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PII: S0040-4039(16)30199-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.02.090
Reference: TETL 47365

To appear in: *Tetrahedron Letters*

Received Date: 15 February 2016
Accepted Date: 24 February 2016

Please cite this article as: Bussolo, V.D., Princiotto, S., Martinelli, E., Bordoni, V., Crotti, P., Dimethyl malonate/ LHMDS system as a new protocol for generating methyl formate anion ($^-$COOMe) in the condensed-phase, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.02.090

Dimethyl malonate/LHMDS system as a new protocol for generating methyl formate anion ($^{-}$COOMe) in the condensed-phase

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Abstract: The treatment of dimethyl malonate with LHMDS in anhydrous THF (condensed-phase) generates, in addition to the expected corresponding lithium enolate, methyl formate anion (or methoxycarbonyl anion, $^{-}$COOMe) which can react with several electrophiles to give corresponding methoxycarbonyl derivatives by nucleophilic substitution reaction.

Dedicated to Professor Charles H. DePuy (1927-2013)

Keywords: Methyl formate anion, Methoxycarbonyl anion, Dimethyl malonate, Condensed-phase, Nucleophilic substitution.

Methyl formate anion (or methoxycarbonyl anion, $^{-}$COOMe) is known to be formed both in the condensed- and gas-phase by deprotonation of methyl formate by another anion.[1] In this process, the electrophilic carbonyl carbon of methyl formate, is transformed into the nucleophilic carbon of methyl formate anion, in a classical umpolung example. In the gas-phase, DePuy and coll. found that formyl proton abstraction, with formation of $^{-}$COOMe and deuterated ammonia, is one of the primary reaction pathways promoted by reaction of deuterated methyl formate with amide ion (NH_2^-): a subsequent exothermic α-elimination reaction leads to the more stable CO and MeO$^-$.[1a]

Methyl formate anion was identified in the condensed-phase, as a consequence of the reaction between $Ni(CO)_4$ and CH_3OK at 313-333 K. Under these conditions, $Ni(CO)_4$ forms complexes with the base with release of CO which, finally, reacts with CH_3O^- to give anion $^{-}COOCH_3$.[2]

In another example, methyl formate anion was demonstrated to be formed in the condensed-phase in the course of the synthesis of α-formyl acids. Actually, when the dianion of a carboxylic

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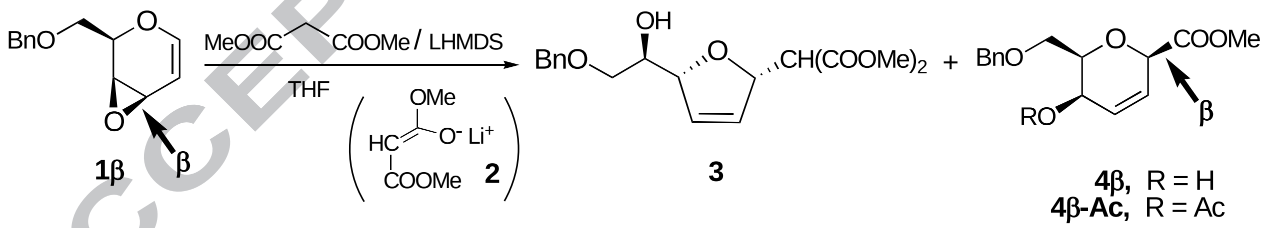
acid was treated with ethyl formate, in addition to the desired acyl substitution product (the α-formyl derivative), a competitive, undesired, acid-base reaction occurred with formyl proton abstraction. The consequent formation of methyl formate anion was demonstrated by quenching the reaction mixture with ^{3}HCl with the obtainment of corresponding ^{3}H-labelled ethyl formate.[3]

In the course of a program directed to evaluate the regio- and stereoselectivity of the nucleophilic addition of metal enolates of methylene active carbonyl compounds (*C*-nucleophiles) to glycal-derived vinyl epoxides, the reaction of D-galactal derived epoxide **1β**[4] with metal enolates of dimethyl malonate was initially considered.

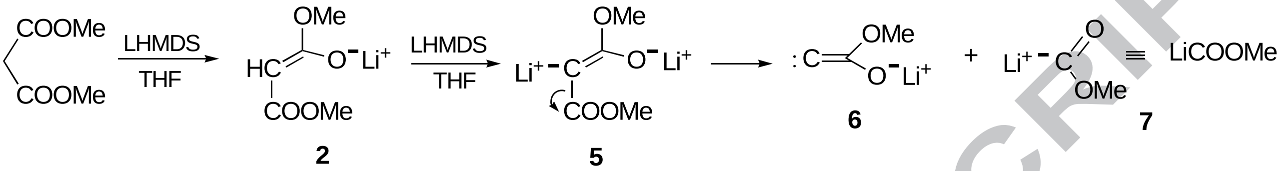
The addition of epoxide **1β** to a THF solution of 1:1 dimethyl malonate/LHMDS (3 equiv), reasonably containing the corresponding lithium enolate **2**, afforded, after 4 h at room temperature, a crude reaction product consisting of *cis*-2,5-disubstituted-2,5-dihydrofuran **3**[5] (35%) and an *1,4-addition product* (65%) in which the residue of the starting nucleophile, the di-(methoxycarbonyl)-methyl group [–CH(COOMe)$_2$], turned out to be reduced to a simple methoxycarbonyl group (–COOMe) (Scheme 1). In other words, the –CHCOOMe portion of the original enolate/nucleophile **2** appeared lost. All the collected ^{1}H NMR evidences unexpectedly indicated for this major reaction product the structure of methyl β-glycosylcarboxylate derivative **4β**, subsequently confirmed by an accurate examination of the corresponding 4-*O*-acetyl derivative **4β-Ac** (Scheme 1).

Scheme 1



The formation of methyl β-glycosylcarboxylate derivative **4β** pointed to the presence in the reaction mixture, under the reaction conditions used, of an unexpected nucleophilic species, as methoxycarbonyl anion ($^{-}$COOMe). Actually, control experiments appropriately carried out indicated that the mixture of 2,5-dihydrofuran **3** and methyl β-glycosylcarboxylate **4β** is stable under the reaction conditions and that methyl β-glycosylcarboxylate **4β** is formed only when LHMDS is used as the base for generating the metal enolate species: the use of weaker bases as *t*-BuOK and *t*-BuOLi was unsuccessful. These observations let us think that lithium enolate of dimethyl malonate **2**, formed, as usual, by reaction of equimolar amounts of dimethyl malonate and LHMDS, could partially undergo a further deprotonation by the strong base to give dianion **5**. A subsequent α-elimination process leads to carbene-anion species **6** and nucleophile ⁻COOMe, as the corresponding lithium salt LiCOOMe (**7**) (Scheme 2).

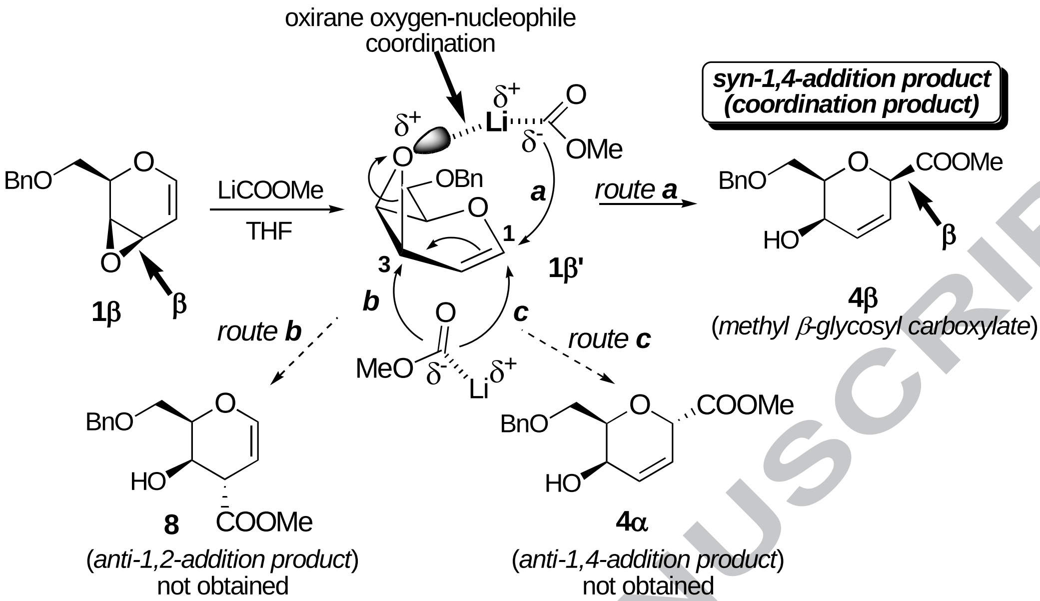
Scheme 2



While carbene-anion **6** probably decomposes, nucleophilic attack of LiCOOMe to epoxide **1β** leads to methyl β-glycosylcarboxylate **4β** as the only addition product, in which the configuration (β) of the obtained *C*-glycoside is the same as that (β) of the starting epoxide **1β**, in a typical example of *syn-1,4-addition* process (Schemes 1 and following Scheme 3).

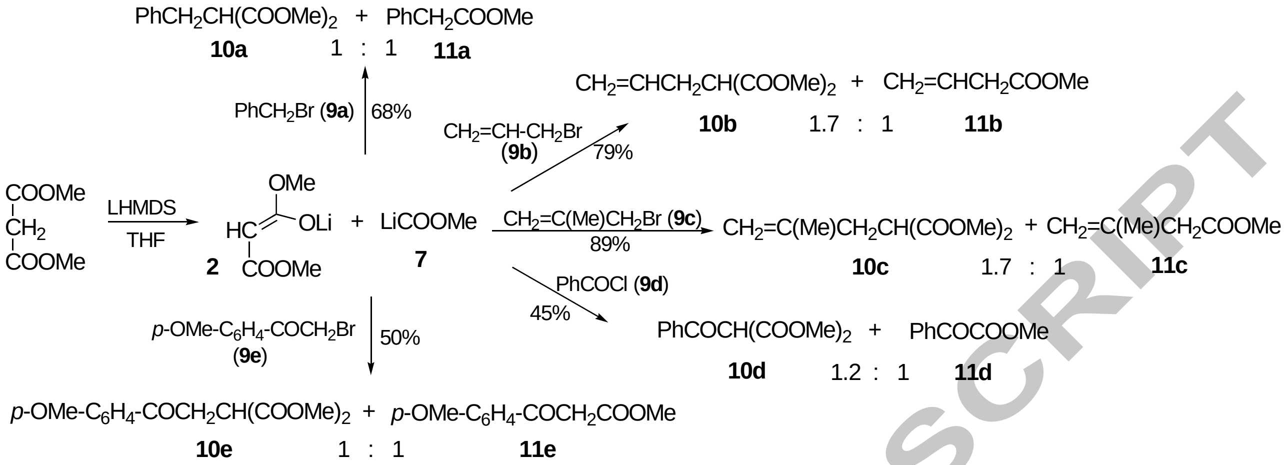
The completely 1,4-regio- and β-stereoselective formation of methyl β-glycosyl carboxylate **4β** is in accordance with the typical behavior of D-galactal-derived vinyl epoxide **1β**, in addition reactions by a nucleophile, as LiCOOMe, bearing the highly coordinating lithium cation.[4b,c] Actually, by the occurrence of a coordination with the oxirane oxygen through the metal ion, as shown in structure **1β' (**Scheme 3), nucleophile LiCOOMe is brought on the β face of the epoxide and, in this way, it is correctly oriented for an entropically favored conjugated attack to vinyl C(1) carbon from the same side to give β-glycosyl derivative **4β**, as experimentally found (*route* ***a***, Scheme 3). Evidently, the strongly associated nature of the new nucleophilic species LiCOOMe allows only attack through a coordination with oxirane oxygen by lithium cation to give only the corresponding *syn-1,4-addition product* **4β** (*coordination product*)[6,7] while its reactivity as a free, not coordinated nucleophile is weakened. This could be the reason why the corresponding regioisomeric *anti-1,2-addition product* **8** (*route* ***b***) and stereoisomeric *anti-1,4-addition product* **4α** (*route* ***c***) (*non-coordination products*) [6,7] are not observed with this nucleophile under the described reaction conditions (Scheme 3).

Scheme 3



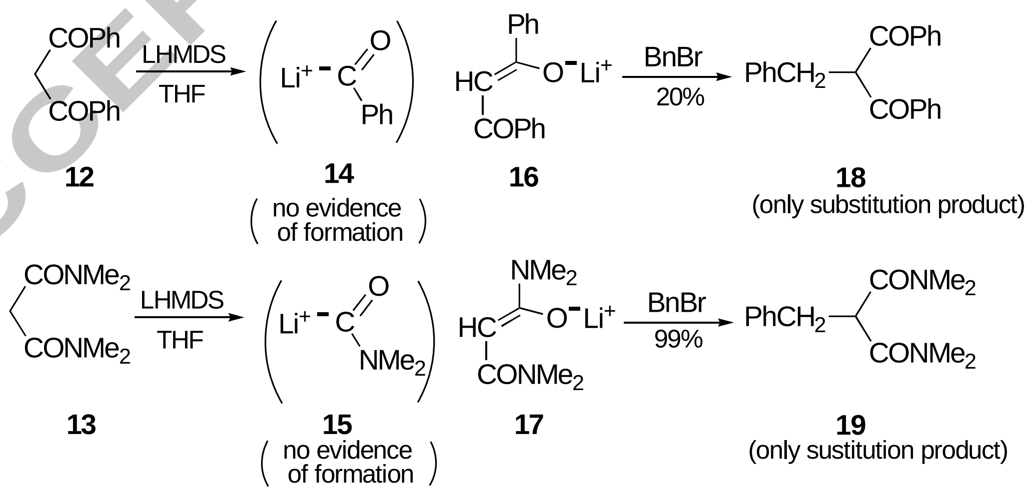
In a preliminary confirmation of the formation of nucleophile LiCOOMe (**7**) in a mixture with lithium enolate **2**, under the above-described protocol, some electrophiles different from the originally used epoxide **1β** were checked. The use of benzyl bromide (**9a**), allyl bromide (**9b**), 2-methylallyl bromide (**9c**), benzoyl chloride (**9d**) and *p*-methoxyphenacyl bromide (**9e**) in the reaction with dimethyl malonate/LHMDS reagent system (1 equiv) led to an 1:1 (in the case of **9a** and **9e**), 1.2: 1 (in the case of **9d**) and 1.7: 1 mixture (in the case of **9b** and **9c**) of the two corresponding substitution products, the expected malonyl derivatives **10a-e** and the "unexpected" methoxycarbonyl derivatives **11a-e** (45-89% conversion, Scheme 4), accompanied by unreacted dimethyl malonate (55-11%) (^{1}H NMR). In all cases, the crude reaction mixtures were subjected to preparative TLC and malonyl derivatives **10a-e**[8a-e] and methoxycarbonyl derivatives (methyl esters **11a-c**,[9a-c] methyl α-keto ester **11d**[9d] and methyl β-keto ester **11e**[9e]) were separated and identified by ^{1}H NMR and/or comparison with reported data (see Supplementary data).[8,9]

Scheme 4



The interesting results obtained with dimethyl malonate/LHMDS system prompted us to check the possible extension of the new protocol to other symmetric methylene active compounds. In particular, because interested in the possibility of generating other unusual nucleophiles as benzoyl anion **14**[1c] and the particularly important *N,N*-dimethylcarbamoyl anion **15**, useful in carbamoylation reactions,[10] we directed our attention to dibenzoyl methane (**12**) and *N,N,N',N'*-tetramethylmalondiamide (**13**) (Scheme 5).

Scheme 5



Several reaction conditions were checked by using benzyl bromide as the electrophile in the reaction with **12**/LHMDS and **13**/LHMDS systems (different reaction temperature, different benzyl bromide/**12**- or **13**-LHMDS ratio). Unfortunately, the common addition product, 2-

benzyl-1,3-diphenyl-1,3-propandione (**18**)[11] (20% conversion and presence of unreacted **12**, 80%) and benzyl- *N,N,N',N'*-tetramethylmalondiamide (**19**)[12] (99% conversion) from **12** and **13**, respectively (^{1}H NMR), were the only substitution products to indicate that in these cases the corresponding lithium enolates **16** and **17** were the only nucleophiles present in the reaction mixtures (Scheme 5).[13]

All these results would indicate that the behavior of dimethyl malonate in the presence of LHMDS is unique and, contrary to our expectations, the dimethyl malonate/LHMDS protocol cannot be extended to other methylene active compounds and, as a consequence, cannot be considered as a general protocol for the generation of unusual nucleophilic species. At the moment, we don't see the reason and don't have an explanation for this behavior apparently limited to dimethyl malonate.

Typical procedure for the generation of methyl formate anion from dimethyl malonate/LHMDS system and its reaction with an electrophile. *Reaction of dimethyl malonate/LHMDS system with benzyl bromide.* A 1 M LHMDS solution in anhydrous THF (1.0 mL, 1.0 mmol) was treated at 0°C with a solution of dimethyl malonate (0.132 g, 1.0 mmol) in anhydrous THF (3.0 mL) and the reaction mixture was stirred at the same temperature for 1 h. A solution of benzyl bromide (0.171 g, 0.12 mL, 1.0 mmol) in anhydrous THF (0.5 mL) was added dropwise at 0°C and the reaction mixture was stirred for 18 h at room temperature. Dilution with Et_2O and evaporation of the washed (saturated aqueous NaCl) organic solution afforded a crude reaction mixture (0.160 g) consisting of a 35:33:32 mixture of dimethyl benzylmalonate (**10a**), methyl phenylacetate (**11a**) and unreacted dimethyl malonate (^{1}H NMR) which was subjected to preparative TLC by using a 9:1 hexane/AcOEt mixture as the eluant. Extraction of the two most intense bands (the faster moving band contained **10a**) afforded pure dimethyl benzylmalonate (**10a**) (0.048 g) and methyl phenylacetate (**11a**) (0.029 g).[8a,9a]

Acknowledgements

This work was supported by the University of Pisa (University Funds 2013-2015). Professor Gloria Uccello-Barretta and Dr Federica Balzano of the Dipartimento di Chimica e Chimica Industriale of the University of Pisa are gratefully acknowledged for NMR experiments.

Supplementary data

Supplementary data (experimental details for all reactions and corresponding products) associated with this article can be found in the online version, at doi:

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5. The regio- and stereoselective formation of 2,5-disubstituted-2,5-dihydrofuran systems, as **3**, by reaction of glycal-derived vinyl epoxides, as **1β**, with metal enolates of methylene active compounds, will be the subject of a forthcoming paper from our laboratory.
6. In accordance with previous results with glycal-derived epoxides,[7] the simplified nomenclature of *coordination product* is given to *syn-1,4-addition product* **4β**, because supposed to be formed through an oxirane oxygen-nucleophile coordination (*route **a***, Scheme 3). Analogously, *anti-1,2-addition product* **8** and *anti-1,4-addition product* **4α**, even if not obtained, are simply identified as *non-coordination products* because they could be formed only by attack of a free, non-coordinated nucleophile at C(3) (*route **b***) and C(1) carbon (*route **c***) of epoxide **1β**, respectively (Scheme 3).
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12. New compound: see Supplementary data.

13. In an alternative rationalization, both the usual lithium enolates **16** and **17** and the unusual benzoyl **14** and dimethylcarbamoyl anion **15** are formed, but **16** and **17** could be decidedly more reactive nucleophiles than **14** and **15** (at least under the reaction conditions used) to the point that only the corresponding S_N2 products **18** and **19** are formed and found in the reaction mixtures.

Ref. TETL 47365

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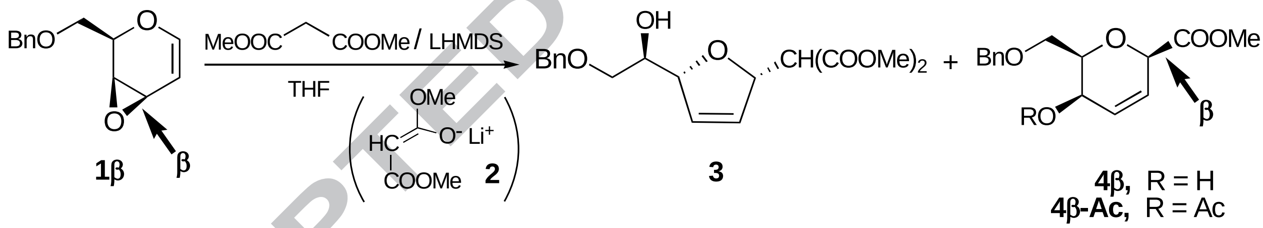
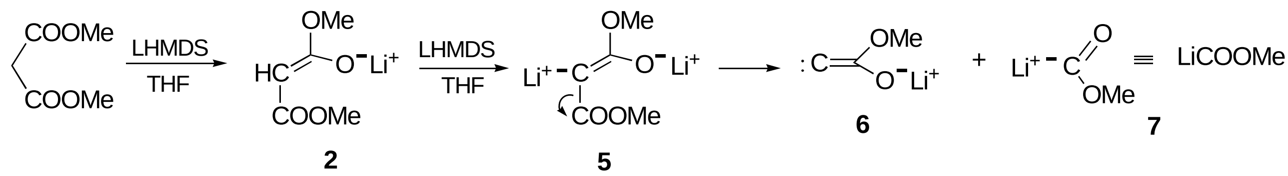
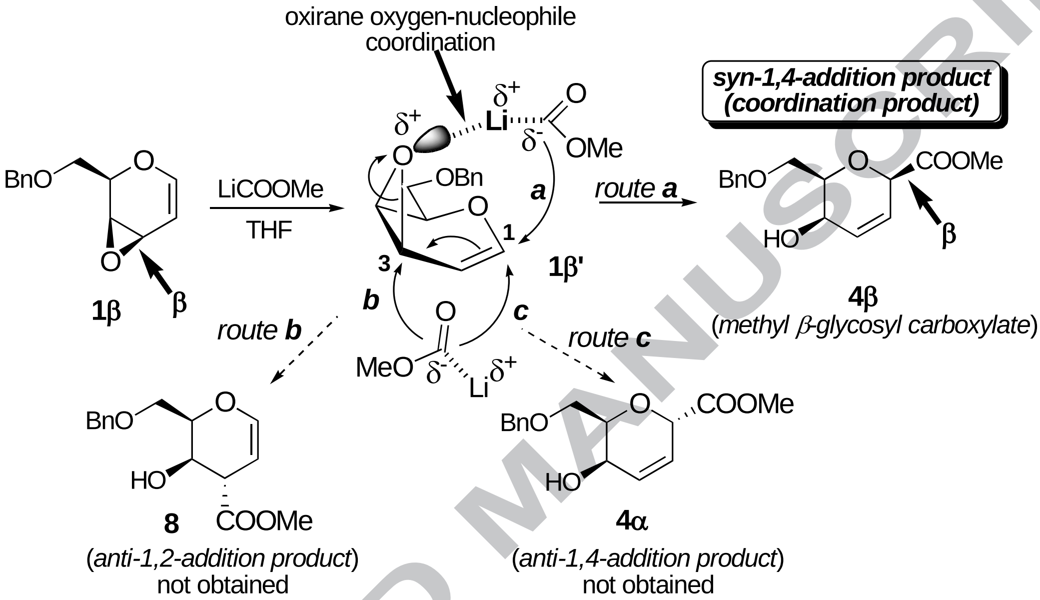
Captions to Schemes 1-5



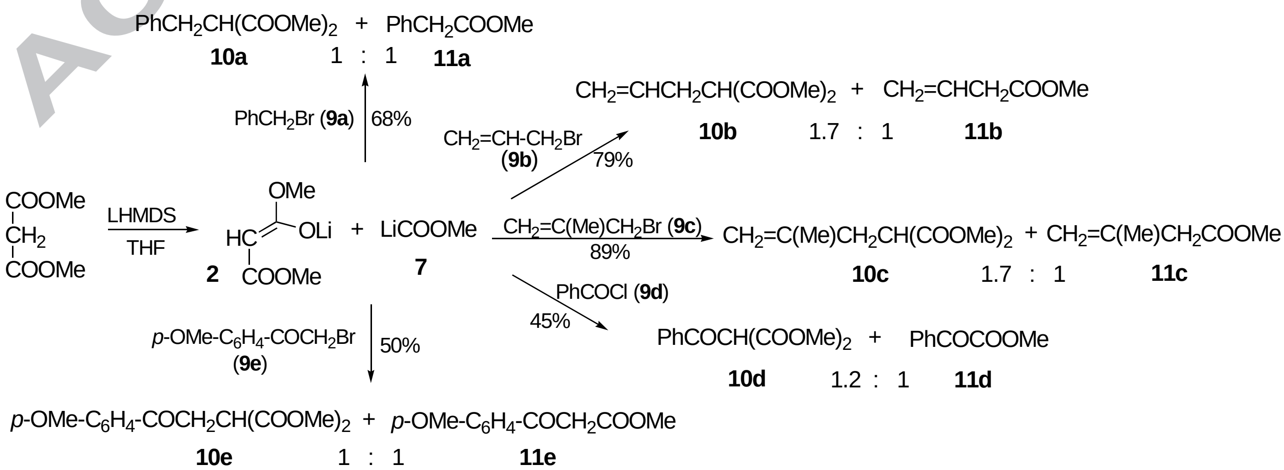
Scheme 1. Reaction of vinyl epoxide **1β** with dimethyl malonate/LHMDS system.



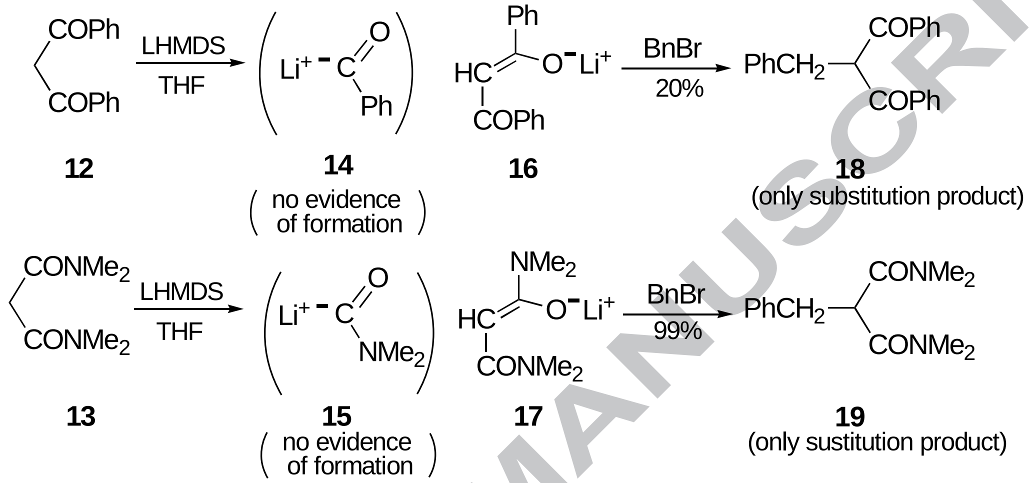
Scheme 2. Temptative rationalization of the formation of lithium methyl formate (LiCOOMe, **7**) by treatment of dimethyl malonate with LHMDS.



Scheme 3. Completely 1,4-regio- and syn-stereoselective addition of LiCOOMe to vinyl epoxide **1β**.



Scheme 4. Products obtained by reaction of dimethyl malonate/LHMDS system with electrophiles (benzyl-, allyl-, phenacyl bromide, benzoyl chloride).



Scheme 5. Products obtained by reaction of dibenzoylmetane/LHMDS and *N*,*N*,*N*',*N*'-tetramethylmalondiamide/LHMDS systems with benzyl bromide.

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Highlights

1. A new protocol for the formation of methyl formate anion in the condensed-phase is given.

2. The protocol is based on the treatment of dimethyl malonate with LHMDS.

3. A mechanism based on a double deprotonation of dimethyl malonate is proposed.

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