Mechanochemical assisted chemoselective and stereoselective hydrogen-bonding catalyzed addition of dithiomalonates to enones

Żaneta A. Mała, Mikołaj J. Janicki, Robert W. Góra, Krzysztof A. Konieczny and Rafał Kowalczyk*

Wroclaw University of Science and Technology, Department of Bioorganic chemistry

rafal.kowalczyk@pwr.edu.pl

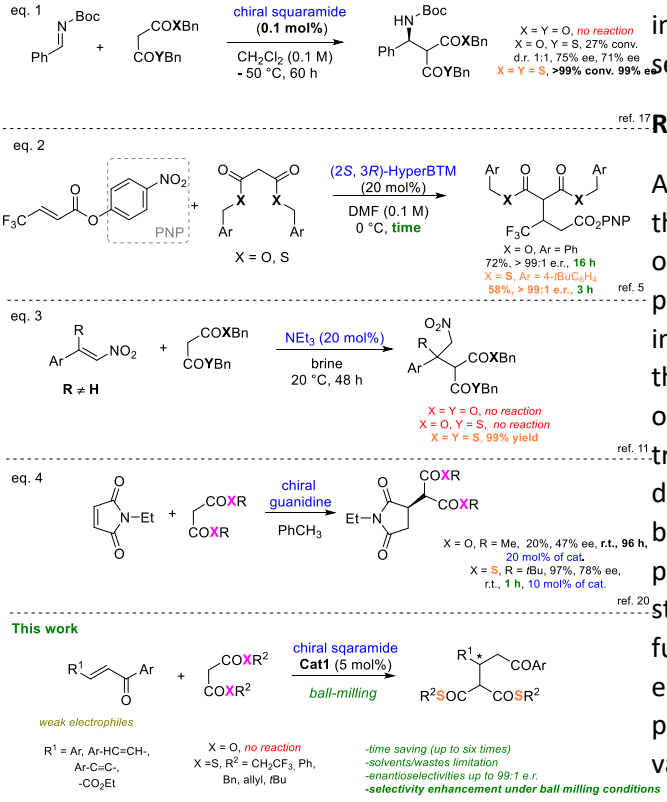
Dithiomalonates proved to be active nucleophiles in the stereoselective additions to chalcones, dienones, and en-ynones affording the desired Michael adducts with good to high yields and enantioselectivities. In contrast, the analogous dibenzyl malonate remained inactive. Bifunctional Cinchona-based squaramides secured the effective chirality transfer and the selectivity towards Michael adducts of various bisthiomalonates following the *soft enolization* approach. The thioester's nature impacted the reactivity and stability of the reactants or products. While the reactions performed in solution led to the products, the required time along with byproducts formation such as thio-Michael adducts, limiting the applicability of reactive dithioesters. On the contrary, reactions performed under solvent-free, ball milling conditions furnished adducts up to six times faster, with subtly or no byproduct generation. Therefore, the mechanochemical approach revealed to be an effective tool for supporting the hardly effective reactions under standard solution conditions. Detailed KS-DFT studies supported the experimental observations shedding more light on the intricate active nucleophile formation, and different chemical reaction pathways, as well as indicating the crucial transitions state governing the observed stereoselectivities

Introduction

The addition of malonates to various Michael acceptors has been utilized as an important transformation leading to versatile intermediates in asymmetric synthesis.[1] The well-studied examples of stereoselective malonate additions concern reactions of simple aliphatic esters with nitroalkenes[2] and, to a lesser extent, chalcones[3]. However, the addition of stabilized nucleophiles as malonates to the less reactive acceptors[4] has still remained an unsolved task[5]. Beside the common malonates, conjugated additions of benzyl malonates provide an alternative source of *d1* synthon that is relatively stable under acidic conditions.[6] Thus, its transformation would enlarge the useful valuable tools for such essential C-C bond disconnections. Nevertheless, dibenzyl malonate additions to moderate electrophiles as chalcones are limited to the application of inorganic or strong bases in multifunctional hydrogen-bonding systems[7], chiral phase transfer (PTC) catalysis[8] or BINOL-BuLi systems[9]. Otherwise, additional reactions required prolonged time up to 144 h[10], elevated temperatures or excess of nucleophile. Nevertheless, in contrast to benzylideneacetones, chalcones remained unreactive under some iminium catalysis.[6] Combining both reagents as dibenzyl malonate and sterically demanding β,β-disubstituted nitroalkane resulted in no transformation under triethyl amine assistance. A successful replacement of oxo-esters by thioesters resulted in the desired adduct formation in nearly quantitative yield[11], but reaction required „on water" conditions (Scheme 1, eq. 3). The essential acceleration of Michael addition of *S*,*S*-bis(4-tert-butyl)benzyl)-propanebis(thiolate) to β-trifluoromethyl α,β-unsaturated ester has recently been reported (Scheme 1, eq. 2).[5]

Higher acidity of the α-proton of thioester than in analogous oxoesters[12] allows for a gentle generation of enolate. That feature has been widely employed in asymmetric catalytic reactions of malonic acid half thioesters (MAHTs) and oxyesters (MAHOs) as ester enolate equivalents reactions[13] and, as an even more distinct example, applied in nature[14]. Notably, the first step in the metabolism of fatty acids involves deprotonation of Cα-H

hydrogen atom and thus, the thioesters offer greater reactivity in comparison to esters. The limited sulphur and oxygen pπ-pπ orbital interactions result in the lack of stability of the C=S(+) interaction in comparison to C=O(+) of the resonance forms of esters. Hence, thioesters are better acylating agents than esters resulting in increased reactivity by about 100-fold towards aminolysis and about 2000-fold towards carbon-centered nucleophiles while keeping the greater stability on the hydroxide and thus increased stability under hydrolytic conditions.[15] In this light, dithiomalonates were successfully utilized as malonate surrogates[16] with the promise to provide enhanced reactivity towards challenging Michael acceptors and other C-C bond forming reactions (Scheme 1).[17] Dithiomalonates were thus applied in organocatalyzed and stereoselective additions to unsubstituted[18] or β-trifluorinated nitroalkanes[19], maleimides[20], and benzoylformates (Scheme 1, eq. 4). Nevertheless, reported transformations are limited to relatively strong electrophiles together with the application of mainly single dithiomalonate derivative.



Scheme 1. Application of dithiomalonates as malonate surrogates in creation of stereogenic centers

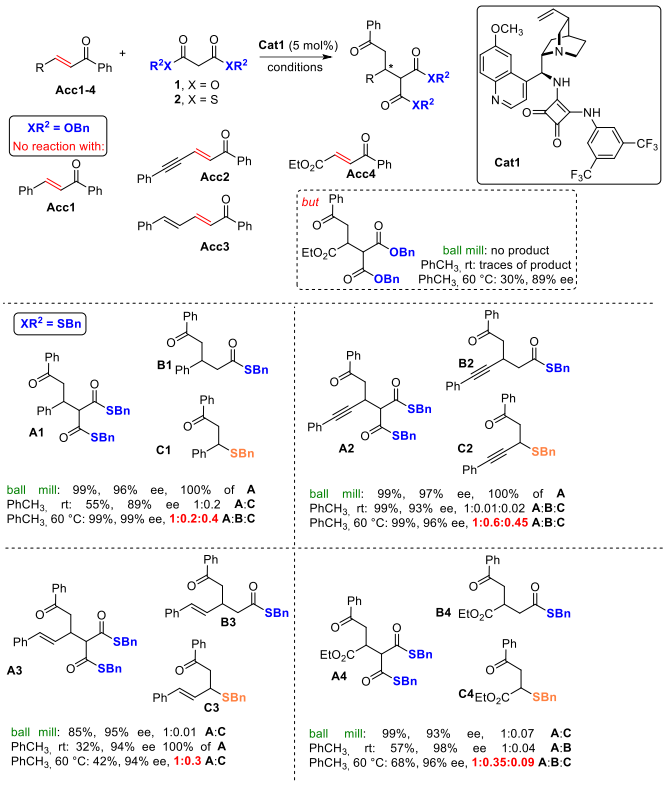
Along with the facile reactivity, the thioester group introduced to adduct could be transformed[21] into alcohols[22], carbonyl derivatives as aldehydes[23], ketones by addition of Grignard reagents[24], or organozinc in Fukuyama[25], and a variety of Liebeskind-Srogl cross-coupling[26] reactions. Finally, the S-to-N[27] or S-to-O-acyl transfers[28] including Corey-Nicolau macrolactonization[29] of thioesters indicate they could be recognized as carboxylic acid derivatives while offering the increased reactivity not achieved by the analogous esters[30] or in a large extent, to amides into which could be easily transformed.

Herein, we report the Cinchona-alkaloid based squaramide-catalysed additions of thiomalonates to medium-reactive chalcones or challenging Michael acceptors as en-ynones and dienones. Bifunctional catalyst with tertiary amine unit allowed the mild nucleophile activation avoiding the application of strong or nucleophilic bases. Studying the transformations of bismalonates of tuned reactivity, the application of solventless conditions mediated by mechanochemistry impacted the reaction progress, yields and selectivities well.

Results and discussion

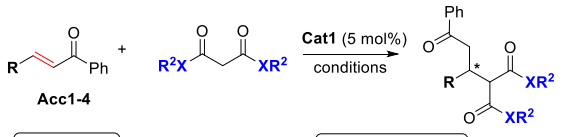
Aiming to define the reactivity of the thiomalonates in comparison to analogous oxoesters, the first experiments were performed applying a pair of nucleophiles, including dibenzyl malonate 1 and analogous thioester 2 (Scheme 2). While the application of inorganic base or DABCO in a base-catalysed transformations led to thioester decomposition‡, only the combination of both basic moiety and hydrogen bonding unit provided the Michael adduct formation starting from thiomalonates (see the ESI† for a full list of catalysts studied). Inspired by the soft enolization of thioester deprotonation performed by citrate synthase[31] and synthetic variant in bifunctional urea catalysed Mannich

reaction[32], another but tertiary amine-squaramide system[33] was chosen (**Cat1**, Scheme 2) for gentle nucleophile generation and stabilization. Activation of the bismalonates and thiomalonates along with the stabilization of resulted nucleophile revealed Cinchona—based squaramide **Cat1** proving its superiority among the tested potential catalysts. Diversified α,β-unsaturated ketones (Acc1-Acc4) were then subjected to reaction with malonate 1 in solution at room or elevated temperature[34]. Only benzoyl acrylate (Acc4) was transformed into the product, albeit with low yield, while the others remained unreactive under Cinchona squaramide **Cat1** assistance. The other tested catalysts proved to be less efficient (see the ESI†). In contrast, less reactive than benzoyl acrylate (**Acc4**) acceptors as chalcone (**Acc1**) en-ynone (**Acc2**) and dienone (**Acc3**) reacted with bisthioester **2** leading to Michael adducts (Scheme 2). However, the sustainable effects were observed only in ball-milling mediated transformations[35]. It is worth noting that the solvent-free conditions failed when oxoesters were subjected. On the contrary, solventless conditions mediated by mechanochemistry afforded the desired Michael adducts almost exclusively (product type A) with no erosion of enantiomeric purity in comparison to reactions performed in solution. Nevertheless, the reactions that occurred under standard conditions in toluene resulted in a loss of selectivity since the products of decarboxylations (type B) and sulpha-Michael additions (type C) were detected. Moreover, a profound drop in selectivity was noted at elevated temperatures in the case of all tested acceptors. Thiol residue in monothioesters could be applied to tune the reactivity of the thioester by impacting the nucleophilicity and acidity of the αC-H bond.[36] However, more active thioester resulted from the increased electron-withdrawing character of thiol component in **3** and **4** could induce competing ketene formation[32,37] releasing the highly reactive thiol nucleophile and therefore leading to unwanted sulpha-Michael adducts type C.



Scheme 2. Reactivity and selectivity of oxoester **1** and thioester **2** under standard conditions in toluene (48 h) ad solvent-free mediated by ball milling. Conversions were provided and the enantioselectivity referrers to desired adducts of type A.

Intrigued by the effects that governed the selectivity, reactions of diversified thioesters were performed (Scheme 3 and 4).



XR² = SPh (3)

R = Ph, A5
ball mill: 99%, 96% ee, 1:0.07:1.1 **A**:**B**:**C**
$PhCH_3$, rt: 30%, 43% ee 1:2.8:14 **A**:**B**:**C**
$PhCH_3$, 60 °C: **100% of sulfa-Michael**

R = PhCC, A6
ball mill: 99%, 97% ee, 1:0.3 **A**:**C**
$PhCH_3$, rt: 19%, 98% ee 1:1.4 **A**:**C**
$PhCH_3$, 60 °C: **99%, 98% ee, 1:4.7 A:C**

R = PhHC=CH, A7
ball mill: **no product**
$PhCH_3$, rt: **100% of sulfa-Michael**
$PhCH_3$, 60 °C: **100% of sulfa-Michael**

R = CO_2Et, A8
ball mill: 99%, 94% ee, 1:0.1:0.3 **A**:**B**:**C**
$PhCH_3$, rt: **100% of sulfa-Michael**
$PhCH_3$, 60 °C: **1:6.5:10.7 A:B:C**

XR² = SCH_2CF_3 (4)

R = Ph, A9
ball mill: 35%, 29% ee, 1:0.04:0.4 **A**:**B**:**C**
$PhCH_3$, rt: **no product**
$PhCH_3$, 60 °C: 38%, 80% ee, 1:0.7:**4.4** **A**:**B**:**C**

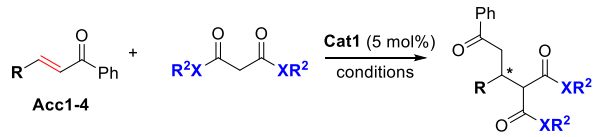
R = PhCC, A10
ball mill: 13%, 34% ee, 1:0.4 **A**:**C**
$PhCH_3$, rt: **no product**
$PhCH_3$, 60 °C: 38%, 86% ee, 1:0.03:0.2 **A**:**B**:**C**

R = PhHC=CH, A11
ball mill: **no product**
$PhCH_3$, rt: **no product**
$PhCH_3$, 60 °C: 19%, 49% ee, 1:0.2:1.2 **A**:**B**:**C**

R = CO_2Et, A12
ball mill: 21%, 20% ee, 1:0.4:0.2 **A**:**B**:**C**
$PhCH_3$, rt: 81%, 22% ee 1:0.1 **A**:**B**
$PhCH_3$, 60 °C: 68%, 71% ee, 1:0.2 **A**:**B**

Scheme 3. Selectivity in the reactions of -SPh (**3**) and -SCH_2CF_3 (**4**) bisthiomalonates catalysed by **Cat1**.

Although any attempt to utilize phenoxybismalonate as a potential nucleophile did not yield any product, the application of reactive thioesters **3** and **4** led to a mixture of products. With exception of product **A12**, ball milling-mediated reactions were superior to those performed in a solution. Even though the water was added to the milling chamber, no sulfa-Michael adduct was detected. Thus, a suspicion that the water was responsible for the decomposition of the thioester group was not of any further concern. The thioester remained stable under such conditions due to no thiol addition product formation. In contrast, sulfa-Michael adduct C was formed as a major component of the reaction mixture when the reaction was carried out at elevated temperatures. Assuming that the selectivity was mainly dependent on the nucleophile's nature, reactions with alkyl thioesters 5 and 6 were performed to support the hypothesis (Scheme 4).



$XR^2 = SCH_2CH{=}CH_2$ (5)

R = Ph, A13
ball mill: 94%, 96% ee
$PhCH_3$, rt: 40%, 90% ee
$PhCH_3$, 60 °C: 77%, 95% ee

R = PhCC, A14
ball mill: 72%, 94% ee
$PhCH_3$, rt: 71%, 97% ee
$PhCH_3$, 60 °C: 85%, 96% ee

R = PhHC=CH, A15
ball mill: 91%, 98% ee
$PhCH_3$, rt: 42%, 98% ee
$PhCH_3$, 60 °C: 69%, 96% ee

R = CO_2Et, A16
ball mill: 99%, 91% ee
$PhCH_3$, rt: 97%, 88% ee
$PhCH_3$, 60 °C: 99%, 94% ee

$XR^2 = SC(CH_3)_3$ (6)

R = Ph, A17
ball mill: 20%, 93% ee
$PhCH_3$, rt: **no product**
$PhCH_3$, 60 °C: 42%, 76% ee

R = PhCC, A18
ball mill: 60%, 89% ee
$PhCH_3$, rt: 27%, 96% ee
$PhCH_3$, 60 °C: 62%, 97% ee

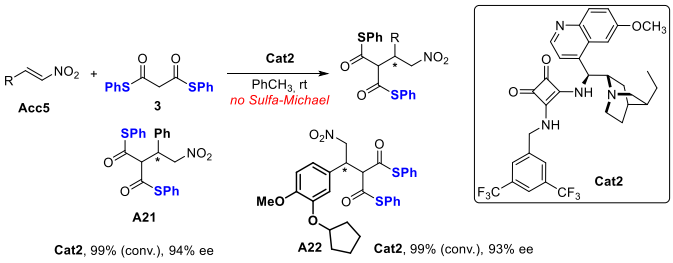
R = PhHC=CH, A19
ball mill: 19%, 91% ee
$PhCH_3$, rt: **no product**
$PhCH_3$, 60 °C: **no product**

R = CO_2Et, A20
ball mill: 99%, 96% ee
$PhCH_3$, rt: 88%, 99% ee
$PhCH_3$, 60 °C: 68%, 97% ee

Scheme 4. Reaction outcome of allyl (5) and tert-butyl (6) thioesters

Alkyl thioesters **5** and **6** exhibit lower activity as acylating agents. Thereby, as a less prone to enolization, they provided Michael adducts exclusively. Furthermore, transformations performed under ball milling conditions led to products with comparable yields and enantioselectivities for allylthioester **5**. Bulky tert-butyl thioester **6** reacted poorly with chalcone (**Acc1**), en-ynone (**Acc2**) and dienone (**Acc3**) in solution at room temperature. The yields reached moderate values only at the elevated temperature. However, applying a more electrophilic acceptor **Acc4** resulted in the formation of product under all tested conditions. Ball mill-mediated transformation outperformed those obtained in solution in terms of yield and with comparable enantioselectivity. In addition, selective product formation required, in fact, shorter reaction times.

Based on these observations, we may conclude that the activity of the nucleophile can be tuned by the subtle changes of the thiol moiety in bisthioesters. The effect is of greater importance when a Michael adduct of limited reactivity is subjected to a reaction. It is worth mentioning nitroalkenes, characterized by greater electrophilicity to chalcones, form products **A21**[18] and **A22** selectively even for tiophenolate ester **3** within minutes (Scheme 5). Transformation of the nucleophile into stable Michael adduct was facilitated by precipitation of the product from toluene as solvent (for details, see ESI†). Moreover, the excellent yields and enantioselectivities remained independent of the reaction conditions, which significantly contrasts the transformations of enones.



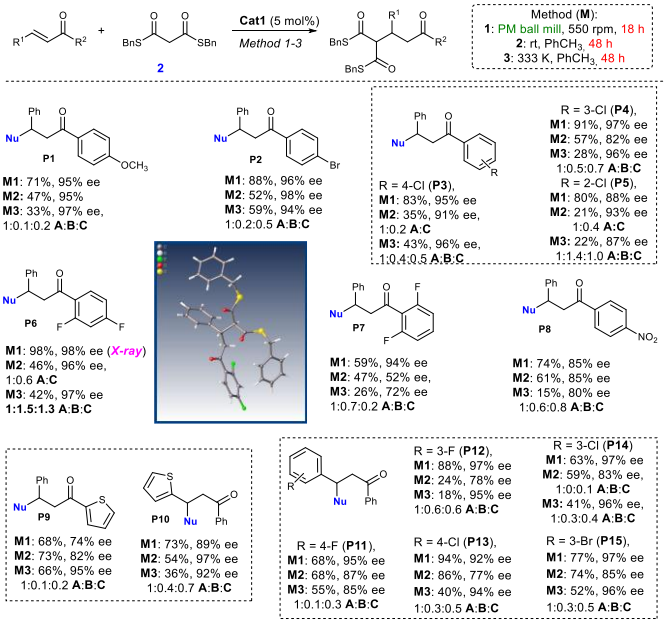
Scheme 5. Reaction of nitroalkenes with bistiophenolate **3** in solution without formation of any Sulfa-Michael adduct

Dibenzyl bisthiomalonate **2**, as the middle-active nucleophile from the study, was chosen as a representative substrate and was further subjected to reactions with a diversity of chalcones. Application of squaramide **Cat1** (5

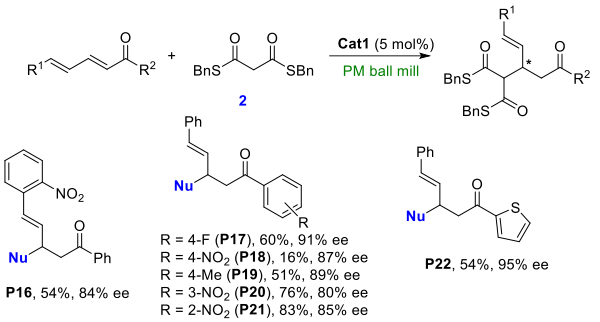
mol%) provided access to various chiral adducts with moderate to excellent yields (Scheme 6). Reactions performed under ball milling conditions resulted in the formation of product type A exclusively. In contrast, reactions under standard solvent conditions resulted in the formation of sulpha-Michael adducts (for details, see the ESI†). However, adducts A, B, and C were detected at elevated temperatures in toluene. In addition, an evident drop in yields was noted for reactions performed in solution, although these reactions required 48 hours to proceed instead of 18 hours under ball milling conditions. Therefore, the results of mechanochemical-assisted transformations outperformed those in a solvent regarding selectivity and yield of desired Michael adduct while affording products with comparable stereoselectivities. The stereochemical outcome of the transformation was only slightly affected by the substitution pattern of aryl ketone in chalcones. Although 2-chloro substituted reagent led to adduct P5 with 88% of ee, the demanding 2,6-difluorosubstituted acceptor was surprisingly transformed to chiral product P6 with 98% of ee. Nevertheless, 4-nitro and 2-tiophene derivatives reacted to give products P8 with 85% ee and 74% ee (**P9**), respectively. On the other hand, modulation of reactivities of the double bonds in studied chalcones revealed that the type of aryl moiety impacted the yields by not enantioselectivities.

The green profile of the mechanochemical approach was proved by comparing the green metrics, including E factor, mass intensity, reaction mass efficiency, and molar efficiency. The operations performed to synthesize product **P6** in the ball mill outperformed those obtained in the solution (see the ESI† for details).

Intrigued by the effects achieved by applying solventless conditions, the less reactive dienones were subjected to reactions with benzyl thiomalonate (Scheme 7).



Scheme 6. Stereoselective addition of benzyl bisthiomalonate 2 to various chalcones under ball milling conditions (method 1) and in solution (methods 2 and 3, respectively).



Scheme 7. Mechanochemical mediated additions of benzyl thiomalonate 2 to various dienones

It is noteworthy that the dienones were defined as demanding substrates to Michael additions[38], and in general, distinctly longer times were required to complete the reactions. However, although desired products **P16**-**P22** were formed with lower yields than adducts to chalcones, the enantioselectivities suffered to a later extent providing the 1,4-Michael adducts with enantioselectivities ranging from 80 to 95%.

Interested on the impact of ball milling on the product distribution and the loss of selectivity in the transformations performed in a solution, we would like to rationalize the experimental observations using Kohn-Sham density functional theory (KS-DFT) calculations,

assuming the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. Based on the reported mechanisms[39], we assumed the plausible reaction path involved the base-mediated activation of nucleophile followed by deprotonation. Further binding of the resulting nucleophile by the two-centered hydrogen bonding units allowed the acceptor to interact with the protonated amine. The orientation of both nucleophile and electrophile allowed for product formation with effective chirality transfer. To explain the lack of reactivity of dibenzyl malonate, we aimed to elucidate a speculative activation mechanism of the diester through proton abstraction. Thus, we performed KS-DFT computations summarizing the results in Fig. 1.

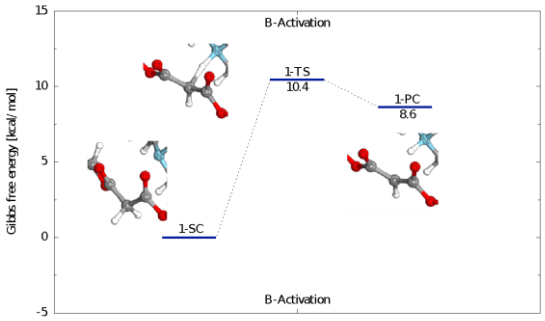


Fig. 1 – The Gibbs free energy profile for the activation of diester in the presence of the catalyst calculated at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex.

The ground-state geometry optimization of the complex containing diester and the catalyst **C1** (1-SC) revealed that the alpha hydrogen atom and the basic unit of the catalyst are well separated, and the corresponding CH----N distance amounts to 3.32 Å in 1-SC. Subsequently, we found a transition-state structure for the proton abstraction process (ΔG(1-TS) = 10.4 kcal/mol, see Fig. 1) and the product complex geometry (ΔG(1-PC) = 8.6 kcal/mol, see Fig. 1). Despite of the relatively low energy barrier (10.4 kcal/mol) for intermolecular proton transfer, we suspect that the discussed reaction may not work due to the lack of attractive interaction between CH----N moieties in 1-SC resulting in the moderate distance (3.32 Å) between the acid hydrogen atom and the tertiary amine form catalyst. Consequently, such an energetically stable arrangement of diester nearby the catalyst could be a limiting factor for the proton abstraction process. Furthermore, the moderate energy difference (8.6 kcal/mol) between substrate and product complexes indicates that the reversibility of the protonation step can be a dominant process since the activated nucleophile is not energetically stable. Indeed, the experimental observations revealed the diester remained inert, subjected to any reaction in the presence of the catalyst **Cat1**.

In turn, we performed similar computational explorations for the activation step in dithioester containing Ph-CH_2-S moiety (Fig. 2) instead of Ph-CH_2-O depicted in Fig. 1.

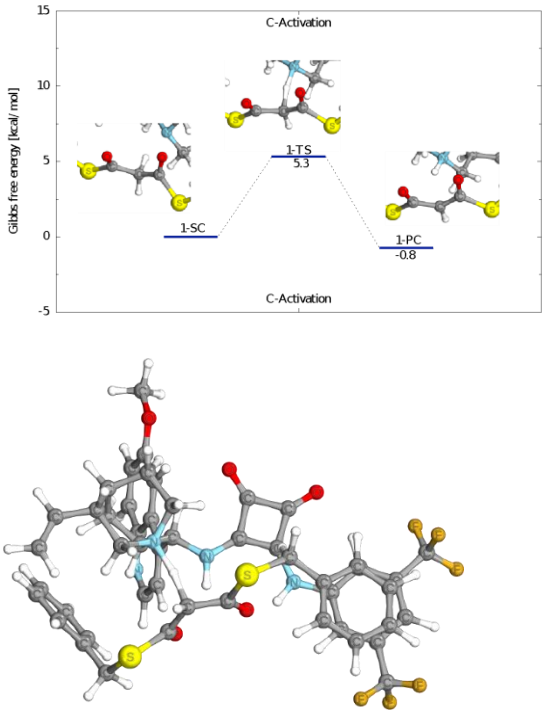


Fig. 2 – The Gibbs free energy profile for the activation of 2 in the presence of the catalyst calculated at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex. On the bottom is presented the 1-TS projection.

We found that the energy barrier of the proton abstraction from dithioester is essentially lower (5.3 kcal/mol, see Fig. 2) compared to

diester (10.4 kcal/mol, see Fig. 1) The activated dithioester complex is more stable by 0.8 kcal/mol than 1-SC complex (see Fig. 2). Therefore, we assume that the activation process of the benzyl dithiomalonate **2** should undergo more efficiently, and it agrees with the obtained experimental results. It is also worth adding that the activation step for benzyl thioester 2 and thiophenolate diester **3** might work similarly since the proton abstraction process requires only 6.7 kcal/mol (see Fig. 3) which is 1.4 kcal/mol higher than needed for dibenzyl thiomalonate **2** (Fig. 2). A mechanistic rationale for the addition reaction pathways of both 2 and 3 dithioesters to the chalcone in the presence of the catalyst **Cat1**, assuming toluene as the solvent, is proposed in Fig. 3 and 4, respectively.

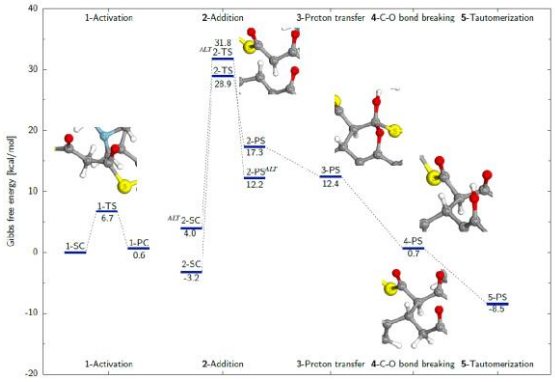


Fig. 3 – The Gibbs free energy profile for the addition reaction of dithioester 3 to chalcone assisted by the catalyst Cat1 obtained at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex

In the initial step, assuming thiophenolate diester 3, the nucleophile activation proceeds to employ the tertiary amine unit of the bifunctional catalyst via the proton abstraction (ΔG(1-TS) = 6.7 kcal/mol) from dithioester. Such a reaction results in the formation of a stable complex (ΔG(1-PC) = 0.6 kcal/mol) of the catalyst and deprotonated dithioester, inducing the changes in an electron density between carbonyl groups, including the CH moiety. Since the carbon atom in the CH moiety in the activated nucleophile is negatively charged (-0.46 e), we can expect the addition of dithioester to chalcone through the formation of the C-C bond (1.87 Å, 2-TS) having a substantial Gibbs free energy barrier (ΔG(2-TS) = 28.9 kcal/mol). Additionally, we also found an alternative transition-state structure leading to opposite configuration of the product (ΔG(2-TSALT) = 31.8 kcal/mol, ΔΔG = 1.9 kcal/mol). Since the Gibbs free energy barriers for the formation of the C-C bond are high, we may assume that the Michael addition is the rate-determining step in the investigated reaction. In other words, it means that the efficiency of the addition reaction may be pretty low under standard conditions. Indeed, these theoretical results are consistent with experimental observations. If the system overcomes the energy barrier (2-TS), a cyclization process occurs through the formation of the C-O bond between the formed enol and the thioester group (ΔG(2-PS) = 17.3 kcal/mol, see Fig. 3). Though peculiar, cyclisation is the process related to lactonization resulting from S-to-O acyl transfer during the synthesis of Myxopyronin40 or during biomimetic lactonization to afford 3,4-Dihydropyranones[28d]. Subsequently, backward proton transfer from the catalyst to the intermediate (ΔG(3-PS) = 12.4 kcal/mol), following proton transfer breaking the newly formed C-O bond (ΔG(5-PS) = 0.7 kcal/mol, see Fig. 3) and the tautomerization process of the intermediate results in the final product formation (ΔG(5-PS) = -8.5 kcal/mol, see Fig. 3).

Considering the discrepancy of the observed reaction outcome when the different thiomalonates were used, employing the addition of benzyl dithiomalonate **2** to chalcone was also studied in Fig. 4. The initial nucleophile activation of nucleophile 2 occurring in the presence of the catalyst and through the deprotonation process can easily procced by the transition-state geometry (ΔG(1-TS) = 5.3 kcal/mol see Fig. 4). Having the activated nucleophile (1-PC in Fig. 4), the system might reach the 2-TS transition-state geometry (ΔG(2-TS) = 4.2 kcal/mol). A found

alternative orientation (see Fig. 4) of the activated nucleophile within the complex of the catalyst might lead to another transition state 2-TSALT (ΔG(2-TSALT) = 26.1 kcal/mol). Significant transition states energy difference in the addition step (21.9 kcal/mol, see Fig. 4) clearly indicates the excellent enantioselectivities in reactions performed under solvent, and solvent-free conditions regardless of the temperature.

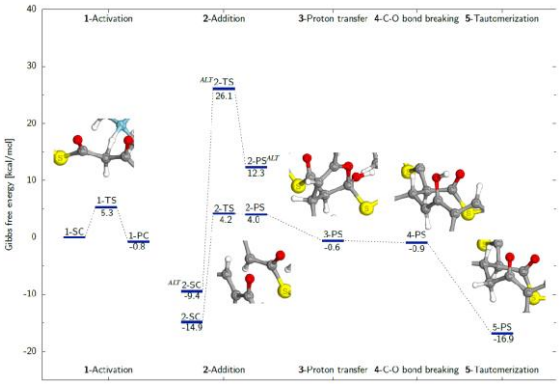
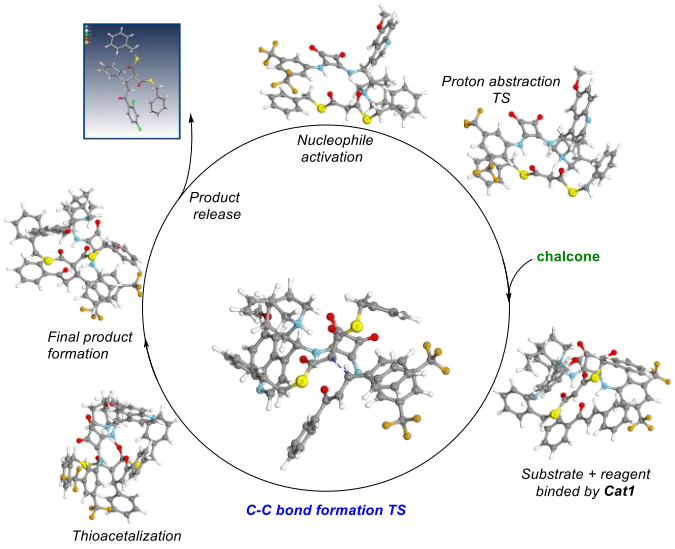


Fig. 4 – The Gibbs free energy profile for the addition reaction of dithioester **2** to chalcone assisted by the catalyst Cat1 obtained at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex.

Although the postulated reaction paths for nucleophiles **2** and **3** are analogous, the addition of dibenzyl thiomalonate could occur more feasibly because the addition of the activated nucleophile **3** compared to **2** to the chalcone requires significantly less energy to reach the 2-TS transition-state geometry (Fig. 4). Consequently, the substantial energy difference of the alternative transition states secures the enantioselectivity limiting the chirality transfer and leading to an opposite enantiomer. Based on the detailed mechanism analysis employing the KS-DFT theory and the X-ray[§] of the product P6 (see Scheme 6), we proposed a plausible mechanism in order to rationalize the chirality transfer to the product in Scheme 8.



Scheme 8. Plausible mechanism of the chirality transfer with the highlighting of the crucial transition state resulting in the C-C bond formation

The preorientation of the chalcone involves the binding of the ketone by a two-centered hydrogen-bonding system of squaramide. The protonated tertiary amine is responsible for binding and stabilization of the activated nucleophile. Furthermore, in a postulated reaction mechanism, the π-π interactions between the phenyl group of chalcone and the bis-trifluormethylated arylidene unit of squaramide could additionally induce stabilizing interactions and the orientation of the substrate and reagent. Thus, the (S)-adduct is formed as an enol, which attacks the neighbouring thioester group, leading to thioacetal. The final proton transfers led to the desired product, of which the release allows the catalyst **Cat1** to close the catalytic cycle.

Regarding the formation of the undesired Sulfa-Michael adducts that could be additionally rationalized by studying the reaction path for less activated Michael acceptor, the reaction of 3 with en-ynone was deliberated (Fig. 5). After the initial step of the nucleophile activation, the expected dithioester addition to en-ynone through the formation of the C-C bond (1.87 Å, 2-TS) is marked by the high energy barrier (ΔG(2-TS) = 32.9 kcal/mol, see Fig. 5). An alternative transition state of the addition of the activated nucleophile to en-ynone, leading to an

opposite configuration in a product, was also found (ΔG(2-TSALT) = 34.2 kcal/mol, ΔΔG = 1.3 kcal/mol, see Fig. 5). Despite the low transition states energy difference, there is an essential energy difference between substrate complexes (2-SC, ΔΔG = 3.1 kcal/mol, Fig. 5) which seems to support the observed enantioselectivities also reached in solution (see Scheme 2).

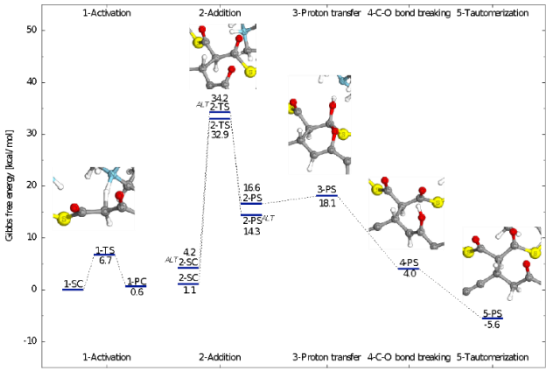


Fig. 5 – The Gibbs free energy profile for the addition reaction of dithioester **3** to the conjugated en-ynone assisted by the catalyst obtained at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex

The relatively high energy barrier implies the conclusion the efficiency of the addition reaction may be quite low under the standard conditions (see Fig. 5). Indeed, these theoretical results are consistent with experimental observations. After overcoming the transition-state energy barrier (2-TS in Fig. 5), a cyclization process (ΔG(2-PS) = 16.6 kcal/mol) followed by the proton transfer from the catalyst to the intermediate (ΔG(3-PS) = 18.1 kcal/mol) can occur. Subsequently, the breaking of the newly formed C-O bond followed by subsequent proton transfer (ΔG(5-PS) = 4.0 kcal/mol) and the tautomerization process afforded the final product (ΔG(5-PS) = -5.6 kcal/mol). Nevertheless, the described reaction path (Fig. 5) is similar to the one presented for the addition of 3 to chalcone (Fig. 3). It does not explain the lack of selectivity resulting in formation of undesired mainly Sulpha-Michael adduct C. Having the activated nucleophile in the presence of the catalyst, we identified another chemical route (see Fig. 6) leading to the breaking of the C-S bond (ΔG(1-TC) = 24.8 kcal/mol) that enables the detachment of the Ph-S moiety from the deprotonated dithioester (ΔG(1-PC) = 15.4 kcal/mol). Decomposition of 3 can occur through the backward proton transfer from the catalyst to the sulphur atom (1-TS, Fig. 6). It is worth mentioning that the initing reaction proton is at a distance of 2.91 Å from the sulphur atom in the substrate complex (1-SC) in Fig. 6. Since there is a substantial H---S distance, the intermolecular proton transfer could rather occur at an elevated temperature. Under such conditions, we could expect that the increased vibrational motion of the N-H bond in the catalyst (see Fig. 6) should facilitate the detachment of the proton from the catalyst and transfer it to the sulphur atom. Interestingly, the C-S bond rupture (1-TS, see Fig. 6) requires 24.8 kcal/mol, which is about 8 kcal/mol lower than the addition step in Fig. 5.

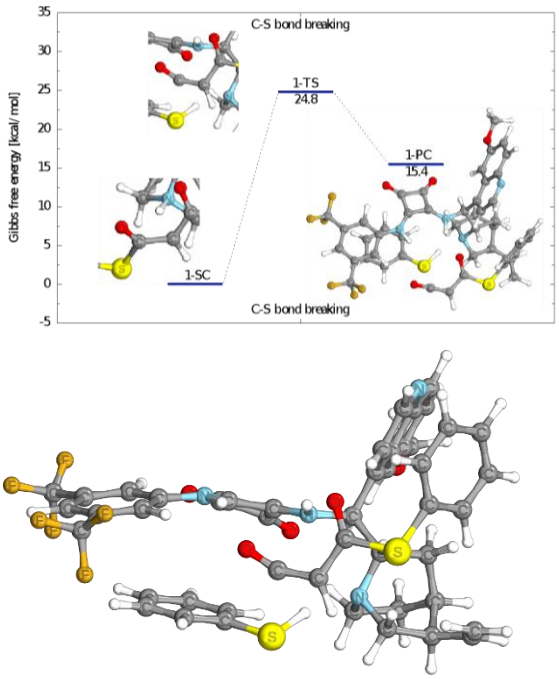
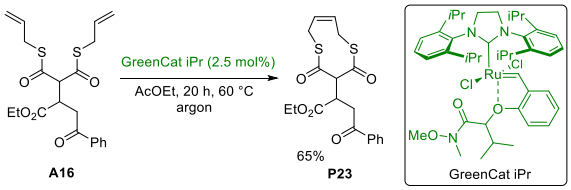


Fig. 6 – The Gibbs free energy profile for the detachment of the Ph-S moiety from the activated nucleophile calculated at the ωB97xD/PCM(Toluene)/def2-TZVP level of theory. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex. On the bottom, the plausible 1-TS projection.

The formation of thiocarboxyketene as the rate-determining step of the selective

monoalcoholysis of dithiomalonates was postulated to proceed under neutral conditions[37b], while the thiophilic copper-assisted41 or silver-mediated ketenes formation37a were applied to the synthesis of butenolides or dioxinones, respectively. The release of the thiophenoxide from bisthiomalonate provides a strong nucleophile which reactivity outperforms the thiomalonate. Hence, the Sulfa-Michael adduct dominates or is an exclusive product when the desired reaction of acceptor with **3** is rather slow. Therefore, our KS-DFT calculations suggest that the release of the thiophenolate moiety could be devised as the main chemical route, especially at an elevated temperature. Moreover, this assumption agrees very well with experimental findings.

The chemical stability of the thioester in the presence of the base could modulate the self-reactivity influencing the proton abstraction step and thus activation of the nucleophile. Besides the acylating ability of the thioester group that is the most employed reactivity[21,27b], the introduction of the terminal alkene allowed for diversifying the adduct's structure without the replacement of the sulphur-based group. Hence, the ring-closing metathesis proceeded well to form a nine-membered heterocycle with a 65% yield (90% ee) by applying GreenCat *i*Pr catalyst (Scheme 9) under gentle conditions without precautions of water or solvent impurities.[38,42] Moreover, the catalyst removal from the crude reaction mixture was greatly feasible.



Scheme 9. Ring-closing metathesis of the Michael adduct **A16.**

Conclusions

Solvent-free, ball milling mediated conditions allowed for conducting the addition of diversified in electron nature thiomalonates in a highly stereoselective manner affording Michael adducts exclusively with enantioselectivities mostly exceeding 90% ee. On the contrary, the analogous reaction in a solution or at elevated temperature results in a non-selective process requiring longer reaction times. The superiority of the thiomalonates over oxoesters was proved for benzyl and phenyl esters, while the latter mainly remained unreacted. Both our KS-DFT calculations and experimental results were used to elucidate reactivity differences in studied reactions. Hence, the activation of benzyl malonate requires over 10 kcal/mol for a proton abstraction, while the corresponding thioester is only about 5 kcal/mol. Moreover, the crucial stabilization of the nucleophile is far greater, whereas the intermediate formed from benzyl ester remains in close energy level to the transition state moving forward the deprotonation step. On the other hand, the lack of the selectivity in reactions employing thiophenolates was ascribed to the less energetical demanding decomposition of the activated nucleophile that, in combination with a relatively high energy level of Michael addition TS at about 30 kcal/mol, resulted in the formation of a mixture of detected products of A, B, and C-types. Therefore, we proved the Michael addition of thiomalonates to the medium electrophilic alkenes could be efficiently performed in an enantio- and chemoselective way, applying chiral bifunctional squaramides under solvent-free conditions in a ball mill. The mechanochemical method allowed us to save the reaction time, limit the possible product distribution and the resulting simplification of product purification finally required fewer solvents consumption and thus, indicating the sustainability profile of the presented approach.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ However, in contrary to strong inorganic bases responsible for adduct decomposition, DABCO turned out to promote S, S'-diethyl dithiomalonate addition to cyclic enones (for further details, see ref. 16)

§CCDC 2159654 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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