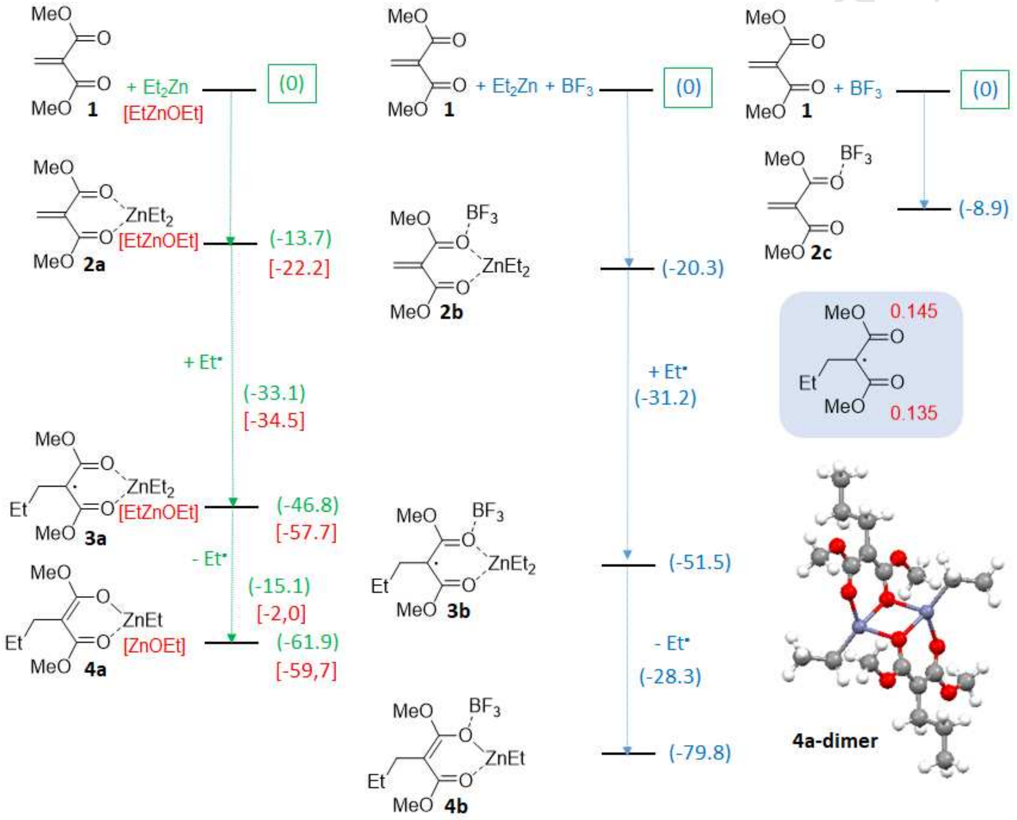
Scheme 6.

2. Results and Discussion

2.1. Computational Data

Theoretical calculations were achieved at the M06-2X/aug-cc-pVTZ//M06-2X/aug-cc-pVDZ level of theory using dimethyl methylidenemalonate **1** as model substrate. The enthalpic profile of the multi-step process was determined under two different conditions, namely, when using diethylzinc alone in the absence of any additive and in the presence of BF_3. The data are summarized in Scheme 7.[16]

When diethylzinc is used alone, the coordination of the substrate to the metal stabilizes the system by 13.7 kcal/mol (**2a**).[17] Due to the fact that coordination enhances the reactivity with respect to the addition of the nucleophilic alkyl radical ($Et^•$), the addition step is exothermic by 33.1 kcal/mol, that is, 2 kcal/mol more exothermic than the addition of ethyl radical to non-complexed dimethyl methylidenemalonate. It leads to a new stationary state, namely, the complexed α-alkoxycarbonyl radical **3a**. The most striking feature of the profile is that the homolytic cleavage of the Zn-Et bond leading to zinc enolate **4a** should be exothermic by 15.1 kcal/mol. This means that complex **4a** where zinc is chelated by a ligand close to acetylacetonate is strongly stabilized. Additionally, it must be pointed that the two oxygen atoms cumulate a 0.290 total spin density in the isolated radical. Calculations also showed that the dimerization of enolate **4a** would further stabilize the system by 44 kcal per mol.[16]



Scheme 7. Enthalpies in kcal/mol for the step-wise radical-polar crossover process in the presence and in the absence of BF_3 and spin densities at the oxygen atoms in the isolated α-alkoxycarbonyl radical calculated at the M06-2X/aug-cc-pVTZ//M06-2X/aug-cc-pVDZ level of theory

According to the above data, the commonly admitted radical-polar crossover mechanism matches with these addition reactions. The presence of a phenyl substituent in the actual substrate should however temper the global exothermicity compared to the model due to the loss of conjugation stabilization energy in the addition step.

Cooperative effect was observed in complexing **1** with both Et_2Zn and BF_3. The formation of complex **2b** stabilizes the system by 20.3 kcal/mol which is more than each of the Lewis acids taken separately.[18] Not surprisingly, the addition step leading to radical **3b** is exothermic by 31.2 kcal/mol, and the homolytic cleavage of the C-Zn bond, which regenerates $Et^•$, releases 28.3 kcal/mol. The resulting enolate **4b** is doubly stabilized by chelation and additional coordination to BF_3.

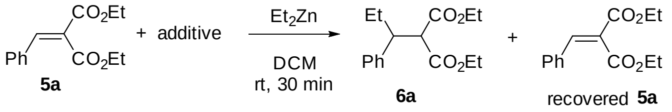
It must be noted that considering Et_2Zn as the complexing agent is an oversimplification. In aerobic medium, the oxidation of dialkylzinc involves the formation of peroxyalkyl and alkoxyalkylzinc species that could play exactly the same role as Et_2Zn in the process. In the presence of an excess of dialkylzinc with respect to oxygen the zinc peroxides are reduced into zinc alkoxides which under our experimental conditions are more likely to be involved.[19,5b] In EtZnOEt, the BDE of the C-Zn bond is increased by 3.6 kcal per mol with respect to diethylzinc and the enthalpy of the corresponding elementary steps are given in square brackets in Scheme 7. The transfer step leading to the zinc enolate bearing an ethoxy group would be exothermic by only 2 kcal per mol, the resulting enolate is much less stabilized but the overall process remains highly exothermic.

The overall enthalpic balance was also found exothermic for the addition of ethyl radical mediated with triethylborane (-58.1 kcal/mol).[20] This favorable enthalpic balance is likely to explain why dimethyl benzylidenemalonate behave as an exception among α,β-unsaturated esters.[15]

2.2. Experimental results

The results obtained from reacting diethylzinc with diethyl benzylidenemalonate **5a** and diethyl butylidene malonate **5b** are summarized in Table 1 and Table 2. When diethylzinc was used alone not least than 8 equivalents of diethylzinc were necessary for the full consumption of **5a**. As shown in Figure 1, monitoring the reaction by ^1H NMR revealed that the reaction was almost completed within 30 min as evidenced by the relative integration of the signals of the expected product **6a** and the starting material. However, **5a** was nearly fully recovered after work-up (hydrolysis with a solution of NH_4Cl) (Table 1, entry 1). Hydrolysis would promote the retro-reaction.

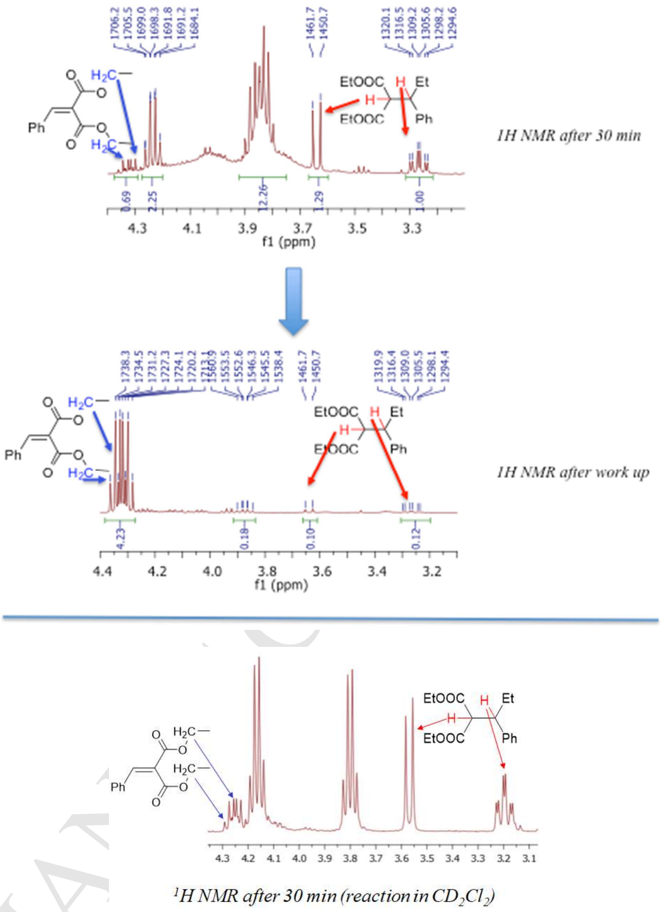
Table 1. Reactivity of benzylidenemalonate **5a**



Entry	Substrate	Additive (equiv)	$ZnEt_2$ (equiv)	**6a**:**5a**[a]	Yield of **6a**
1	**5a**	-	8	10:90	5%[b]
2	**5a**	-	8	>99:1	75%[c]
3	**5a**	-	4	>99:1	72%[c]
4	**5a**	BF_3•OEt_2 (1.1)	2	>99:1	60%[b]
5	**5a**	TMSCl (1.1)	2	>99:1	50%[b]
6	**5a**	CuCl (8)	8	>99:1	64%[b,d]

[a] Ratio determined by ^1H NMR of the crude mixture after work-up. [b] Yield determined by ^1H NMR using sulfolene as internal reference. [c] The crude reaction was concentrated before treatment; isolated yield. [d] A significant amount of hydrogenated **5a** (**5aH**) (**6a**:**5aH** = 75:25) was isolated in admixture to product **6a**. The yield was corrected.

It was not totally excluded that the final adduct could be detected instead of the zinc enolate by adding deuterated chloroform to a sample of the reaction mixture.[21] However, another experiment was achieved in deuterated DCM after bubbling air throughout the NMR grade solvent. The ^1H NMR spectrum of the reaction mixture after 30 min, showed that product **6a** was the major component as if the medium would already contain a proton or a hydrogen atom donor. The formation of **6a** in the reaction performed in deuterated DCM excluded the solvent from the list of suspected donors. Thus, the formation of **6a** that seemed reasonably predicted on the basis of the hydrolysis of an intermediate enolate turned out not to be this simple. It is to be noted that the interaction of **6a** with Zn(II) does not significantly alter the proton chemical shifts compared to the isolated product.



^1H NMR after 30 min (reaction in CD_2Cl_2)

Figure 1.

When the reaction mixture was concentrated under vacuum before hydrolysis, i.e., evaporating not only the solvent but also excess diethylzinc, no backward reaction was promoted and **6a** was isolated in 75% yield. This experiment suggested that the excess of unreacted dialkylzinc in the medium might be responsible for promoting the retro-addition upon hydrolysis (entry 2).[22] This was confirmed by a test reaction conducted in the presence of only 2 equivalents of diethylzinc overnight. According to ^1H NMR analysis, conversion was partial, the ratio of **6a**:**5a** was 1.5:1 before hydrolysis. It was exactly the same after direct work-up with saturated NH_4Cl solution.

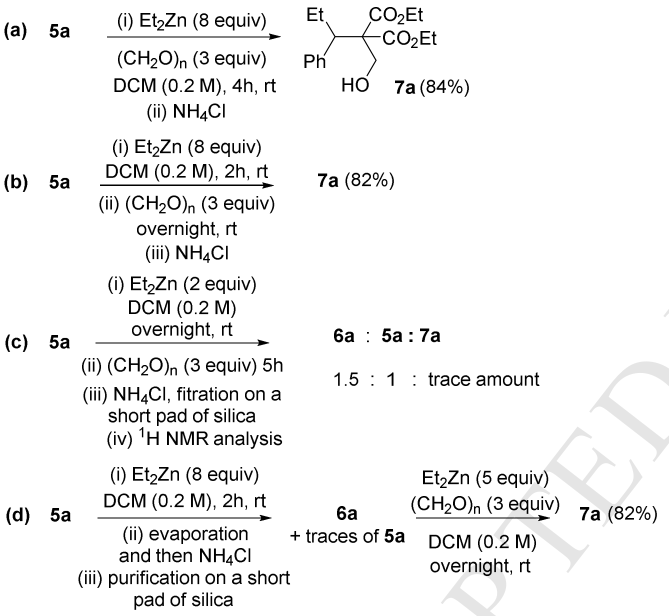
The oxygen dissolved in the non-degassed solvent may not be sufficient to efficiently initiate the chain mechanism. Bubbling air for 30 min through the solvent before starting the reaction allowed the reaction to be completed with only 4 equivalents of diethyl zinc (entry 3). A large excess of diethylzinc was still necessary. Again **6a** was isolated in 72% yield after evaporation of the reaction mixture before work-up

In order to stabilize or even trap the speculated intermediate enolate different additive were added to the reaction medium. As shown in Table 1, entry 4, the interest of adding BF_3•OEt_2 to the reaction medium as recommended by Tomioka and co-workers[12] was confirmed. Only 2 equivalents of Et_2Zn were necessary to reach completion and the backwards reaction was not observed.

Similarly, the addition of TMSCl as a potential trap for the enolate, led to the expected adduct in 50% yield and **5a** was fully consumed in the presence of only 2 equivalents of diethylzinc (Table 1, entry 5). However, the ^1H NMR analysis of a sample showed that **6a** was already present in the reaction medium before work-up. The role of TMSCl might just be to change alkoxyzinc species into the corresponding zinc chlorides.

Finally (entry 6), in order to check the possible role of the zinc peroxides formed in the reaction medium during the oxidative process,[23] the addition of CuCl as reducing agent just before work-up revealed also efficient in preventing the backward process. In all likelihood this last result is rather the consequence of transmetallating the remaining organozinc species present in the reaction medium. It points again to the role of excess diethylzinc in promoting the retro-reaction. It is worth noting that, a significant amount of hydrogenated **5a** (**5aH**) was detected in this latter experiment.

Addition of benzaldehyde to the reaction medium at the very beginning of the reaction did not result in the isolation of any aldol, but the reaction might be reversible.[24] Formaldehyde was shown to be an efficient trap under the experimental conditions reported by Tomioka.[13a] Additional experiments were undertaken with paraformaldehyde as enolate trap. These experiments were conducted at room temperature in the absence of BF_3•OEt_2. The data are reported in Scheme 8.

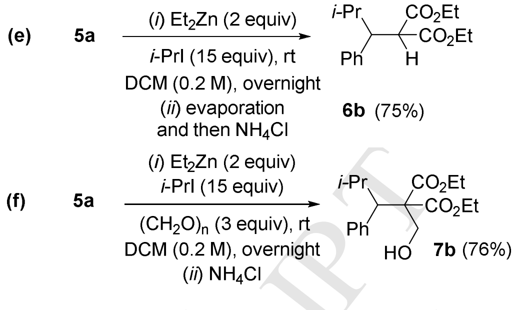


Scheme 8. Experiments performed with paraformaldehyde

As shown in equations (a) and (b), aldol **7a** was isolated in high yield whether the reaction was performed one-pot or paraformaldehyde was added in a second step, after **5a** had been reacted with diethylzinc (8 equivalents) for 2h. These results sound as if an enolate was effectively formed in the medium. However, the ^1H NMR analysis of an experiment performed in the presence of only 2 equivalents of diethylzinc with sequential addition of formaldehyde is controversial (eq. (c)). After diethylzinc had been nearly fully consumed by reaction with **5a** to give a 1.5:1 ratio of **6a** to recovered **5a**, the addition of paraformaldehyde did not significantly change the ratio of the two compounds. Only trace amount of aldol was detected. The experiment summarized by equation (d) demonstrates that in fact in the presence of formaldehyde, diethylzinc act as a base to deprotonate **6a**, and this results in aldol formation.[25] This did not prove that an enolate was actually generated in the first step of the sequential procedure reported in equation (b).

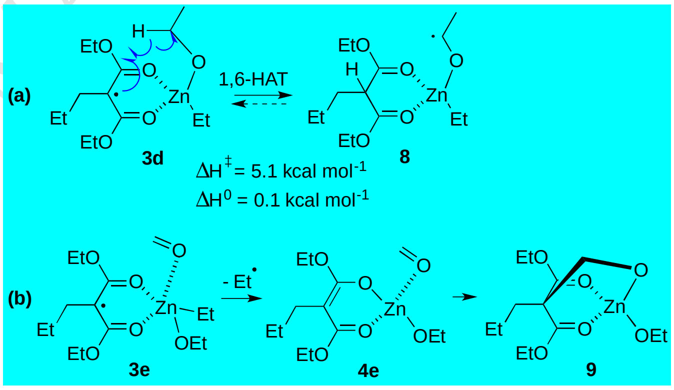
These new data support the conclusion that the presence of formaldehyde as an extra ligand of diethylzinc would modify the reactivity and promote the formation of an enolate intermediate.

To get sure that the mechanism still started with a radical addition step, experiments were achieved in the presence of excess *i*-PrI as a relay, in order to add exclusively isopropyl radical rather than ethyl radical. The results are summarized in Scheme 9.



Scheme 9. Reactions performed in the presence of *i*-PrI

In the presence of 15 equivalents of *i*-PrI, the expected adduct was isolated in 75% yield. Again ^1H NMR analysis before hydrolysis showed that **6b** was already present in the medium before work-up. However, only two equivalents of diethylzinc were necessary to reach completion. As a consequence, it is worth mentioning that due to the full consumption of Et_2Zn, evaporation before hydrolysis was unnecessary. No backwards reaction was detected upon direct hydrolytic work-up, under which conditions the yield of isolated **6b** improved up to 85%. The one-pot experiment reported in equation (f) led to the corresponding aldol in 76% isolated yield. Therefore, the radical mechanism was valid.



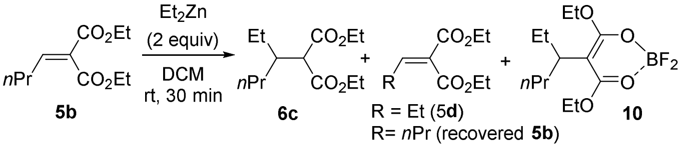
Scheme 10. Alternative mechanisms

As already mentioned above, the formation of EtOZnEt in a medium were diethylzinc is present in excess with respect to dioxygen is likely on the ground of the known diethylzinc oxidation process.[26] We suspect that when diethylzinc is used alone no enolate is formed. The reaction is not a chain process and excess of diethylzinc is necessary to reach completion. An alternative mechanism involving an internal hydrogen atom transfer was therefore envisaged. All the more because with this complexing species the formation of the enolate is much less exothermic (Scheme 7). Effectively, a mechanism implying internal hydrogen atom transfer (HAT) from a partially oxidized zinc species might be responsible for the formation of complexed radical **8** (Scheme 10, (a)). The model reaction turned out to be nearly athermal (+0.1 kcal/mol endothermicity) with a very low activation energy (+5.1 kcal/mol activation enthalpy), which suggests the possible reversibility of the process. However, no fast evolution of radical **8** was found plausible on theoretical ground nor could be proved experimentally. This proposal remains speculative. Intermolecular H-transfer from oxidized zinc species, favored by polar effects, could be envisaged as well.

The speculative character also holds for the proposal that in the presence of formaldehyde as extra ligand, aldol formation would occur in the coordination sphere of pentacoordinated Zn(II) (Scheme 10, (b)). According to theoretical calculations, the complexation of formaldehyde leading to radical **3e** stabilizes the system by 2.3 kcal/mol. The release of ethyl radical from **3e** is athermal and the formation of aldolate **9** is exothermic by 17.3 kcal/mol. The overall aldol reaction could either proceed in two steps via enolate **4e** or follow a concerted path.

Eventually, complementary experiments were carried out by using diethyl butylidenemalonate (**5b**) as radical acceptor. The results are given in Table 2.

Table 2. Reactivity of butylidenemalonate **5b**



Entry	Additive (equiv)	ZnEt$_2$ (equiv)	Products ratio	Isolated Yield (%) 6c	10
1	-	8	6c:5b[a] 1:1.8	38%	
2	-	8	6c:5b[a] >99:1	72%[b]	
3	BF$_3$•OEt$_2$ (1.1)	2	6c:10[a] 1:1.65	28%[b]	40[b]

[a] Ratio determined by ^{1}H NMR of the crude mixture. [b] The reaction was fully evaporated before work-up.

Retro-addition was also observed, but to a lesser extent, when **5b** was reacted with 8 equivalents of diethylzinc (Table 2, entry 1). This suggested that extended conjugation brought to the radical acceptor by the phenyl substituent contributes to ease the reversion phenomenum. Again, the ^{1}H NMR analysis of a sample after 30 min, according to the protocol previously followed for **5a**, showed the total disappearance of the starting material and the presence of **6c** before work-up.

With such a substrate, the addition process could formally be expected to revert back to a mixture of propylidene (**5d**) and butylidenemalonate (**5b**). It is important to emphasize that alkene **5d** was not detected. This remains a clue, even though the amount of recovered substrate was low (38%). An enthalpic effect is hardly plausible.

The experiment performed in the presence of BF$_3$•OEt$_2$ (Table 2, entry 3) led to an additional information. After work-up compound **6c** was isolated in admixture with enolate **10**. This demonstrated that the reaction intermediate, whatever it may be (likely the doubly complexed zinc enolate analogue of **4b**, Scheme 7), could evolve upon hydrolysis towards the boron enolate **10** resistant enough to hydrolysis to be isolated by column chromatography.

Another intriguing point remained to be addressed. What did trigger the reversal reaction upon work up in the absence of additive? According to Ockham's razor principle, the simplest explanation is often the best one. At first glance, the recovery of the starting material via a retro-Michael process, triggered at room temperature upon work-up, could be envisaged provided that a zinc enolate is formed in the reaction medium upon hydrolysis.[27,28] As suggested above, the influence of extended conjugation in the substrate seems to be a structural parameter favoring the reverse process.

3. Conclusion

The above data led us to conclude that, in the absence of any additive, the reaction of alkylidene malonates with diethylzinc would evolve directly towards the products that were initially thought to result from the protonation of a zinc enolate. An alternative route involving 1,6-H transfer from an ethoxyzinc group is tentatively proposed. Intermolecular H-transfer from oxidized zinc species, favored by polar effects, could be envisaged as well. However, the fact remains that on the ground of the mononuclear complexes taken as models, the reaction enthalpies calculated for the radical-polar crossover mechanism makes it highly plausible. Much to our surprise, no direct experimental evidence could be put forward to prove the formation of the speculated zinc enolate. One-pot reactions were achieved in the presence of paraformaldehyde. Addition of the latter to the reaction medium undoubtly modifies the reactivity of diethylzinc, but the isolation of an aldol remains indirect evidence for the intermediacy of zinc enolate. Formaldehyde acts as extra ligand and the generation of the aldol could be triggered in the coordination sphere of pentacoordinated Zn(II).

The benefit of additives such as BF$_3$ (previously used by Tomioka and co-workers) and TMSCl to modify the course of the reaction was confirmed. Only the presence of BF$_3$ would actually promote the formation of an enolate.

The backward reaction (retro-Michael addition) can be triggered at work-up depending upon reaction conditions. All experiments point to the fact that excess diethylzinc present in the reaction medium at the time of hydrolysis is responsible for the reversion.

This study, in a field that has already been so much explored, might have looked unnecessary and may seem somewhat half-done. It points out that as pertinent as could be the simple models that were devised to rationalize and predict reactivity, reality is never that simple. This reactivity of alkylidene and benzylidene malonates is a typical case of a reaction not as trivial as it might sound.

4. Experimental Section

4.1. Computational details

All the calculations were performed using the Gaussian 09 package.[29] The geometry of all species was optimized at the M06-2X/aug-cc-pVDZ level of theory. Single point energy calculations were performed at the M06-2X/aug-cc-pVTZ level of theory to obtain more accurate results. Vibrational frequencies were calculated at the M06-2X/aug-cc-pVDZ to insure, that the obtained geometries were minima and to calculate thermodynamics values. As recommended for calculations implying heavy atoms, diffuse and polarized functions were used to take nonbonding interactions with zinc into account more accurately. For all radical species, spin contamination was low, values ≤ 0.76 were found, i.e. very close to the ideal value of 0.75 for a doublet state (S=1/2) (see: SI).

4.2. General procedures

Commercially available solvents and reagents were used as purchased. CH_2Cl_2 (GC grade) was used as solvent, it was stored on molecular sieves. Analytical thin layer chromatography was performed on pre-coated silica gel plates. NMR spectra were recorded at 300 MHz or 400 MHz (^{1}H) and 75 MHz or 100 MHz (^{13}C) using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm. Signals due to residual protonated solvent or to the deuterated solvent served as the internal standards to calibrate the spectra (^{1}H NMR, $CHCl_3$, 7.26 ppm; ^{13}C NMR, $CDCl_3$, 77.16 ppm). Multiplicity is indicated by one or more of the following descriptors: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). The *J* values are given in Hz.

Diethyl 2-benzylidenemalonate (**5a**) was prepared according to a known procedure from diethyl malonate and butyraldehyde.[30] NMR spectra were identical to those previously reported in the literature. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 1.25 (t, *J* = 7.1, 3H), 1.31 (t, *J* = 7.1, 3H), 4.40 (q, *J* = 7.1, 2H), 4.26 (q, *J* = 7.1, 2H), 7.30–7.45 (m, 4H) 7.72 (s, 1H).

Diethyl butylidenemalonate (**5b**) was prepared according to a known procedure from diethyl malonate and butyraldehyde.[30] NMR spectra were identical to those previously reported in the literature. **^{1}H NMR (400 MHz, $CDCl_3$) δ**: 0.91 (t, *J* = 7.4, 3H), 1.23 (t, *J* = 7.1, 3H), 1.28 (t, *J* = 7.1, 3H), 1.47 (sext, *J* = 7.4, 2H), 2.25 (q, *J* = 7.6, 2H), 4.19 (q, *J* = 7.1, 2H), 4.26 (q, *J* = 7.1, 2H), 6.95 (t, *J* = 7.9, 1H).

General procedure for the reaction of diethylzinc with substrates 5a and 5b: Dialkylzinc (2, 4 or 8 equiv) was added under argon, at room-temperature, to a solution of **5** (1 equiv, 0.2 M), in the presence or in the absence of additive (BF_3•OEt_2, TMSCl) in non-degassed dichloromethane. The mixture was stirred for 30 min at room temperature and quenched with saturated NH_4Cl. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica pad.

Reactions conducted with 5a:

- The reaction was conducted according to the general procedure in the presence of diethylzinc (3.2 mL, 1 M in hexane, 8 equiv) and diethyl 2-benzylidenemalonate **5a** (0.40 mmol, 90 µL, 1 equiv) in DCM (2 mL). After 30 min, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction. After work-up, **5a** was nearly fully recovered and **6a** was detected in 5% (NMR yield using butadiene sulfone as internal standard).

- The reaction was conducted according to the general procedure in the presence of diethylzinc (3.2 mL, 1 M in hexane, 8 equiv) and diethyl 2-benzylidenemalonate **5a** (0.40 mmol, 90 µL, 1 equiv) in DCM (2 mL). After 30 min, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction. The reaction mixture was totally evaporated and the residue was dissolved in DCM. Saturated NH_4Cl was added and the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica pad. **6a** was isolated in 75% yield (0.3 mmol, 83 mg).

- The reaction was conducted according to the general procedure in the presence of diethylzinc (800 µL, 1 M in hexane, 2 equiv), BF_3•OEt_2 (54 µL, 0.44 mmol, 1.1 equiv) and diethyl 2-benzylidenemalonate **5a** (0.40 mmol, 90 µL, 1 equiv) in DCM to give **6a** (0.24 mmol, 60% yield (NMR yield using butadiene sulfone as internal standard).

- The reaction was conducted according to the general procedure in the presence of diethylzinc (800 µL, 1 M in hexane, 2 equiv), TMSCl (56 µL, 0.44 mmol, 1.1 equiv) and diethyl 2-benzylidenemalonate **5a** (0.40 mmol, 90 µL, 1 equiv) in DCM to give **6a** (0.20 mmol, 50% yield (NMR yield using butadiene sulfone as internal standard).

- The reaction was conducted according to the general procedure in the presence of diethylzinc (3.2 mL, 1 M in hexane, 8 equiv) and diethyl 2-benzylidenemalonate **5a** (0.40 mmol, 90 µL, 1 equiv) in DCM. After 30 min, CuCl (3.2 mmol, 316 mg, 8 equiv) was added to the reaction mixture. After filtration on a silica pad, and evaporation, a mixture containing **6a** (0.254 mmol, 64% yield (NMR yield using butadiene sulfone as internal standard) and **5aH** in a 74:26 NMR ratio was isolated. Compound **5aH** was identified as 1,1-diethylcarboxy-2-phenylethane from the characteristic signals reported below.

Diethyl 2-(1-phenylpropyl)malonate (**6a**):[31] **^{1}H NMR (400 MHz, $CDCl_3$) δ**:0.72 (t, *J* = 7.3, 3H), 0.93 (t, *J* = 7.1, 3H), 1.29 (t, *J* = 7.1, 3H), 1.54–1.67 (m, 1H), 1.71–1.83 (m, 1H), 3.27 (td, *J* = 11.0 and 3.6, 1H), 3.64 (d, *J* = 11.0, 1H), 3.87 (q, *J* = 7.1, 2H), 4.24 (q, *J* = 7.1, 2H), 7.18-7.30 (m, 5H). **^{13}C NMR (100 MHz, $CDCl_3$) δ**: 11.6 (CH_3), 13.7 (CH_3), 14.1 (CH_3), 27.0 (CH_2), 47.4 (CH), 58.7 (CH), 61.0 (CH_2), 61.5 (CH_2), 126.7 (=CH), 128.2 (=CH), 128.4 (=CH), 140.8 (=C), 167.8 (C=O), 168.7 (C=O), HRMS (ESI): *m/z*: calcd for $[M + H^+]$ $C_{16}H_{23}O_4$: 279.1591, found 279.1597.

1,1-Diethylcarboxy-2-phenylethane (5aH):[32]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (t, *J* = 7.1, 6H), 3.21 (d, *J* = 7.9, 1H), 3.64 (t, *J* = 7.9, 2H), 4.11–4.21 (m, 2H, AB part of an ABX_3 pattern), 7.16–7.29 (m, 5H).

Reactions conducted with 5a in the presence of paraformaldehyde:

- Equation a, Scheme 8: the reaction was conducted according to the general procedure in the presence of diethylzinc (1.6 mL, 1 M in hexane, 8 equiv), $(CH_2O)_n$ (18 mg, 3 equiv.) and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL). After 4 h, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction. After work-up and purification by flash chromatography on silica gel, **7a** was isolated in 84% yield (52 mg, 0.168 mmol).

- Equation b, Scheme 8: the reaction was conducted according to the general procedure in the presence of diethylzinc (1.6 mL, 1 M in hexane, 8 equiv), and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL). After 2 h, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction and the formation of **6a**. $(CH_2O)_n$ (18 mg, 3 equiv.) was added and the reaction was stirred overnight. After work-up and purification by flash chromatography on silica gel, **7a** was isolated in 82% yield (50 mg, 0.163 mmol).

- Equation c, Scheme 8: the reaction was conducted according to the general procedure in the presence of diethylzinc (0.4 mL, 1 M in hexane, 2 equiv), and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL). After one night, the ^{1}H NMR spectrum of a sample revealed a 1.5:1 ratio of **6a**:**5a**. $(CH_2O)_n$ (18 mg, 3 equiv.) was added and the reaction was stirred for 5 h. After work-up, the ^{1}H NMR spectrum of the crude mixture the ratio of **6a** to **5a** remained unchanged.

- Equation d, Scheme 8: the reaction was conducted according to the general procedure in the presence of diethylzinc (1.6 mL, 1 M in hexane, 8 equiv), and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL) for 2 h. After evaporation of the reaction, work-up and filtration on a short pad of silica, the ^{1}H NMR spectrum of the mixture revealed a 10:1 ratio of **6a**:**5a**.

The product was diluted in DCM (1 mL) and diethylzinc (1 mL, 1 M in hexane, 5 equiv) and $(CH_2O)_n$ (18 mg, 3 equiv.) were added. After one night, the reaction was stopped. After work-up, and purification by flash chromatography on silica gel, **7a** was isolated in 82% yield (50 mg, 0.163 mmol).

Diethyl 2-(hydroxymethyl)-2-(1-phenylpropyl)malonate 7a:

^{1}H NMR (400 MHz, CDCl$_3$) δ: 0.72 (t, *J* = 7.3, 3H), 1.28 (t, *J* = 7.1, 3H), 1.32 (t, *J* = 7.1, 3H), 1.84 (ddq, *J* = 2.4, 14.6 and 7.3, 1H), 2.08 (ddq, *J* = 11.7, 14.6 and 7.3, 1H), 2.25 (br s, 1H), 3.17 (dd, *J* = 11.7 and 2.4, 1H), 3.78 (AB pattern, J_{AB} = 11.5, 2H), 4.23 (q, *J* = 7.5, 2H), 4.24-4.32 (m, 2H), 7.19-7.32 (m, 5H). **^{13}C NMR (100 MHz, CDCl$_3$) δ**: 12.9 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 25.2 (CH_2), 51.0 (CH), 61.3 (CH_2), 61.5 (CH_2), 64.5 (C), 65.9 (CH_2), 127.2 (=CH), 128.3 (=CH), 129.2 (=CH), 139.0 (=C), 170.6 (C=O), 170.7 (C=O), HRMS (ESI): *m/z*: calcd for [M + H$^+$] $C_{17}H_{25}O_5$: 309.1697, found 309.1701.

Reactions conducted with 5a in the presence of *i*-PrI:

• Equation e, Scheme 9: the reaction was conducted according to the general procedure in the presence of diethylzinc (0.4 mL, 1 M in hexane, 2 equiv), *i*-PrI (0.3 mL, 15 equiv.) and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL). After one night, the reaction was evaporated. After work-up and purification by flash chromatography on silica gel, **6b** was isolated in 75% yield (44 mg, 0.15 mmol). The same reaction performed over one night and worked-up without evaporation gave after purification **6b** in 85% yield (50 mg).

• Equation f, Scheme 9: the reaction was conducted according to the general procedure in the presence of diethylzinc (0.4 mL, 1 M in hexane, 2 equiv), $(CH_2O)_n$ (18 mg, 3 equiv.), *i*-PrI (0.3 mL, 15 equiv.) and diethyl 2-benzylidenemalonate **5a** (0.20 mmol, 45 µL, 1 equiv) in DCM (1 mL). After one night, work-up and purification by flash chromatography on silica gel, **7b** was isolated in 76% yield (49 mg, 0.152 mmol). Trace amount of **7a** were detected from the ^{1}H NMR spectrum.

Diethyl 2-(2-methyl-1-phenylpropyl)malonate 6b[15]: **^{1}H NMR (300 MHz, CDCl$_3$) δ**:0.82 (d, *J* = 6.8, 3H), 0.84 (d, *J* = 6.8, 3H), 0.92 (t, *J* = 7.1, 3H), 1.29 (t, *J* = 7.1, 3H), 2.01 (pseudo oct, *J* = 5.5, 1H), 3.39 (dd, *J* = 11.4 and 4.9, 1H), 3.85 (m, 2H), 3.95 (d, *J* = 11.4, 1H), 4.25 (m, 2H), 7.10-7.28 (m, 5H). **^{13}C NMR (75 MHz, CDCl$_3$) δ**: 13.4 (CH_3), 14.1 (CH_3), 17.6 (CH_3), 21.5 (CH_3), 30.3 (CH), 50.9 (CH), 55.9 (CH), 60.9 (CH_2), 61.2 (CH_2), 126.7 (=CH), 127.6 (=CH), 129.3 (=CH), 138.0 (=C), 167.8 (C=O), 168.7 (C=O).

Diethyl 2-(hydroxymethyl)-2-(1-phenylpropyl)malonate 7b: **^{1}H NMR (300 MHz, CDCl$_3$) δ**: 0.62 (d, *J* = 6.6, 3H), 1.10 (d *J* = 6.6, 3H), 1.30 (t, *J* = 7.2, 3H),1.30 (superimposed br s, 1H), 1.37 (t, *J* = 7.2, 3H), 2.45 (dsept, *J* = 10.3 and 6.6, 1H), 2.98 (d, *J* = 10.2, 1H), 3.51 (AB pattern J_{AB} = 11.3, 2H), 4.15-4.45 (m, 4H), 7.06-7.30 (m, 5H). **^{13}C NMR (75 MHz, CDCl$_3$) δ**: 13.9 (CH_3), 14.0 (CH_3), 21.6 (CH_3), 22.8 (CH_3), 32.2 (CH), 56.8 (CH), 61.5 (CH_2), 61.7 (CH_2), 63.1 (C), 68.3 (CH_2), 127.0 (=CH), 128.5 (=CH), 129.3 (=CH), 140.5 (=C), 171.3 (C=O), 171.4 (C=O), HRMS (ESI): *m/z*: calcd for [M + H$^+$] $C_{18}H_{27}O_5$: 323.1853, found 323.1854.

Reactions conducted with 5b:

• The reaction was conducted according to the general procedure in the presence of diethylzinc (3.76 mmol, 3.76 mL, 1 M in hexane, 8 equiv) and **5b** (0.47 mmol, 108 µL, 1 equiv) in DCM (2 mL). After 30 min, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction. After work-up, **5b** was partially recovered in admixture with **6c** (1:1.75 ^{1}H NMR ratio). After purification by flash chromatography on silica gel **6c** was isolated in 38% yield (0.179 mmol, 44 mg).

• The reaction was conducted according to the general procedure in the presence of diethylzinc (3.76 mmol, 3.76 mL, 1 M in hexane, 8 equiv) and **5b** (0.47 mmol, 108 µL, 1 equiv) in DCM (2 mL). After 30 min, the ^{1}H NMR spectrum of a sample revealed the completion of the reaction. The reaction was totally evaporated and the residue was dissolved in DCM. Saturated NH_4Cl was added and the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica pad. **6c** was isolated in 72% yield (0.338 mmol, 82 mg).

• The reaction was conducted according to the general procedure in the presence of diethylzinc (0.94 mmol, 0.94 mL, 1 M in hexane, 2 equiv), BF_3•OEt_2 (0.51 mmol, 65µL, 1.1 equiv) and **5b** (0.47 mmol, 108 µL, 1 equiv) in DCM (2 mL) to give **6c** and **10** in a 40:60 ratio (^{1}H NMR ratio, crude mixture: 80 mg). The mixture was purified by column chromatography on silica gel using ethyl acetate/pentane (5/95) as eluent. The first chromatographic fraction, contained boron enolate **10**, isolated as a colorless oil (21 mg, 0.09 mmol, 18% yield). The second fraction (50 mg) was a mixture of **6c** and **10** (**6c** (0.113 mmol, 28%), **10** (0.075 mmol, 22%)).

Ethyl (E)-2-(((difluoroboranyl)oxy)(ethoxy)methylene)-3-ethylhexanoate (10): **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 0.79 (t, *J* = 7.4, 3H), 0.85 (t, *J* = 7.3, 3H), 1.37 (t, *J* = 7.1, 6H), 1.41–1.57 (m, 6H), 2.50 (tt , *J* = 5.9 and 9.6, 1H), 4.42 (q, *J* = 7.1, 4H). **^{13}C NMR (100 MHz, CDCl$_3$) δ**: 12.5 (CH_3), 14.2 (CH_3), 14.3 (CH_3), 14.5 (CH_3), 21.0 (CH_2), 26.4 (CH_2), 35.2 (CH), 35.5 (CH_2), 65.1 (CH_2), sp^2 C were not detected.**^{19}F NMR (376 MHz, CDCl$_3$, CCl$_3$F) δ**: -144.1 (s, 2F).**^{11}B NMR (128 MHz, CDCl$_3$, BF$_3$.Et$_2$O) δ**: 0.82 (br, BF_2). HRMS (ESI): *m/z*: calcd for [M + H$^+$] $C_{13}H_{24}O_4BF_2^+$: Calcd: 293.1733, Found: 293.1730.

Diethyl 2-(1-ethyl-butyl)malonate (6c). **^{1}H NMR (400 MHz, CDCl$_3$) δ**: 0.85 (t, *J* = 7.3, 6H), 1.25 (t, *J* = 7.2, 6H), 1.30–1.47 (m, 6H), 2.09 (sext, *J* = 7.4, 1H), 3.38 (d, *J* = 7.7, 1H), 4.17 (q, *J* = 7.1, 4H). **^{13}C NMR (100 MHz, CDCl$_3$) δ**: 11.0 (CH_3), 14.2 (CH_3), 15.5 (CH_3), 19.9 (CH_2), 23.7 (CH_2), 32.9 (CH_2), 39.5 (CH), 55.4 (CH), 61.2 (CH_2), 169.3 (C=O). Trace amounts of hydrogenated **5b** (**5bH**) were identified through the following signals in the proton NMR spectrum, **δ**: 1.75 (q, *J* = 7.5, 1H), 3.33 (t, *J* = 7.5, 1H).

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16 Zn(II) is tricoordinated in some of the calculated species. The model can be considered as useful as the reactions were performed in a weakly basic solvent. For the incidence of solvation in THF, see: Del Pozo, J.; Pérez-Iglesias, M.; Alvarez, R.; Lledós, A.; Casarez, J. A.; Espinet, P. *ACS Catal.* **2017**, *7*, 3575–3583.

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18 Coordination to BF_3 alone results in an overall 8.9 kcal/mol stabilization of the system. The reaction should proceed through addition to **2b**.

19 (a) Seyferth, D. *Organometallics* **2001**, *20*, 2940–2955 and pioneering references cited therein. (b) Abraham, M. H. *J. Chem. Soc.* **1960**, 4130–4135.

20 The calculated exothermicities are: -5.9 kcal/mol for the complexation of methylidene malonate, -33.1 kcal/mol for the addition step and -19.0 kcal/mol for the cleavage of the C-B bond that regenerates ethyl radical.

21 In order to check the possible formation of an enolate by ^1H NMR, a sample was evaporated and re-dissolved in $CDCl_3$, this protocol might be responsible for the protonation of the expected enolate.

22 Additionally, when the reaction conducted in the presence of 8 equivalents of diethylzinc was diluted by adding 20 ml of DCM before proceeding to hydrolysis, no reversion was observed. This last experiment strongly suggested that whatever zinc species would be responsible for the reversion, the reversion would be a bimolecular process slowed down by dilution.

23 See ref. 5b and previous refs cited therein.

24 According to ^1H NMR of the crude mixture, in the presence of 3 equiv of PHCHO, the reaction led to a mixture containing **6a**:**5a**:PhCHO:phenethyl alcohol in a 0.6:0.2:1:2.8 ratio.

25 Diethylzinc has already been used as a base in THF to promote the formation malonate anion in Pd-catalysed allylations, see: Fuji, K.; Konoshita, N.; Tanaka, K. *Chem. Commun.* **1999**, 1895–1896..

26 As evidenced by the calculations EtOZnEt is a better Lewis acid than Et_2Zn, the energy of its LUMO is 0.2 eV lower than that of the unoxidized species. The Mulliken charge at Zn is +0.59 for EtOZnEt, it is only +0.35 for Et_2Zn.

27 According to theoretical calculations performed on the enolate bearing a hydroxyl group at zinc, the retro-process would be endothermic by 22.3 kcal/mol. But it would be exothermic by 1.8 kcal/mol if the released EtZnOH species remained complexed to the regenerated benzylidene malonate.

28 Significant amounts of retro-Michael product were mentioned in Tomioka's reports on Me_2Zn-mediated radical additions, see refs 12c, 13b.

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