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LiTMP-LiBr complex-induced lateral lithiation and cross ester condensation: direct access to isocoumarins from 2-methoxy *o*-toluate esters†

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A LiTMP-LiBr complex facilitates a novel cross-ester coupling of 2-methoxy *o*-toluate esters to directly yield isocoumarin without the formation of any carbonyl intermediate. Aggregation plays a pivotal role in driving proximity-induced lateral lithiation and expediting acylation. In addition to many natural product precursors, the synthesis of (+)- and (–)-lunatinins is shown.

1*H*-Isochromen-1-one is a key structural feature of numerous bioactive isocoumarins, which are prevalent in fungi, bacteria, plants, and marine organisms and exhibit diverse biological activities.[1] Over the years, extensive research has culminated in the development of diverse synthetic approaches to obtain these privileged structures.[2] One well-established, effective, and convergent strategy for isocoumarin synthesis involves lateral lithiation and acylation of 2-methoxy *o*-toluic acid derivatives followed by subsequent lactonization.[3] This approach features wide applicability for introducing diverse substituents at the C3 position by utilizing readily available acylating agents such as acid chlorides, esters and amides.[4]

The deprotonative metalation of benzylic C–H groups is a valuable method for forming new C–C and C–X bonds.[5] Notably, the lateral lithiation of *o*-toluic acid **1** and its amide **2** produce a stable dianion (**I**), which selectively attacks various electrophiles, particularly acylating agents, resulting in the formation of the corresponding keto-derivatives (**3** or **4**).[6] Suitable tactics are then required to cyclize the keto derivatives to the desired isocoumarins (Scheme 1a).[7] On the other hand, for *o*-toluate esters **6**, lateral lithiation is complicated due to the stability of the arylogous enolate intermediate (**II**), which leads to self-condensation to give dimerized product **7**.[8] The Staunton group reported the reaction of *o*-toluate esters with Wienreb amides through lateral lithiation and acylation to yield keto-esters **8** (Scheme 1b).[9] Notwithstanding its good applicability, the approach is somewhat limited in terms of yield, primarily due to the dimerization of the ester. Additionally, a base-mediated enolization is required to convert ketoderivative **8** into isochromenone **9**. Additionally, the use of acid chlorides[10] produced poor yields along with complex products due to polycondensation. Conversely, esters have remained inert as electrophilic coupling partners in the condensation reactions of ortho-toluate esters to date.[11]

Esters are abundant and viable starting materials in organic synthesis. However, cross-ester condensation, in general, poses a formidable challenge due to the low electrophilicity of the acceptor ester.[12] It is notably susceptible to issues of self-condensation and over-condensation. Self-condensation has been partially alleviated by using excess equivalents of pre-prepared aryl and *tert*-butyl ester enolates (**V**),[13] or by the use of Ti- or Zr-based enolates.[14,15] Nevertheless, cross-ester coupling involving arylogous enolates (**VIII**) remained an unsolved challenge.

Recently, we found that use of chelating metal ions (LiCl) in lateral lithiation effectively suppresses the self-dimerization of *o*-toluate esters.[16] We anticipated that the excess Li salts promoted complex-induced lateral lithiation *via* tight chelation (**III**).[17] Additionally, these salts work in tandem with acylating agents to enhance their electrophilicity, thereby facilitating facile nucleophilic addition (**IV**). This method is only known for Wienreb amides, and they produce only ketone even in the presence of a large excess of base.[8,18] Despite extensive efforts, this reaction yielded self-dimerized ketone **7** consistently as the primary byproduct. Building on this finding, we hypothesized that esters might act as electrophilic partners in lateral lithiation, and unlike Wienreb amides,[19] they could directly produce isocoumarins *via* enolization of ketone intermediate *in situ*.[8] However, preventing self-dimerization of the toluate ester is the biggest hurdle. Generating the stable arylogous enolate as well as activating the acceptor ester simultaneously are crucial to achieve this challenging conversion. We speculated that establishing strong chelation is the key to facilitate this challenging cross-ester coupling; however, this strategy has not been used thus far.

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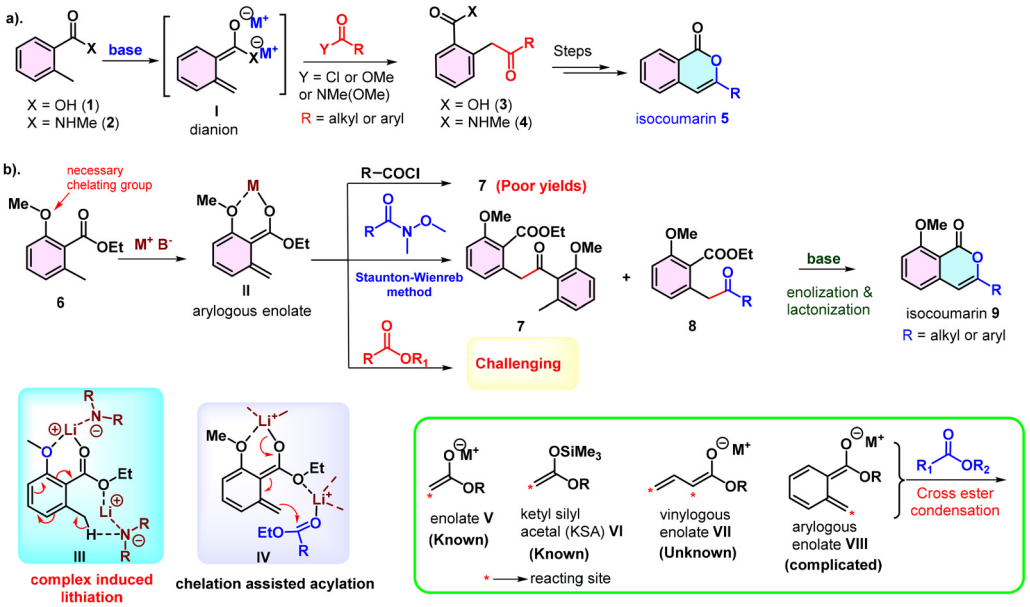
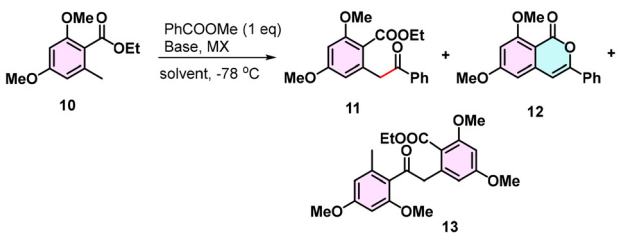


Scheme 1 Complex-induced lateral lithiation, acylation, enolization and lactonization for isocoumarin synthesis. (**III** and **IV**: possible transition states, hypothetical structures).

The reaction of orsellinate **10** with methyl benzoate in the presence of LDA and excess LiCl provided the desired product **12** in 42% yield along with ketone **11** (22% yield; Table 1, entry 1). The reaction conditions were further optimized as shown in Table 1. Changing the additive to LiBr gave only a 20% yield (entry 2), and LiI and $LiClO_4$ and the use of LiHMDS failed to give any desired product.[20] In contrast, the use of LiTMP in combination with LiBr gave a clean conversion with the limitation that the reaction required more than 3 eq. of base to initiate enolate **II** formation (entries 3 and 4). Increasing the equivalents of base and changing the additives to $MgCl_2$, $MgBr_2$ and $ZnCl_2$ provided the desired product maximum yield of **12** in entries 5–7 as 69%.

Table 1 Optimization of tandem cross-ester condensation, enolization and lactonization



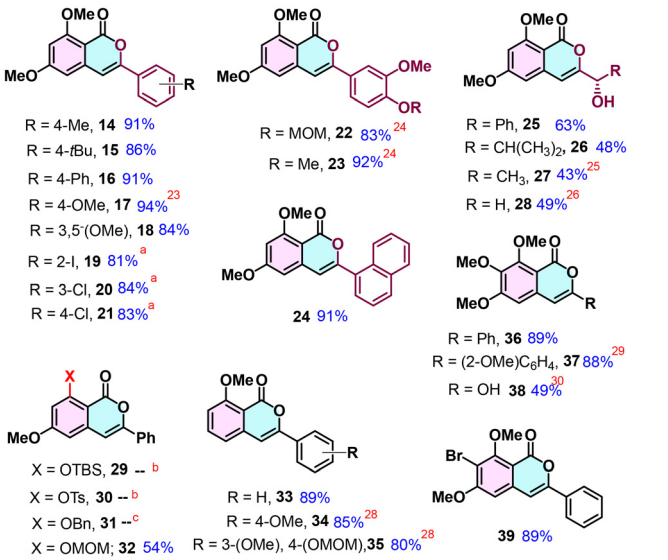
Entry	Reaction conditions	Yields[a,b] (%)
		10 : 11 : 12 : 13
1	LDA (3), LiCl (10), THF	10 : 22 : 42 : 20
2	LDA (4), LiBr (10), THF	50 : 25 : 20 : 0
3	LiTMP (4), LiBr (3), THF	26 : 30 : 37 : 0
		44 : 0 : 51 : 0[c]
4	LiTMP (8), LiBr (3), THF	30 : 0 : 68 : 0
5	LiTMP (5), $MgCl_2$ (3), THF	25 : 0 : 69 : 0
6	LiTMP (5), $MgBr_2$ (5), THF	36 : 0 : 52 : 0
7	LiTMP (5), $ZnCl_2$ (5), THF	78 : 0 : 12 : 0
8	LiTMP (5), LiBr (3), THF : hexane (2 : 1)	0 : 0 : 90 : 0
9	**LiTMP (5), LiBr (3), THF : cyclohexane (2 : 1)**	**0 : 0 : 92 : 0**
10	LiTMP (5), $LiClO_4$ (3), THF : cyclohexane	0 : 0 : 51 : 0

[a] Isolated yields. [b] Conditions A: base was added to a solution of **10**, methyl benzoate and LiBr in THF at −78 °C. [c] Conditions B: methyl benzoate was added to the preprepared enolate of **10** at −78 °C.

The LiTMP-LiBr complex, which is known to produce bromide-induced aggregates to establish a strong chelating complex, has been used to control the stereochemistry of enolates.[21] Speculating that we could achieve similar effects,[22] we added non-polar solvents such as hexane and cyclohexane to produce aggregates, which resulted in excellent yields of **12** (entries 8 and 9). Additives other than LiBr did not produce good yields of **12** (entry 10). More than three equivalents of the LiTMP-LiBr complex were required to generate the enolate, which was indicated by the formation of a red-coloured solution, which underscores the pronounced aggregation effect at play. The intricate aggregate becomes the epicentre for the proximity-induced lateral lithiation through complex **III**, ultimately leading to the generation of stable arylogous enolate species. Within this aggregate, the acceptor ester also participates through **IV**, creating a harmonious molecular environment that sets the stage for acylation and subsequent lactonization. Changes in the base, solvent or additive, however, provided unsatisfactory yields of **12**.[20]

Following the establishment of the standard reaction conditions (entry 11, Table 1), we expanded the applicability and versatility of the method as illustrated in Table 2. Aromatic esters with diverse alkyl and aryl substituents produced the corresponding isocoumarins **14**, **15**, **16** and **24** in >90% yields. The presence of chelating groups on the acceptor ester did not

Table 2 Synthesis of different isocoumarins



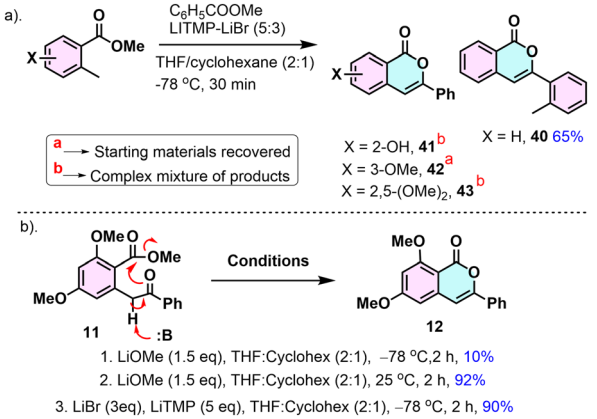
[a] Ester added to the preprepared enolate. [b] Recovered starting material. [c] Complex mixture.

significantly affect the reaction yields, and isocoumarins **17**,[23] **18**, **22**[24] and **23** were produced in 83% to 94% yields. Halogen-substituted esters required a change in the addition sequence; the addition of the ester to the prepared enolate gave isocoumarins **19**, **20** and **21** in good yields of >80%.

Unfortunately, the method did not work with enolizable esters. Most interestingly, esters having an α- or β-hydroxyl functionality produced the corresponding isocoumarin products **25**, **26**, **27**,[25] **28**[26] and **38**[29] in fair yields. This was a very interesting result, given that there was no protecting group involved, which paves the way for the synthesis of such hydroxyl-substituted naturally abundant and pharmacologically important 3-substituted isocoumarins.[27]

Moreover, *o*-toluate esters bearing 2-OTBS and 2-OTs groups showed no reactivity under the standard conditions. The substrate with a 2-OBn group resulted in a complex mixture, and that with an OMOM group provided **32** in 54% yield. 2-Methoxy toluate ester exhibited good reactivity with various aryl esters, yielding isocoumarins **33**, **34**[28] to **35**[28] in excellent yields. Similarly, toluate esters with three methoxy substituents showed good reactivity, affording isocoumarins **36** and **37**[29] in yields exceeding 80%. The presence of a halogen atom in the toluate ester did not affect the reaction outcome, and compound **39** was produced in 89% yield.

Furthermore, role of chelating groups on enolate stability was estimated through control experiments. As shown in Scheme 2a, the absence of the directing group (2-OMe) led to rapid self-dimerization to provide isocoumarin **40** in 65% yield. An unprotected 2-OH group provided complex products, and the reaction of 3-methoxy toluate ester was unsuccessful. These results highlight the significance of the 2-OMe group, which stabilizes the enolate through a tight chelate complex. Conversely, a chelating group at the 5-position, such as that in

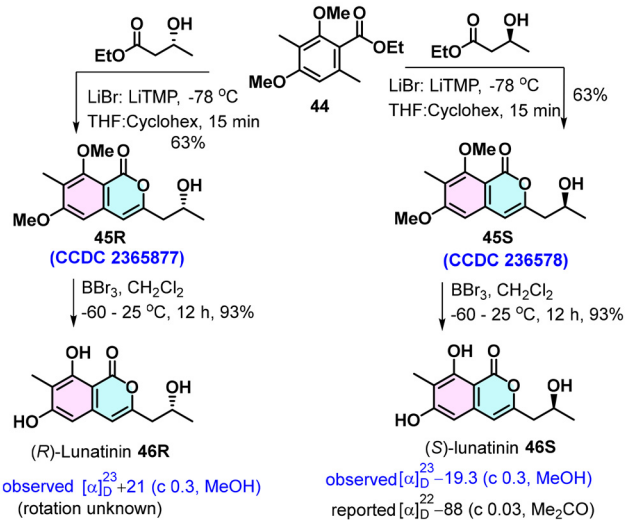


Scheme 2 Control experiments.

2,5-dimethoxy *o*-toluate ester, interferes with the reaction path, resulting in a complex mixture instead formation of **43**.

To understand the reaction mechanism, keto-ester **11** was first prepared and then subjected to cyclization. LiOMe (a byproduct in the reaction) was reacted with the ketone at −78 °C, but proved ineffective in promoting cyclization (Scheme 2b). However, at higher temperatures (25 °C), lactonization was promoted effectively to give **12**. The LiTMP-LiBr complex effectively promoted enolization and cyclization at −78 °C, resulting in complete conversion to **12**. These findings indicate that enolate formation is sequentially facilitated in two stages by the LiTMP-LiBr complex. Isocoumarin is the core structure of many natural products;[1] for example **12** serves as a synthetic precursor for montroumarin.[31] Similarly, several products obtained in this study can serve as synthetic intermediates for scorzocreticin,[23] thumborginols A[28] and B,[24] cytogenin,[26] dimethoxy thumborginol A,[29] diaportin, orthosporin,[25] and other natural 6,8-dihydroxy-7-methoxy isocoumarins.[30]

Lunatinin,[32] which has been isolated from various sources as both the (+)- and (−)-isomers, possesses intriguing biological activities; notably, it shows strong HMG-CoA reductase inhibitory activity (IC_{50} 128 μg mL^{-1}) comparable to the standard drug Lovastatin (IC_{50} 160 μg mL^{-1}).[33] The absolute structure of (−)-lunatinin was established based on ECD studies. We utilized the LiTMP-LiBr complex-induced tandem lateral lithiation, acylation and lactonization of *o*-toluate esters to give isocoumarin and a shortest possible route to lunatinin.[33] The total synthesis commenced with commercial ester **45**. It was coupled with commercially available optically pure methyl (*S*)-3-hydroxybutanoate in the presence of the LiTMP-LiBr complex, producing isocoumarin **45*S*** in 63% yield (Scheme 3). The absolute structure of **45*S*** was confirmed by X-ray analysis. Demethylation of two phenolic groups of **45*S*** using BBr_3 afforded (*S*)-lunatinin (**47*S***) in 93% yield. All the spectral data of synthetic **47*S*** were identical to the reported data; however, the specific rotation $\alpha_D^{23} = -19.3$ (*c* 0.3, MeOH) showed a deviation in magnitude. Similarly, the cross-ester condensation of **44** with methyl (*R*)-3-hydroxybutanoate followed by methyl deprotection provided *R*-lunatinin (**46*R***) in 57% in two steps.



Scheme 3 Total synthesis of (+)- and (−)-lunatinins.

In conclusion, our innovative one-step synthetic route to isocoumarins from 2-methoxyl *o*-toluate esters, employing the LiTMP-LiBr complex, has proven to be a highly efficient and versatile method. This is the first method that shows the influence of aggregates in complex-induced lateral lithiation of toluate esters. This unique feature extends to the first cross-ester coupling of *o*-toluate ester with other esters. The reaction mechanism involves a seamless tandem process, including proximity-induced lateral lithiation, complex induced acylation, enolization, and lactonization. Furthermore, we demonstrated the utility of our method through a concise total synthesis of (+)- and (−)-lunatinins.

Author contributions

RG developed the concept and written manuscript through the contributions of MR. MR conducted all the experiments with the help of SD and RM. All authors have given approval to the final version of the manuscript.

Data availability

All experimental procedures, ^{1}H and ^{13}C NMR data of compounds, and X-ray crystallographic data of compound **45*R*** and **45*S*** are available in the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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