



Enantioselective Catalytic Transformations of Barbituric Acid Derivatives

Claire Segovia, Arthur Lebrêne, Vincent Levacher, Sylvain Oudeyer,
Jean-François Brière

► To cite this version:

Claire Segovia, Arthur Lebrêne, Vincent Levacher, Sylvain Oudeyer, Jean-François Brière. Enantioselective Catalytic Transformations of Barbituric Acid Derivatives. *Catalysts*, 2019, 9 (2), pp.131. 10.3390/catal9020131 . hal-02197279

HAL Id: hal-02197279

<https://normandie-univ.hal.science/hal-02197279>

Submitted on 21 Aug 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Review

Enantioselective Catalytic Transformations of Barbituric Acid Derivatives

Claire Segovia, Arthur Lebrène , Vincent Levacher , Sylvain Oudeyer and Jean-François Brière * 

Normandie University, UNIROUEN, INSA Rouen, CNRS, COBRA, 76000 Rouen, France; claire.segovia@inv.univ-rouen.fr (C.S.); arthur.lebrene@insa-rouen.fr (A.L.); vincent.levacher@insa-rouen.fr (V.L.); sylvain.oudeyer@univ-rouen.fr (S.O.)

* Correspondence: jean-francois.briere@insa-rouen.fr; Tel.: +33-235-522-464

Received: 20 December 2018; Accepted: 15 January 2019; Published: 1 February 2019



Abstract: Since the beginning of the 20th century, numerous research efforts made elegant use of barbituric acid derivatives as building blocks for the elaboration of more complex and useful molecules in the field of pharmaceutical chemistry and material sciences. However, the construction of chiral scaffolds by the catalytic enantioselective transformation of barbituric acid and derivatives has only emerged recently. The specific properties of these rather planar scaffolds, which also encompass either a high Brønsted acidity concerning the native barbituric acid or the marked electrophilic character of alkylidene barbituric acids, required specific developments to achieve efficient asymmetric processes. This review covers the enantioselective catalytic reactions developed for barbituric acid platforms using an organocatalytic and metal-based enantioselective sequences. These achievements currently allow several unique addition and annulation reactions towards the construction of high valued chiral heterocycles from barbituric acid derivatives along with innovative enantioselective developments.

Keywords: organocatalysis; asymmetric synthesis; barbituric acid; alkylidene barbituric acid; metal based-catalysis; cycloaddition; annulation reaction

1. Introduction

1.1. Context

Barbituric acid **1**, namely 2,4,6-(1*H*,3*H*,5*H*)-pyrimidinetrione, and derivatives are fascinating building blocks in organic synthesis (Figure 1). This story dates back to 1894 when von Baeyer reported on the preparation of barbituric acid [1]. Later, in 1903, Fisher and von Mering highlighted the pharmacological properties of 5,5-diethyl barbituric acid, the so-called barbital, as a potent hypnotic agent [2]. Ever since, barbituric acid derivatives served as starting materials for the elaboration of thousands of complex architectures useful in medicinal chemistry, a field of research covered by several exhaustive reviews [3–6]. Selected examples of bioactive compounds in this series are depicted in Figure 1, which highlights scaffolds that possess, at least, one stereogenic center or a tetrasubstituted carbon as a source of chemical diversity and structural complexity. Phenobarbital, involved in the treatment of certain types of epilepsy, derived from the original barbital but displays two different substituents at C-5 position (Figure 1a) [7]. The opportunity afforded by the double functionalization of the C-5 position of barbituric acid allowed the construction of several spiro-compounds and, thus, more rigid architectures highlighted by the development of nucleotide mimics [8], inhibitor of matrix metalloproteinases (MMP) [9] and anticancer agents [10], for example (Figure 1b–d) [11,12]. On the other hand, the synthesis of fused-bicycle derivatives led to ingredients possessing either

antidiabetic [13] or antituberculosis properties (Figure 1e–f) [14]. Besides medicinal chemistry, the photophysical properties of barbituric acid derivatives were exploited in colorimetric or heat detection [15], and provided promising dyes or fluorogenic probes to name a few [16,17].

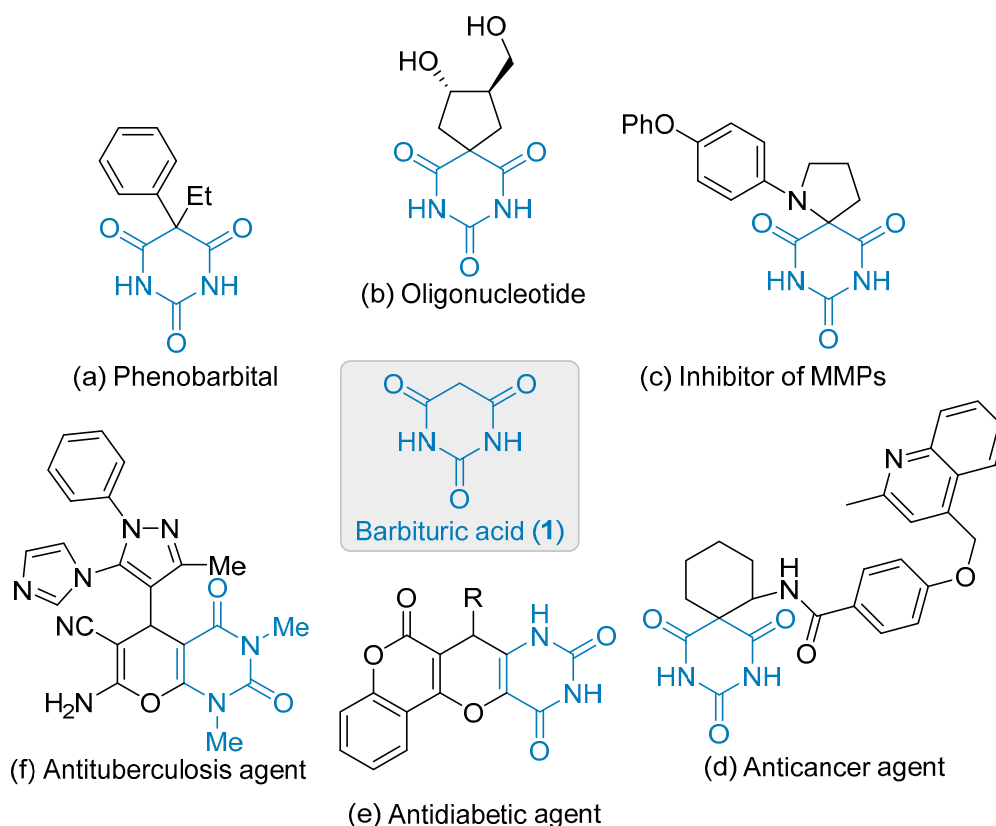


Figure 1. Barbituric acid scaffolds within bioactive architectures.

The versatile properties of products obtained from barbituric acid elicited the motivation of organic chemists to explore its chemistry [3,4,6], and more recent evolutions have met the development of efficient multicomponent reactions (MCR) [16,18]. Despite great synthetic advances in this field of research, the use of diastereoselective sequences or separation techniques (crystallization or chromatography) of racemic mixtures were required for the elaboration of enantiopure architectures of chiral bioactive compounds as depicted in Figure 1 [19]. At the end of the 1990s, the pioneering research of Brunner's group, on the palladium-catalyzed enantioselective alkylation of barbituric acid derivatives have shed light on the potential of this starting material in asymmetric synthesis while pointing out challenges, which have to be overcome with this unique architecture [20–23]. This review intends to cover the literature dealing with the enantioselective catalytic transformations of barbituric acid derivatives, an exercise which is unprecedented to the best of our knowledge. The literature concerning the enantioselective transformations of barbituric acid and alkylidene barbituric acid derivatives will be discussed separately, to focus on specific types of reactions developed for a given barbiturate structure. To give a flavor of the uniqueness of barbituric acid compounds, its properties will first be introduced.

1.2. Properties of Barbituric Acid Derivatives

To gain insight into the reactivity of barbituric acid derivatives, the unique chemical properties of these molecules have to be taken into account. As shown in Figure 2a, barbituric acid **1** displays a rather low pK_a value ($pK_a = 8.4$ in DMSO) [24] lying just above Meldrum's acid **2** well-known for its remarkable acidity ($pK_a = 7.03$ in DMSO) [25,26]. Consequently, barbituric acid **1** and derivatives will

be much more prone to deprotonation by soft bases than dimedone **3** or non-cyclic homologues, such as malonate **4**, for instance. However, direct correlation between the pK_a value and the nucleophilic behavior is not always feasible [27].

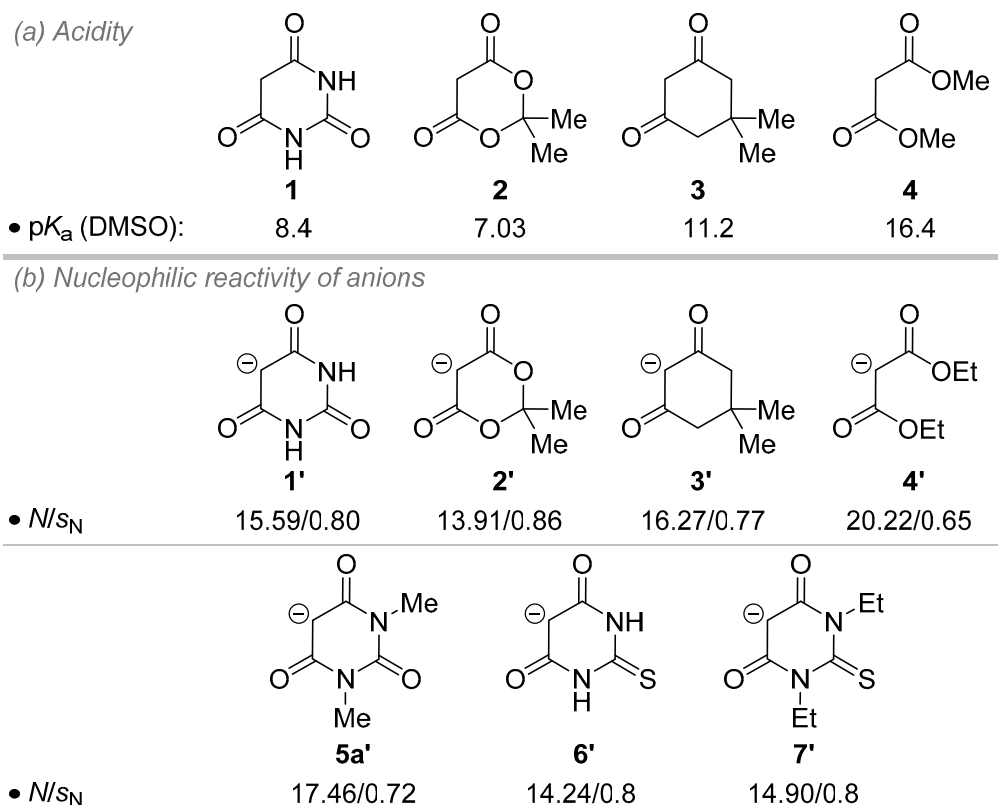


Figure 2. Properties of barbituric acid derivatives. (a) Acidity given in DMSO. (b) Nucleophilic reactivity parameters of anions.

In 2017, Spange and co-workers embarked on the insightful evaluation of the kinetics of derivatives of barbiturate acid anions thanks to the reaction with specific electrophiles, such as benzhydrylium cations and Michael acceptors [28]. Then, the so-called nucleophilicity parameter N and the corresponding nucleophile-specific susceptibility parameter s_N of barbiturate anions **1'** could be determined and compared to related 1,3-dicarbonyl anions **2'**–**4'** (Figure 2b) [27]. Barbituric acid anion **1'** features a nucleophilic character between Meldrum's acid **2'** and dimedone **3'** anions but is much less reactive than malonate anion **4'**, which actually leads to a rather good correlation with the scale of pK_a values. In addition to being more soluble, the 1,3-dimethylbarbituric acid **5a'** reacted faster than the parent anion **1'**, a phenomenon attributed to the electron-donating effect of the N -alkyl groups. Nevertheless, a ground state stabilization of the negative charge of **1'** by hydrogen bonding of the NH moieties might also account for this outcome. In comparison, the anionic thiobarbiturate analogues **6'** and **7'** proved to be less nucleophilic due to superior electron withdrawing properties of the thiocarbonyl versus carbonyl of **1'** for instance. Interestingly, during this study, the O-alkylation reaction has never been observed. Accordingly, a computational study showed that the C-alkylation process is favored both from a thermodynamic and a kinetic point of view. This scenario might be different with harder electrophiles, however.

Mayr and co-workers studied the electrophilicity of benzylidene barbituric acid derivatives (Figure 3) [29], which proved to be a potent electrophile in various conjugate addition reactions or cycloaddition processes (*vide infra*). 5-Arylidene 1,3-dimethylbarbituric acid **8a** has an electrophilicity parameter E similar to 5-arylidene Meldrum's acid **10**, which is in line with the reactivity of benzylidenemalononitriles, such as **12**. For comparison purposes, the benzylidene barbituric acid

derivative **8a** is a much more potent electrophile than the malonate counterpart **11** and, thus, affords interesting reactivity to be exploited in catalysis. Another important feature, relies on the modulation of reactivity by moving from barbiturate **8a** to thiobarbiturate **9a** which displays a superior electrophilicity. The authors attributed this phenomenon to the higher positive polarization of nitrogen in the thiobarbiturate **9a** versus barbiturate **8a** [29].

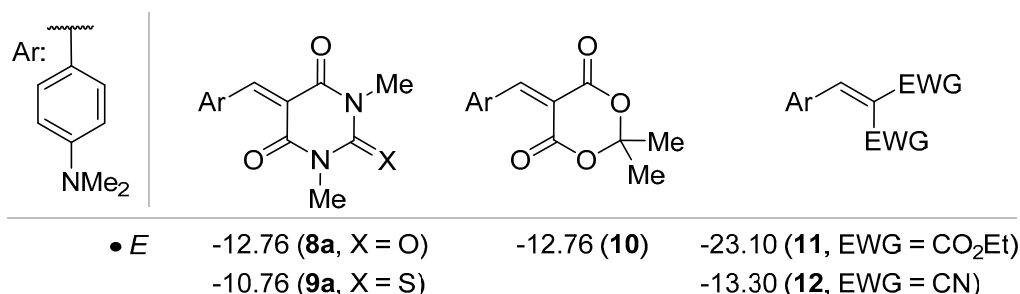


Figure 3. Reactivity issues.

2. Enantioselective Transformations of Barbituric Acid Derivatives

As aforementioned, barbituric acid derivatives are easily deprotonated with regard to their rather low pK_a value. Simple reasoning based upon resonance structures obviously shows that the conjugate base of barbituric acid may undergo either a C-alkylation or an O-alkylation reaction (Figure 4a), an issue known to be dependent on the nature of the electrophile and reaction conditions [28]. Several research groups took advantage of these features to develop enantioselective transformations based on three different strategies (Figure 4b). Barbituric acid derivatives having different *N*-substituents ($R^1 \neq R^2$) are pro-chiral by nature (if $R^3 = H$) and, consequently, they provide the corresponding alkylated products with a stereocenter inside the ring (strategy A). This approach was mainly applied to the formation of tetrasubstituted products ($R^3 \neq H$). On the other hand, symmetrical architectures ($R^1 = R^2$, strategy B) will furnish products along with the construction of a stereocenter outside the ring after the reaction with a pro-chiral electrophile. Finally, annulation processes may take place, through both a C- and O-alkylation sequence (strategy C), allowing the synthesis of fused ring scaffolds while the initial symmetry of the barbituric acid precursor is broken.

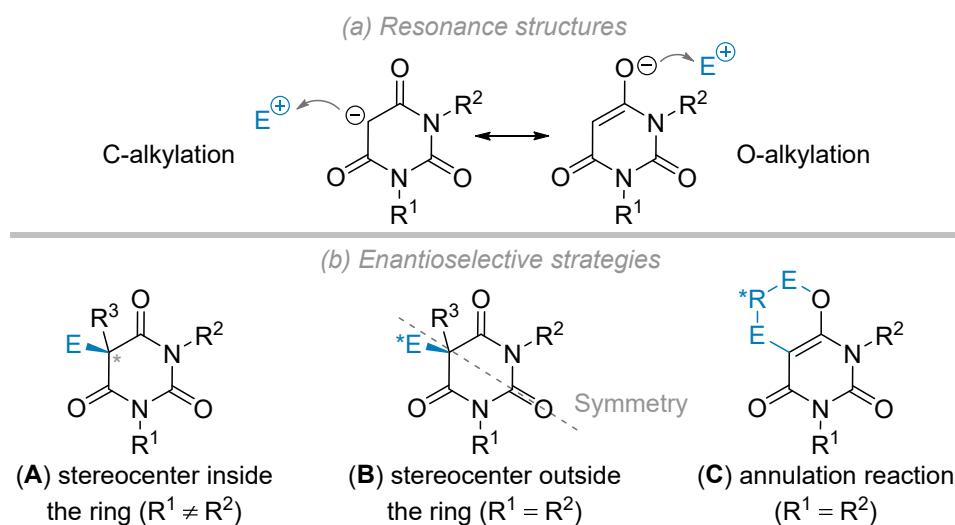
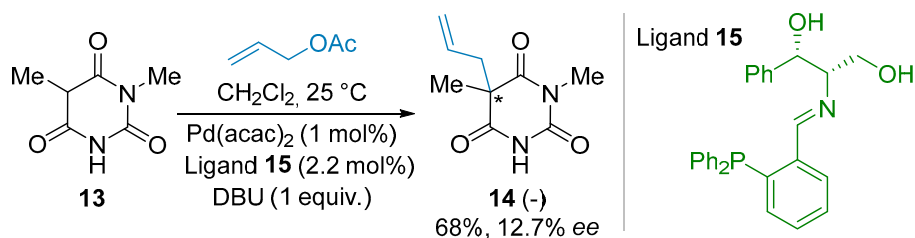


Figure 4. Reactivity issues and asymmetric synthesis. (a) Resonance structures towards C or O-alkylation reaction. (b) Enantioselective strategies.

In the following Section, we will describe the achievement based on these three enantioselective synthetic strategies.

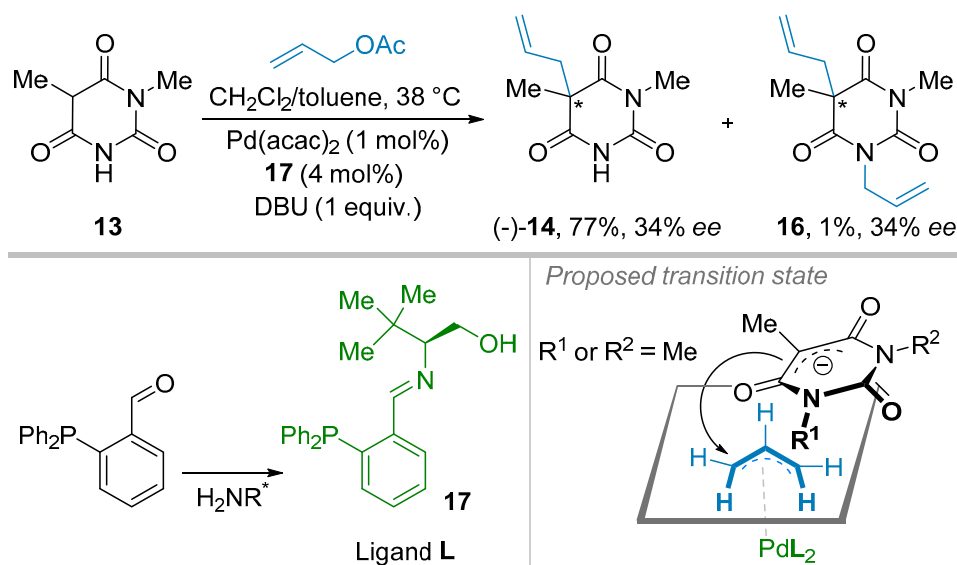
2.1. Addition Reactions with Stereocenters Created Inside the Ring

In the 1990s, the Brunner group published a series of pioneering investigations highlighting the stereoselective alkylation reaction of non-symmetrical barbituric acid derivatives. In 1994 [21], the authors succeeded in the Pd-catalyzed allylation reaction of the 1,5-dimethylbarbituric acid **13** to give the corresponding product **14** in 68% yield and 12.7% *ee* (Scheme 1), along with the creation of an all-carbon tetrasubstituted stereocenter. The process needed the use of a stoichiometric amount of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) as a base to deprotonate the starting material **13**. This beautiful early achievement was allowed with the parallel development of novel chelating chiral phosphine imine ligands, such as **15**.



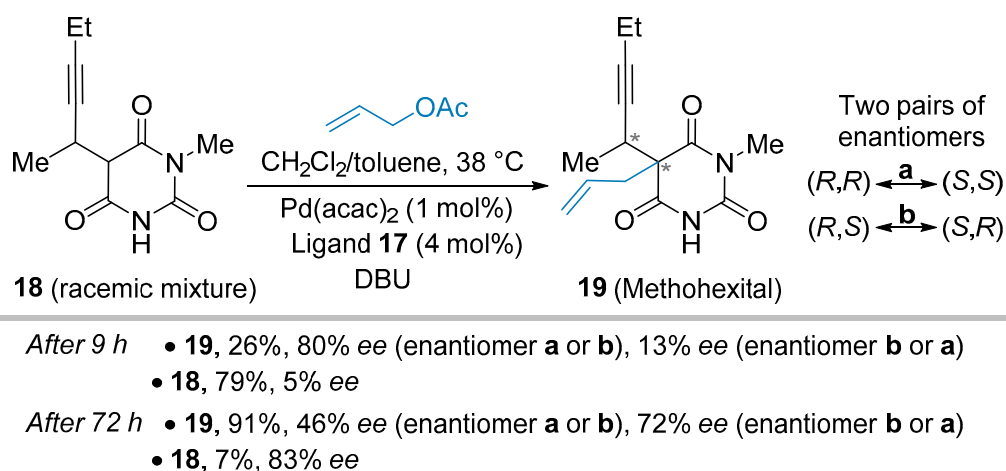
Scheme 1. Pioneering investigations.

During subsequent investigations, this group of researchers took advantage of the readily available phosphine imines like **17**, easily synthesized from the corresponding aldehyde with suitable chiral amines (Scheme 2). Then, 134 various ligands were evaluated in this enantioselective allylation process of **13** [20,23]. The novel phosphine ligand **17** allowed to improve the *ee* up to 34% for product **14**, and another side-product, **16**, which originated from the double allylation reaction was observed in these conditions. Based on preliminary theoretical and NMR investigations, the authors have proposed a transition state wherein the (η^3 -allyl)-palladium complex would possess two phosphine-ligands **L** featuring π - π stacking events between their phenyl rings. Then, the hydroxyl functional group of the ligand may create hydrogen-bonding interactions with the barbituric acid anion to differentiate the two enantiotopic enolate faces (Scheme 2). These pioneering achievements are noteworthy since the pro-chiral incoming anion, and the palladium complex (having the chiral information) are lying at the opposite faces of allylic activated species, which makes the design of a suited ligand for this asymmetric reaction significantly challenging contrariwise to the one used for a pro-chiral electrophile.



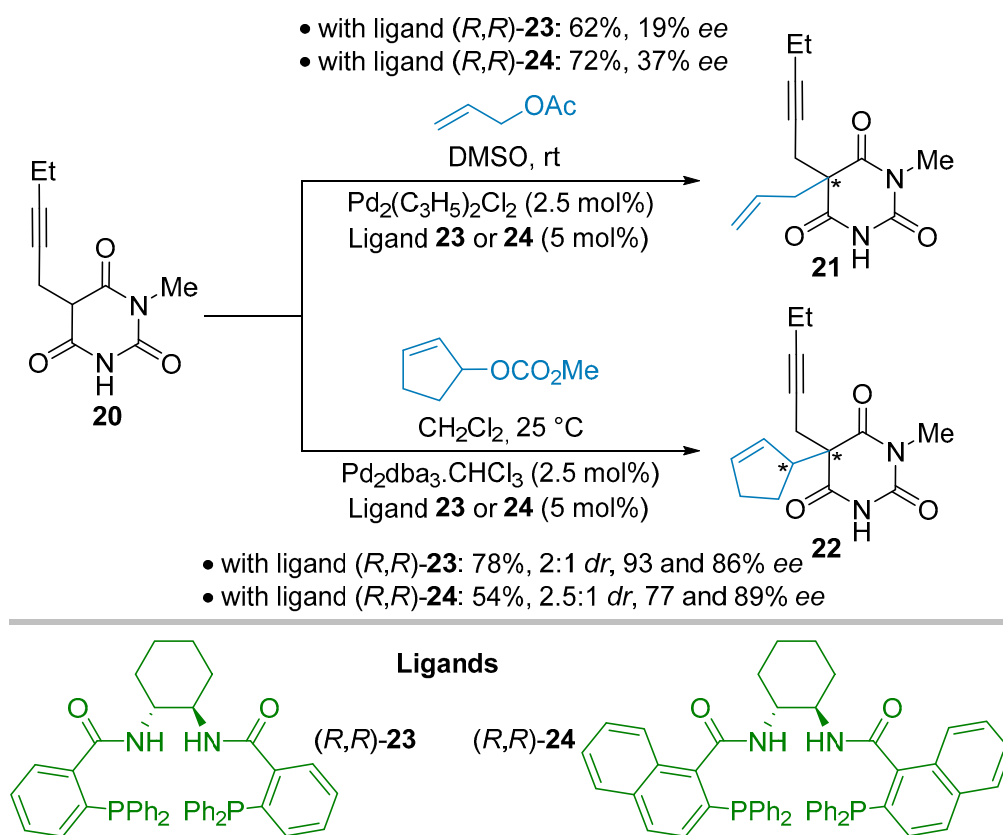
Scheme 2. Ligand optimization for the Pd-catalyzed allylation reaction.

In 1999, Brunner and colleagues tackled the stereoselective synthesis of methohexital **19**, a potent short-time anesthetic (Scheme 3) [22]. As mentioned in the article, the four stereoisomers of barbituric acid derivatives **19** displayed distinct narcotic effects that make asymmetric synthesis a useful constructive-tool in this case. The palladium-promoted allylation reaction was, obviously, a suited approach to **19** but had to challenge the presence of a stereogenic center on 1-methyl-5-(1'-methylpent-2'-ynyl) barbituric acid **18**, in so much as this starting material was used as a racemic mixture. The phosphine imine **17** proved to be the best ligand for this reaction, and an advanced investigation revealed salient features. Indeed, the stereoselective allylation of one of the prostereogenic faces of the transient enolate species took place upon the influence of the chiral ligand **17**, giving two diastereoisomers (**19**, (*R,R*) and (*R,S*), for instance) for a given enantiomer of **18** (for instance, from the one having the *R* propargylic-stereocenter). Additionally, this allylation sequence also led to a kinetic resolution process resulting in the faster transformation rate of either (*R*)-**18** or (*S*)-**18** at the propargylic-stereocenter. In line with these two processes (Scheme 3), the reaction stopped after 9 hours and provided two diastereoisomers **19** with 26% yield and one of them was obtained in up to 80% *ee* (the other one in 13% *ee*). The remaining starting material **18** was recovered in 79% yield and a combined 5% *ee*. After 72 hours of reaction, the enantiomeric excess of the first pair of enantiomers decreased to 46% while the other one reached 72%. Nonetheless, the combined *ee* of the starting material **18** (7%) was improved to 83% in accordance with a kinetic resolution event.



Scheme 3. Synthesis of stereoisomers of methohexital.

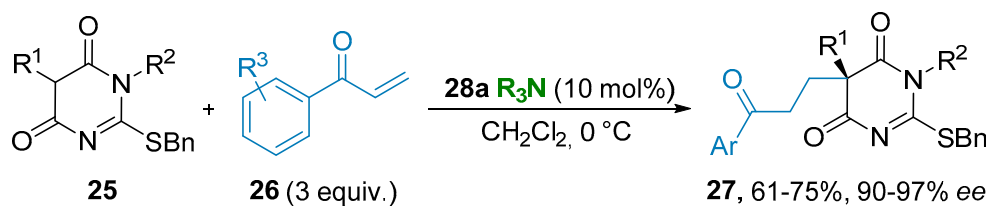
In 2000 the Trost group envisaged the elaboration of a simplified analogue **21** of methohexital, lacking a stereogenic center at the propargylic position (Scheme 4) [30]. The catalyzed asymmetric allylic alkylation reaction (AAA), using the C_2 -symmetrical cyclohexyldiamine ligands **23** or **24** in the presence of palladium chloride species, allowed the transformation of the starting material **20** into the corresponding allylated product **21** albeit in modest 19% yield and 37% *ee*. In this case, the more sterically hindered ligand **24** versus **23**, having two naphthyl moieties, proved to be the most efficient one. The authors moved to a prochiral cyclopentenyl carbonate as electrophile with the hope to favor the stereodifferentiation of the prochiral faces of the enolate intermediate derived from deprotonation of nucleophile **20**. In a similar catalytic system, but in dichloromethane solvent instead of DMSO, the product **22** was obtained in a good 78% yield, modest 2:1 *dr* but with excellent *ees* of 93% and 86% for both diastereoisomers, respectively. This constitutes the highest selectivity obtained at that time for a catalytic metal-based transformation of a non-symmetrical barbituric acid. That is noteworthy as this requires the chiral discrimination between an *N*Me and *N*H amide moieties of the pro-nucleophilic partner **20**.



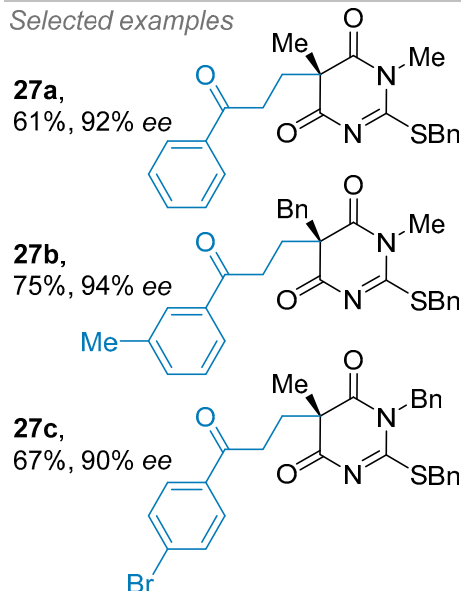
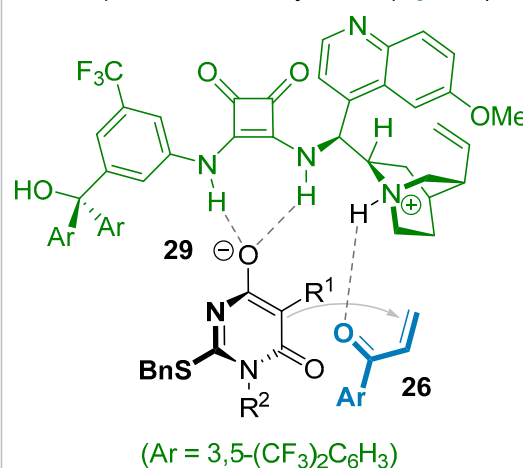
Scheme 4. Catalyzed asymmetric allylic alkylation reaction.

Recently, Palomo and co-workers tackled the enantioselective alkylation reaction of non-symmetrical barbituric acid derivatives making use of an organocatalytic strategy (Scheme 5) [31]. After the observation of very moderate *ees* obtained using (thio)barbituric acid nucleophiles, this research established that 2-alkylthio-4,6-dioxypyrimides **25** were competent barbituric acid surrogates for the conjugate addition reaction to vinyl aryl ketones **26**. Upon the influence of a newly designed squaramide-derived 9-*epi*-amino quinine **28a** organocatalyst, as a chiral Brønsted base, an array of Michael adducts **27** were synthesized in good yields and *ees* ranging from 90 to 97% irrespective of the nature of substituents (R^1 , R^2 , and Ar) on precursors **25** and **26**. To explain the enantioselectivity of this reaction, the authors proposed a transition state in which the bifunctional organocatalyst **28a** would create two hydrogen bonds between the squaramide moiety and the corresponding enolate of barbiturate derivative **25** within the ion-pair **29** (Scheme 5), and more precisely with the most accessible oxy-anion. Then, enones **26** would approach the front-face of the barbiturate enolate escorted by a hydrogen bonding allowed by the quinuclidinium cation moiety.

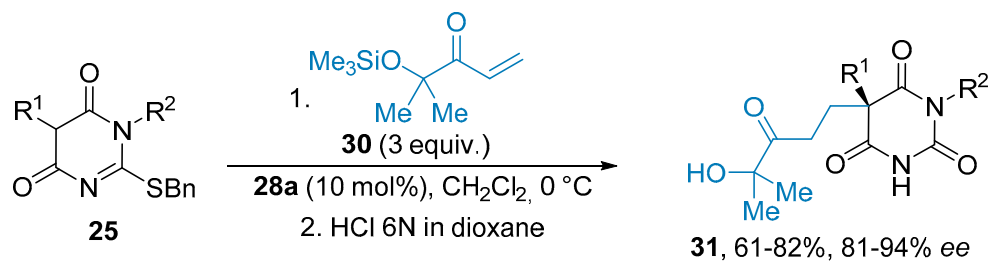
Notwithstanding this major achievement in this field of research, the Michael reaction could not be extrapolated to less reactive acrylate derivatives, and the moderately sterically hindered acrolein led to a modest *ee* of 48% [31]. Nevertheless, this group showed that enone **30** (Scheme 6), a precursor of acrylates or acrolein after oxidative cleavage sequences, was able to undergo the stereoselective conjugate addition of **25** under rather similar organocatalytic conditions to give barbituric acid products **31** with *ees* between 81% and 94%, after an acidic hydrolysis of the 2-benzylthioether moiety. As depicted in Scheme 6, this reaction tolerates various linear and branched alkyl substituents at C5 (R^1), and both alkyl and aryl pendants on nitrogen (R^2) of products **31a-f**. Curiously, as an exception, the precursors **29** with an *iso*-propyl (R^1) did not furnish any product **31g** in these conditions (Scheme 6).



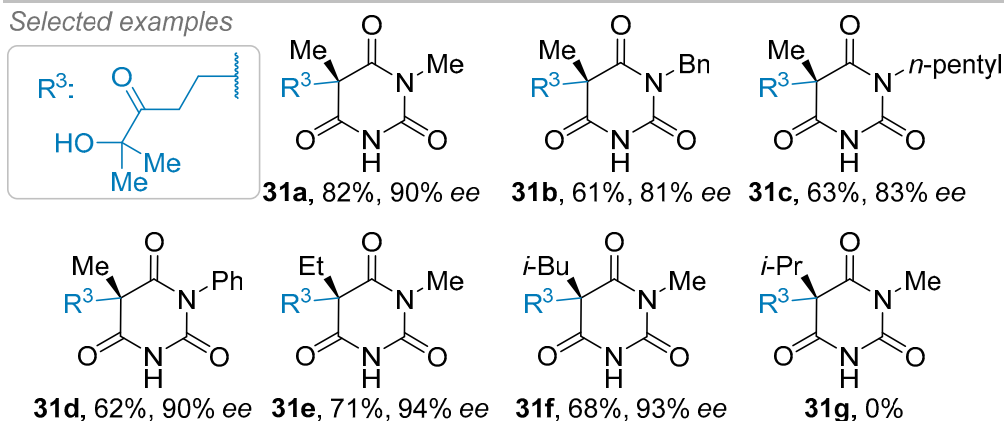
Selected examples

Proposed TS with protonated catalyst **28a** (R_3N^+-H)

Scheme 5. Organocatalytic conjugate addition reaction.

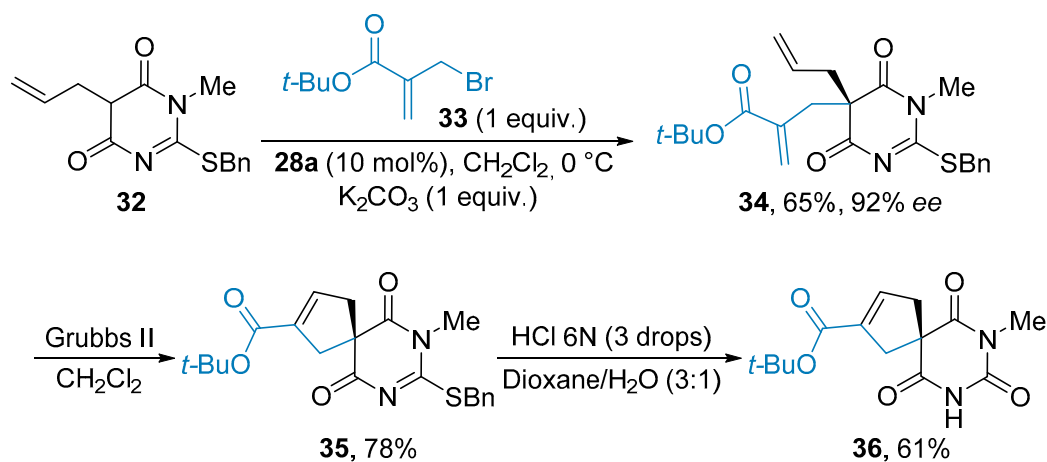


Selected examples



Scheme 6. Organocatalytic Michael reaction to versatile enones.

The scope of this transformation was further broadened during the development of an asymmetric allylation reaction thanks to the potent *Cinchona* derived organocatalyst **28a** (Scheme 7). The reaction proceeded smoothly between barbiturate **32** and the Morita-Baylis-Hillman allyl bromide **33** in the presence of potassium carbonate to neutralize the HBr production. As a representative example, the allylated product **34** was synthesized in 65% yield and 92% *ee*. The optimization demonstrated that the best results were obtained with electrophile **33** having a *tert*-butyl ester and K_2CO_3 proved to be the more suitable base. The authors illustrated the usefulness of the obtained barbiturate derivatives, such as **34**, possessing an all-carbon quaternary stereocenter by performing various transformations [31]. For instance, a metathesis reaction on product **34** furnished the cyclopentene **35** in 78% yield (Scheme 7). Eventually, the barbituric acid architecture **36** was formed upon an acidic hydrolysis.



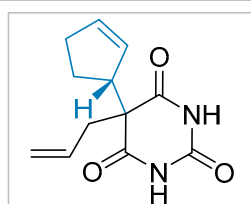
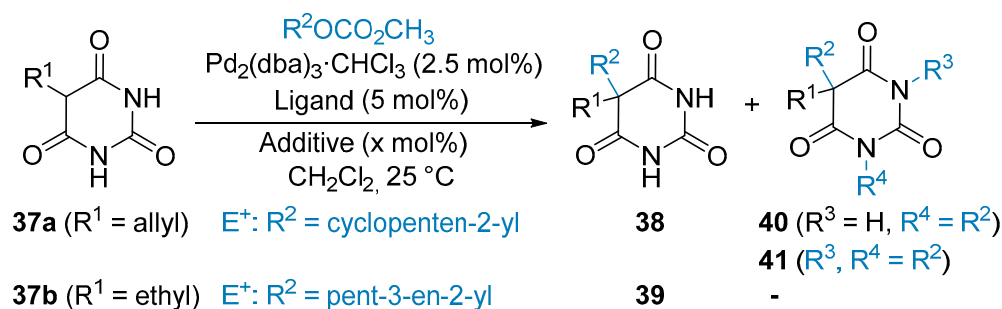
Scheme 7. Organocatalytic allylation reaction.

These achievements constitute a breakthrough in the field of catalytic enantioselective transformations of non-symmetrical barbituric acid derivatives along with the demonstration of useful transformations of the obtained enantioenriched products. In parallel, the development of catalytic asymmetric addition reactions of symmetrical barbituric acid derivatives to prochiral electrophiles has evolved (see Section below).

2.2. Addition Reactions with Stereocenters Created Outside the Ring

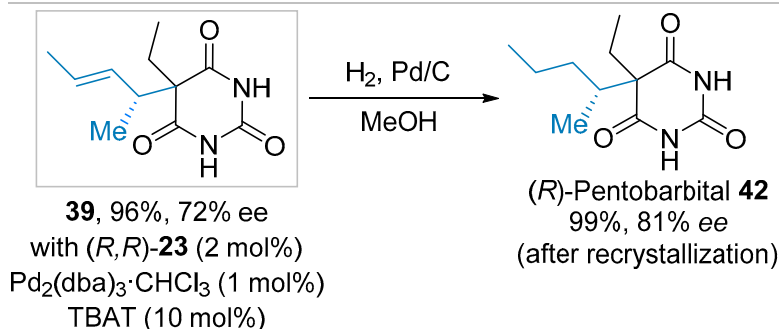
Inspired by previous reports by Brunner et al., dealing with the Pd-catalyzed asymmetric allylic alkylation reaction (AAA) of pro-chiral barbituric acid derivatives [20–23], Trost et al. reported the AAA reaction of symmetrical barbituric acid derivatives in the course of the synthesis of cyclopentobarbital **38** and pentobarbital **42** that are known to exhibit sedative and hypnotic properties, respectively (Scheme 8) [30]. Initial attempt to synthesize cyclopentobarbital **38** from allylic barbituric acid derivatives **37a** ($R^1 = \text{allyl}$) and allylic carbonate in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), ligand (*S,S*)-**23** (5 mol%, see Scheme 4 for structure), and Et_3N (1 equivalent) in CH_2Cl_2 at $25\text{ }^\circ\text{C}$ allowed the formation of the expected product **38** in high enantiomeric excess (84% *ee*). However, moderate isolated yield of 39% was obtained due to the presence of significant amounts of di- and tri-alkylated products **40** and **41**, respectively (**38/40/41** = 4.3:1:1). The presence of polyalkylated products was assigned to the higher solubility and hence reactivity of the first formed monoalkylated product **38** versus barbituric acid **37a**. To solve this issue, the reaction was performed without base but in the presence of an ammonium salt (*n*-Hex₄NBr) playing a dual role of (1) providing a more sterically congested nucleophile resulting in the diminution of polyalkylated products, and (2) increasing interactions between the nucleophile and the ligand, thus, improving the enantiomeric excesses. Indeed, by implementing such conditions and by switching to ligand (*S,S*)-**24** (see Scheme 4),

a selective formation of the cyclopentobarbital **38** was observed in a good isolated yield of 85% and excellent 91% *ee*. The (*R*)-absolute configuration of **38** was proposed using the predictive model previously developed by Trost et al. for such type of ligands and nucleophiles [32]. To synthesize pentobarbital **42** from barbituric acid derivative **37b** and allylic carbonate, the reaction conditions were slightly modified. Indeed, by using the same palladium(0) source ($\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, 1 mol%) in the presence of ligand (*R,R*)-**23** (2 mol%), the mono alkylated product **39** was obtained in almost quantitative yield (96%) and 78% *ee* in 3h providing that 10 mol% of TBAT (tetra *n*-butylammonium triphenyldifluorosilicate) was used as additive. After a hydrogenation step, the enantioenriched pentobarbital **38** was obtained in a quantitative yield and 81% *ee* after a simple recrystallization. (*R*)-**42** is known in the literature, the absolute configuration was eventually ascertained by comparison of the optical rotation.



(*R*)-Cyclopentobarbital **38**

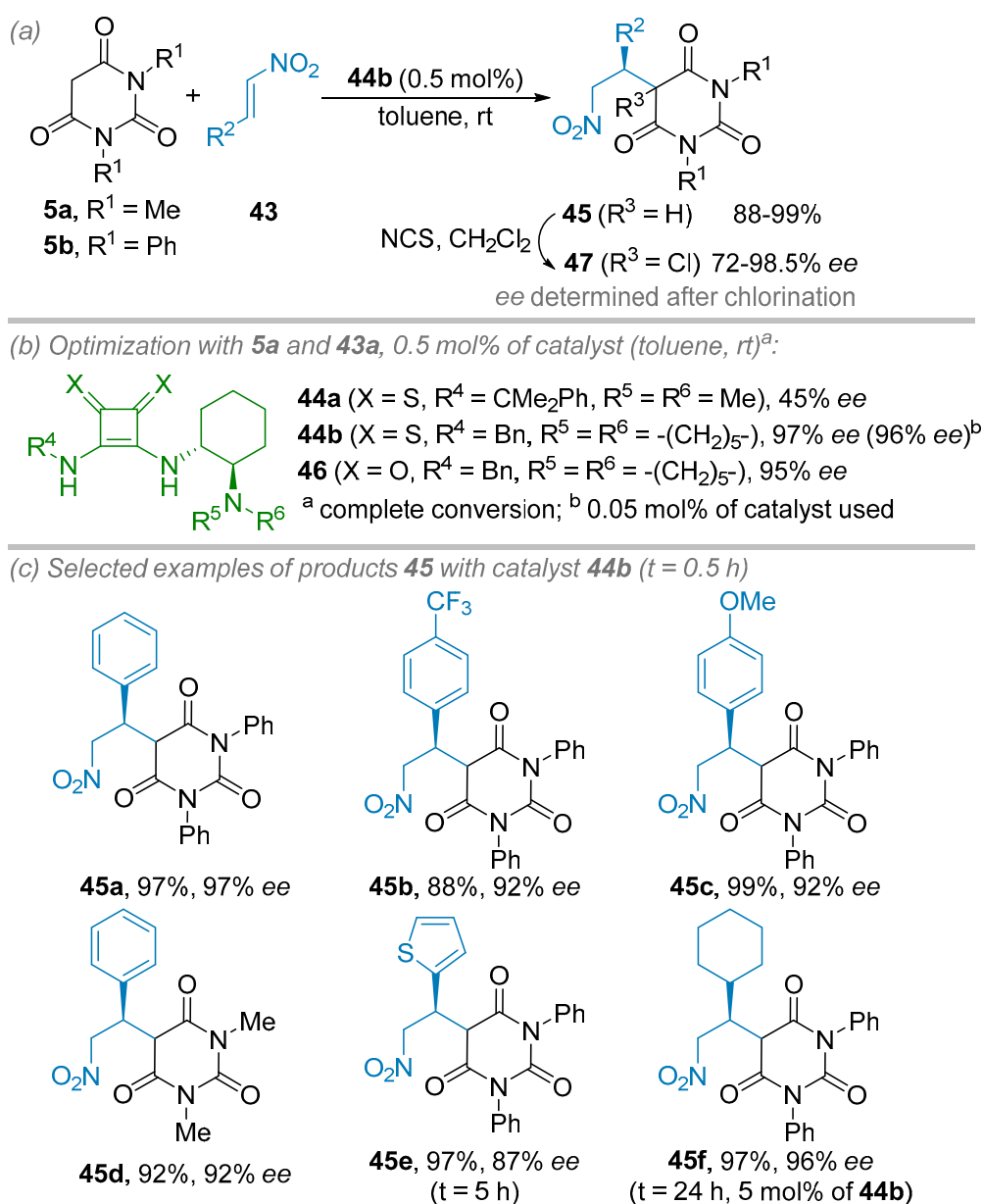
- with ligand (*S,S*)-**23** :
 Et_3N (100 mol%) 39%, 84% *ee* (**38/40/41** = 4.3:1:1)
 $n\text{-Hex}_4\text{NBr}$ (10 mol%) 80%, 94% *ee* (**38/40/41** = 3.6:1:0)
- with ligand (*S,S*)-**24** :
 $n\text{-Hex}_4\text{NBr}$ (10 mol%) 85%, 91% *ee* (**38/40/41** = 1:0:0)



Scheme 8. Pd-catalyzed allylation of mono-substituted 5-barbituric acid derivatives.

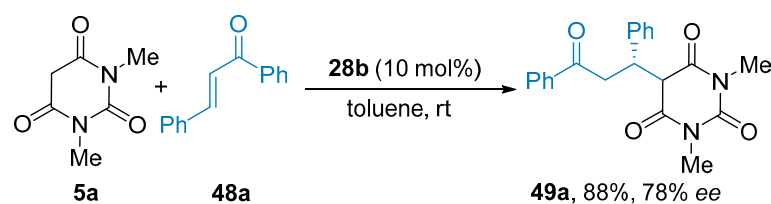
Later, Rawal et al. reported an enantioselective Michael addition of *N,N'*-disubstituted barbituric acid derivatives **5** to β -nitro olefins **43** using chiral thiosquaramides **44** as a bifunctional organocatalyst (Scheme 9) [33]. To circumvent the known solubility issue of the original squaramide catalysts, the authors have developed an unprecedented and more soluble chiral thiosquaramide version **44**. Furthermore, the higher acidity of the N–H bonds of the thiosquaramide moiety was estimated with a lower pK_a of 4 to 5 units in comparison to the squaramide counterpart allowing stronger hydrogen bonding activation events. Several chiral thiosquaramides **44**, having a chiral cyclohexanediamine scaffold, were synthesized in three steps from commercially available butyl squaramate ester in good yields ranging from 67 to 83%. These catalysts were evaluated in the nucleophilic 1,4-addition reaction of *N,N'*-diphenyl barbituric acid **5b** acid to β -nitro styrene **43a**. In each case, complete conversions into adduct **45** were obtained in toluene at room temperature in half an hour along with

ees ranging from 45 to 97% even at catalyst loading as low as 0.5 mol%. Interestingly, a comparison of catalyst **44b** to its squaramide version **46** revealed that both catalysts are very similar in terms of conversion (above 98%) and enantioselectivity (97% *ee* vs 95% *ee*, respectively). It is noteworthy that the reaction could be carried out using only 0.05 mol% of catalyst **44b** in toluene without erosion of both conversion and enantioselectivity (>98%, 96% *ee*). As mentioned by the authors, these reactions were conducted without any precautions under air atmosphere. Thus, by implementing optimized conditions (i.e., 0.5 mol% of catalyst **44b** in toluene at room temperature for 0.5 h to 24 h), several addition products **45** have been obtained in excellent isolated yields and *ees* regardless to the substitution of the barbituric precursors **5** or the β -nitrostyrenes **43** (Scheme 9c). Only for more sterically hindered precursors **5** or **43**, longer reaction times (24 h instead of 0.5 h) and higher catalyst loading (5 mol% instead of 0.5 mol%) were required to maintain the level of isolated yields and *ees*. For HPLC analysis issue (high retention times and broad peaks), the addition products **45** were chlorinated to afford **47** before analysis.



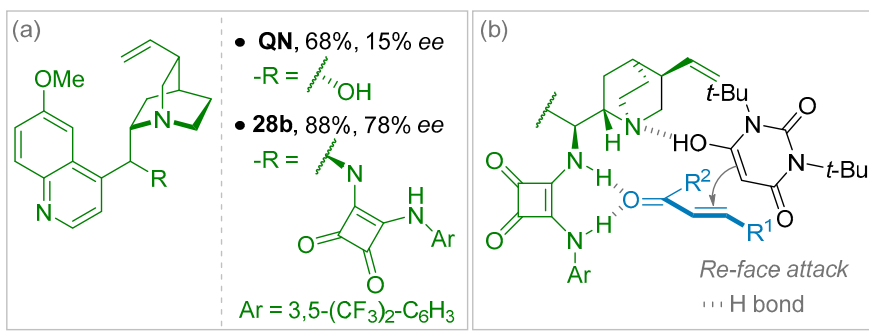
Scheme 9. Organocatalyzed enantioselective Michael addition of N,N' -disubstituted barbituric acid derivatives to β -nitro olefins. (a) General conditions. (b) Catalyst optimization. (c) Scope and limitations.

The same year, Wang and co-workers reported on the enantioselective organocatalytic Michael addition of *N,N'*-dialkylbarbituric acid derivatives **5** to β -substituted enones **48** making use of chiral bifunctional squaramide catalyst **28b** based upon a 9-*epi*-aminoquinine scaffold (Scheme 10) [34]. The screening of reaction parameters was performed using *N,N'*-dimethyl barbituric acid **5a** and chalcone **48a** as model substrates in toluene at 25 °C. Quinine (QN) provided the corresponding addition product **49a** in a good yield of 68%, but *ee* values did not exceed 15% (Scheme 10a). Drastic improvement of the induction was achieved by switching to bifunctional squaramide catalyst **28b** (10 mol%) allowing to obtain product **49a** in 78% *ee*. After an optimization endeavor, the best conditions were set as followed: *o*-xylene as solvent at room temperature in the presence of 10 mol% of catalyst **28b** using *N,N'*-di-*tert*-butylbarbituric acid **5c** as substrate. Then, a survey of the scope of the reaction was undertaken using various substituted enones **48** and barbituric acid **5c** ($R^1 = t\text{-Bu}$, Scheme 10c). A large panel of Michael adducts **49** flanked by mono or di-substituted (electron-withdrawing or electron-donating groups) aryl, heteroaryl could be tolerated as long as R^2 and R^3 substituents are concerned in almost perfect stereoinduction (25 examples, 95–99% *ee*) with, nonetheless, variable isolated yields (44–99%). Aliphatic R^2 group (*n*-Pr) in association with phenyl R^3 group resulted in a slight drop of the *ee* (92%) whereas enones with $R^3 = \text{Me}$, and $R^2 = \text{Ph}$ or *n*-Pr remained unreactive in the reaction conditions. The absolute configuration of compounds **49i** was attributed as (*S*) thanks to single-crystal X-ray analysis. To account for the high level of induction observed, the authors proposed a transition state where the squaramide part of the catalyst **28b** binds to the carbonyl of the enone while the barbituric acid moiety (under its enol form) is well-positioned by the quinuclidine Brønsted base part (Scheme 10b). Thus, an addition to the *Re*-face of the enone is favored.

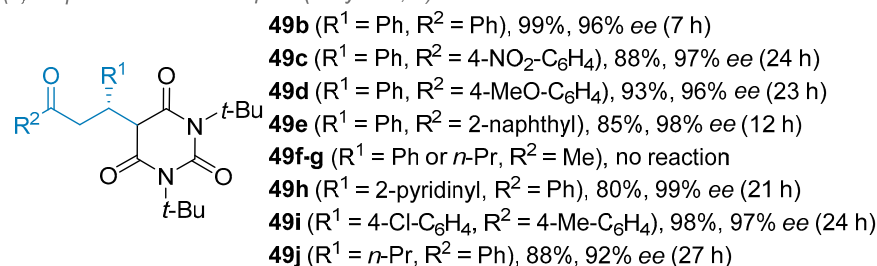


(a) Importance of the bifunctional nature of catalyst **28b** versus QN.

(b) Postulated transition state.



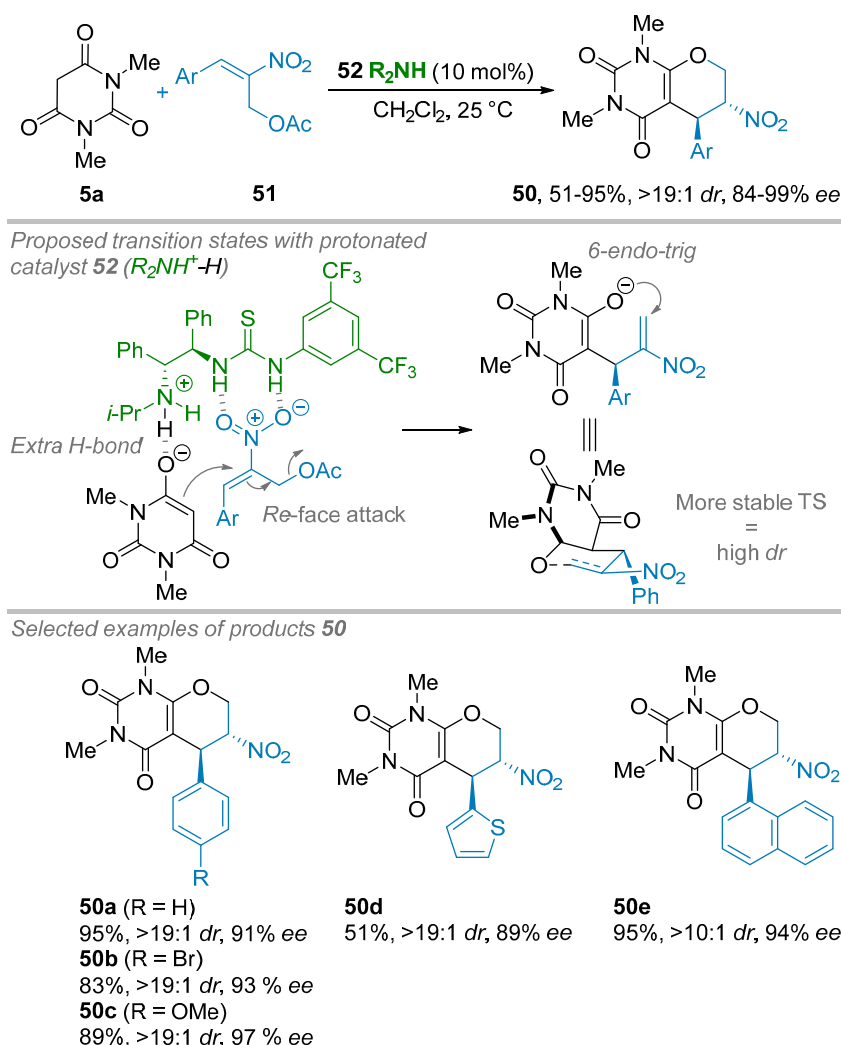
(c) Representative examples (*o*-xylene, rt)



Scheme 10. Organocatalyzed enantioselective Michael addition of *N,N'*-disubstituted barbituric acid derivatives to β -substituted enones. (a,b) Importance of the bifunctional nature of the catalyst in the transition state. (c) Scope and limitations.

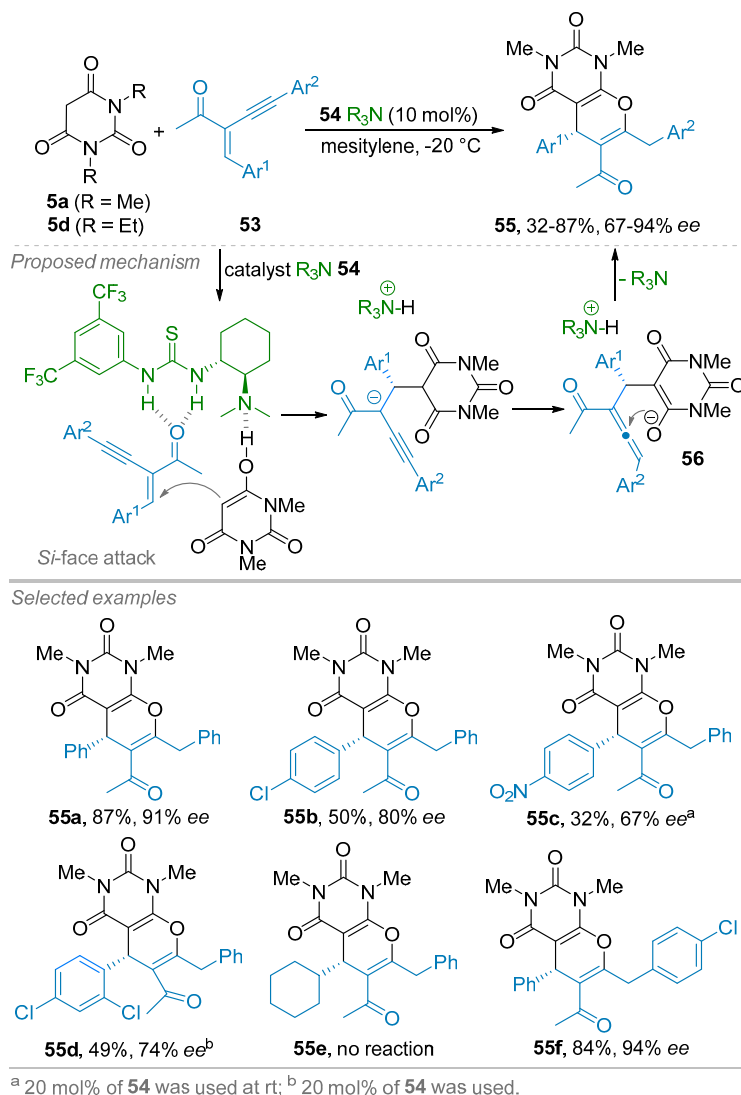
2.3. Annulation Reactions

Barbituric acid derivatives may also be involved in annulation reactions. This approach was first tackled by Chen and co-workers during the synthesis of tetrahydropyrano bicycles **50** (Scheme 11) [35]. Starting from *N,N'*-dimethyl barbituric acid **5a** and Morita-Baylis-Hillman (MBH) acetate of nitroalkene **51**, a domino Michael-oxa-Michael addition reaction was achieved upon organocatalysis. During the reaction investigation, it was found that the original tertiary amine-thiourea bifunctional organocatalyst **52** was superior to the other organocatalysts. Thus, by applying optimized conditions (i.e., 10 mol% of **52**, CH₂Cl₂, 25 °C), the investigation of the scope of the reaction was undertaken. Excellent results were obtained regardless of the substitution pattern on the aromatic ring to give 76–99% isolated yields, *dr* <19:1 and 86–99% *ees*. Polyaromatic or heretoaromatic ring pendants of the MBH adduct **51** were tolerated but at the expense of a slight drop of the diastereoisomeric ratio (*dr* >10:1) or isolated yield (51%), respectively. To account for the high diastereo- and enantioselectivity, the authors proposed a transition state where the amine part of the catalyst would deprotonate the barbituric acid **5a** while its thiourea part binds to the nitro group of the MBH derivative **51**. This results in a well-defined TS allowing an attack of the enolate to the *Re*-face of the nitroalkene **51**. Then, a 6-*endo-trig* annulation took place through a 6-membered ring transition state where the nitro group is in pseudo-equatorial position to minimize steric interactions with an aromatic group, thus, leading to product **50** as *trans*-isomers in high diastereo- and enantioselectivity.



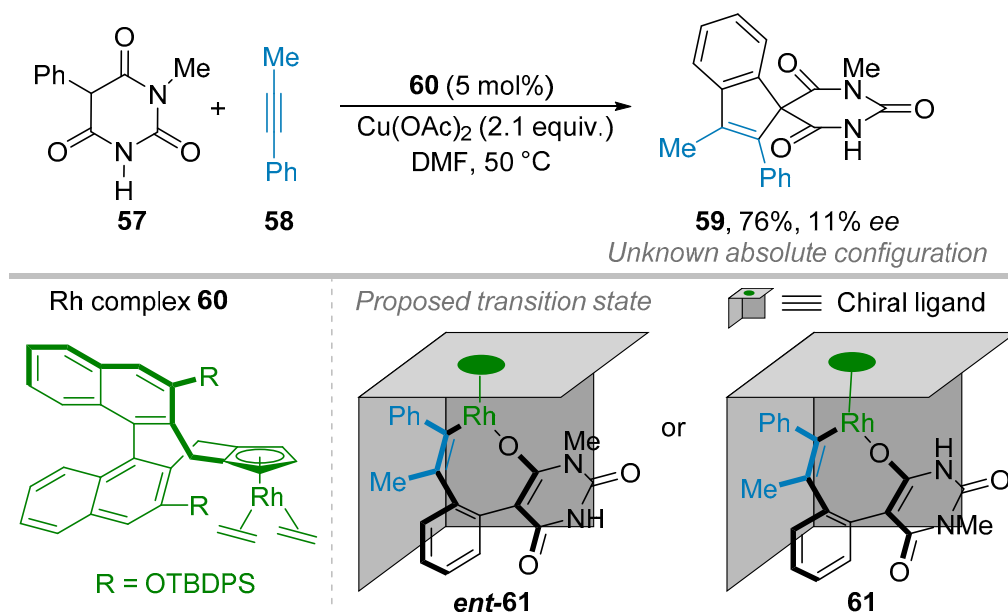
Scheme 11. Organocatalyzed enantioselective Michael-oxa-Michael addition sequence of *N,N'*-dimethyl barbituric acid to Morita-Baylis-Hillman adduct.

One year later, the same group reported on a (3+3) annulation reaction consisted of a similar Michael-oxa-Michael sequence starting from *N,N'*-dimethyl barbituric acid **5a** but in the presence of 2-(1-alkynyl)-2-alken-1-ones **53** as electrophilic partners (Scheme 12) [36]. Thus, by implementing the Takemoto's organocatalyst, possessing an amine-thiourea bifunctional scaffold **54** (10 mol%) in mesitylene at -20°C , almost 20 cyclic products **55** were obtained in fair to good isolated yields (32–87%) and moderate to high *ees* of 67–94%. The substitution of Ar^1 by either electro-withdrawing or -donating groups proved to have a low impact on the *ees* being generally above 80% except for nitro-substituted compounds obtained in 67% *ee* values. This was attributed to possible interactions with the catalyst that hamper the optimal activation process. Contrariwise, substitution of Ar^2 was found to have a positive effect on the asymmetric induction leading to *ees* ranging from 84 to 94%. Generally speaking, the steric effect seems to be detrimental to obtain high yields and enantioselectivities as shown by results obtained with 2,4-dichloro substituent on Ar^1 whereas no reaction was observed when cyclohexyl was used instead of Ar^1 group or in the presence of *N,N'*-diethyl barbituric acid **5d**. From a mechanistic point of view, the authors proposed the activation of the barbituric acid **5a**, under its enol form, by the tertiary amine part of the catalyst meanwhile the thiourea moiety chelates the carbonyl group of the enynone **53** to favor the attack of nucleophile to the *Si*-face of the C–C double bond of **53**. Then, an oxa-Michael addition to the transient allene **56** takes place, thus, affording the (3+3) cycloadduct **55**.



Scheme 12. Organocatalyzed enantioselective Michael-oxaMichael addition sequence of *N,N'*-dimethyl barbituric acid to enynones.

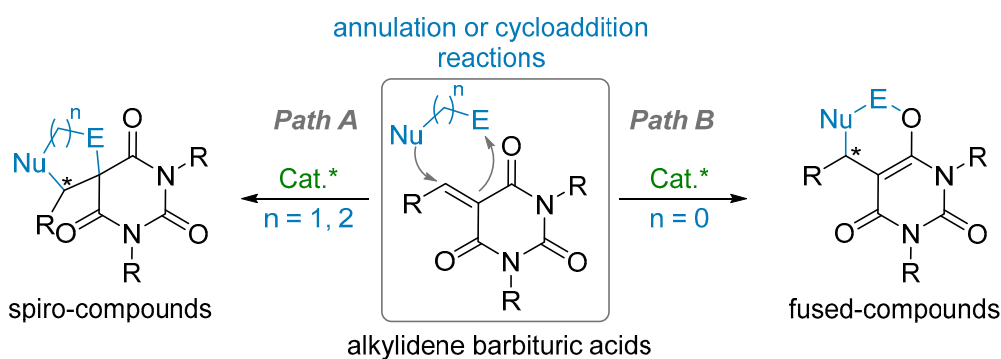
An example of annulation reaction consisted of two consecutive C–C bonds was reported in 2015 by Lam and co-workers during the synthesis of a series of spiro-indenes of type **59** with good to excellent *ees*. However, in this study, a single example was reported which involved the 1-methyl-5-phenylbarbituric acid **57** and alkynes **58** in the presence of chiral rhodium complexes **60** as catalyst and Cu(OAc)₂ as oxidant giving rise to the formation of **59** in good isolated yield (76%) but with only 11% *ee* (Scheme 13) [37]. This low enantioselection was attributed to the fact that both carbonyl functional groups (which act as directing groups for the formation of the rhodacycle **61** in the catalytic cycle) adjacent to the phenyl substituent are electronically and sterically similar. This results in a lack of stereodifferentiation between the two possible transition states (rhodacycles **61** and *ent*-**61**) obtained after the coordination and migratory insertion of the alkyne partner.



Scheme 13. Rhodium(III)-catalyzed enantioselective CH-functionalization-spiroannulation sequence.

3. Enantioselective Transformations from Alkylidene Barbituric Acid

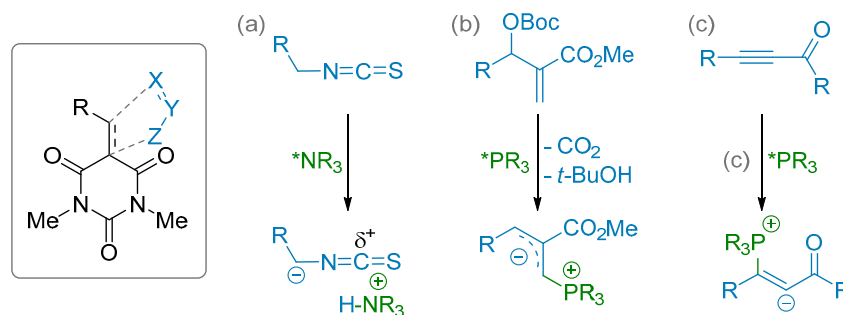
As discussed in the introduction (Cf. § 1.2), alkylidene barbituric acids are highly reactive electron-poor alkene derivatives which have been involved into either cycloaddition or annulation reaction (Scheme 14). On the one hand, under asymmetric catalytic conditions, (3+2) and (4+2) cycloaddition or annulation reactions took place on the C–C double bond and have allowed the construction of spiro-compounds (path A). On the other hand, suitably designed dienophiles led to enantioselective Diels–Alder reactions through the concomitant C–C and C–O bond formation to provide chiral fused-compounds (path B).



Scheme 14. Annulation reaction onto alkylidene barbituric acids.

3.1. (3+2) Cycloaddition Reactions

Alkylidene barbiturates have been involved in (3+2) cycloaddition as found by different research groups. First of all, isothiocyanates were used with amine catalysis (Scheme 15a). Then, Morita-Baylis-Hillman (MBH) adduct or ynone starting materials were reported as dipole precursors along with phosphine catalysis (Scheme 15b,c).

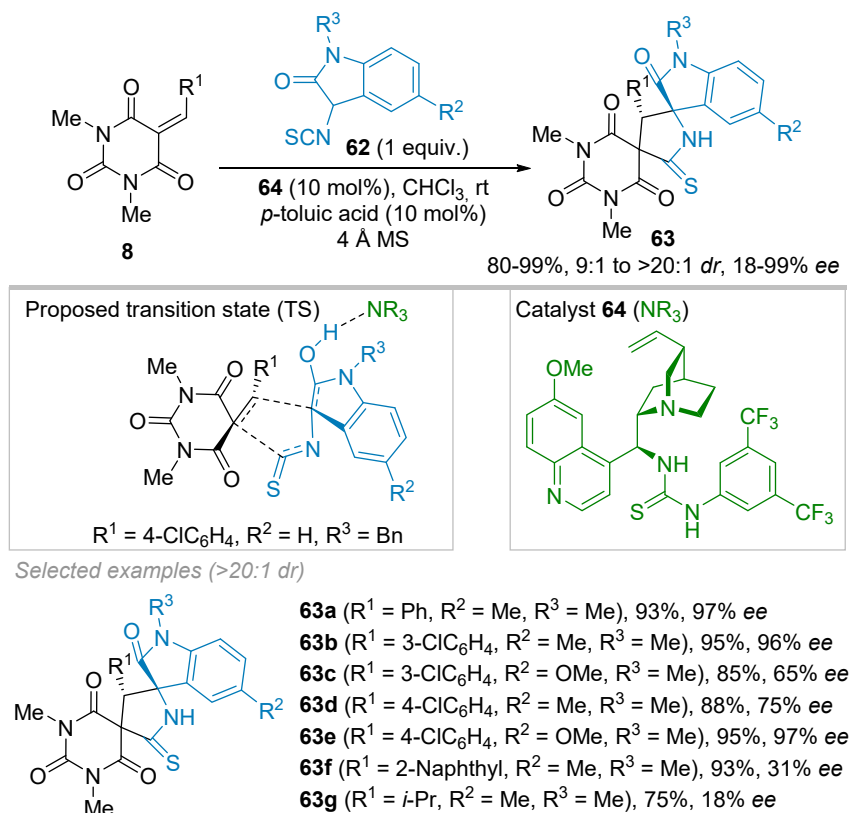


Scheme 15. Reagents in (3+2) cycloaddition with alkylidene barbiturate.

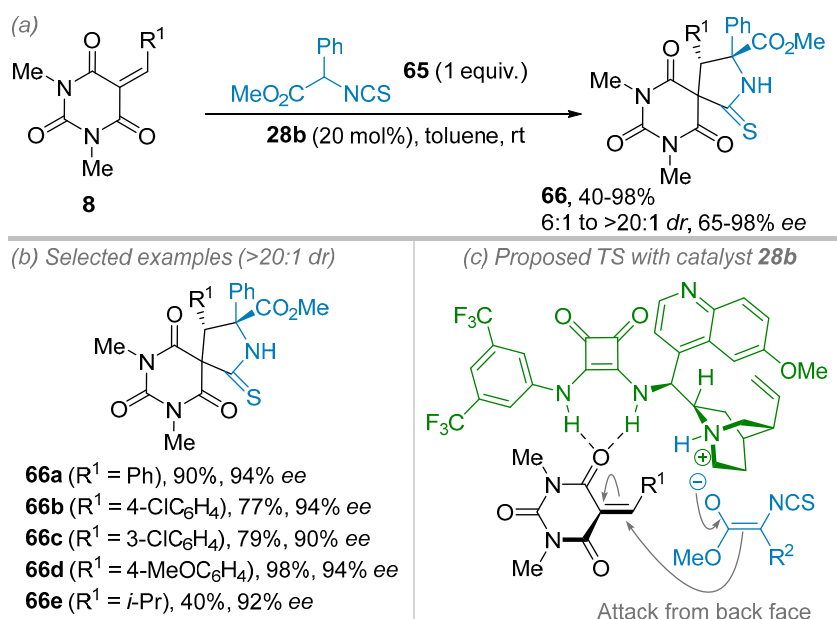
For more than ten years, isothiocyanates have been engaged in catalytic reactions as isothiocyanato amides, esters or phosphonates. In 2015, Liu's group published on a racemic (3+2) cycloaddition between alkylidene barbiturates **8** and 3-isothiocyanato oxindoles **62** catalyzed by triethylamine (Scheme 16) [38]. In 2016, the same authors reported on an enantioselective version catalyzed by a *Cinchona*-based thiourea **64** leading to spirobarbiturates **63** in modest to excellent *ees* and 20:1 *dr* in most cases (Scheme 16) [39]. The best reaction conditions involved the use of 9-*epi*-quinine-thiourea **64** (10 mol%), *p*-toluic acid (10 mol%) and 4 Å molecular sieves in chloroform. According to the proposed mechanism (see TS in Scheme 16), *p*-toluic acid drives the equilibrium of **62** towards its enol form, which forms a hydrogen bond with the tertiary amine of catalyst **64**. The bifunctional nature of organocatalyst **64** allows extra-hydrogen bonding interactions between both the thiourea and barbituric acid moieties, thus, providing a well-organized transition state that favors the selective addition of the nucleophile **62** to one of the two prosterogenic faces of the alkylidene derivative **8**. The scope with regard to alkylidene barbiturates **8** was studied and showed that aryl substituents (R^1) were well-tolerated irrespective to the substitution pattern on the rings ($R^2 = R^3 = \text{Me}$: 80–99% yield, 13:1 to >20:1 *dr*, 75–99% *ee*). Nevertheless, it was demonstrated that the position of substituents significantly influenced the selectivity as shown with 3-chlorophenyl derivative **63b** obtained in 96% *ee* whereas 4-chlorophenyl derivative **63d** was isolated in only 75% *ee*. Moreover, cycloaddition products **63f–g** with 2-naphthyl and *iso*-propyl pendants were synthesized in high 93% and 75% yields, respectively, albeit with a dramatic drop in *ees* (31% and 18% *ees*, respectively), probably due to steric and electronic issues. The scope of 3-isothiocyanato oxindoles **62** has also been surveyed showing that variations of R^2 and R^3 groups were well-tolerated.

In 2018, the Albrecht group tackled the first use of α -substituted α -amino acid-based isothiocyanates **65** in the annulation reaction with alkylidene barbituric acids **8** leading to the spiranic 2-pyrrolidinethiones **66** (Scheme 17) [40]. The original idea was to combine barbituric acid and quaternary α -amino acid, which are both known as bio-relevant architectures. After the screening of solvents and organocatalysts, the best reaction conditions made use of 9-*epi*-quinine-squaramide **28b** (20 mol%) in toluene, leading to **66a** in 95% conversion and 94% *ee* (Scheme 17b). With their optimized conditions in hand, the authors first studied the scope of the reaction from the alkylidene barbiturates point of view. First of all, the substitution pattern of the aromatic part of the benzylidene barbituric acid **8** ($R^1 = \text{Ar}$) had almost no influence on the reaction outcome, and excellent *ees* were generally obtained independently of the nature or the position of the substituents on the aromatic ring. Interestingly, the alkylidene barbituric acids **8** ($R^1 = i\text{-Pr}$) also yielded the corresponding product **66e** with excellent 92% *ee* but at the expense of a lower isolated yield of 40%. To account for the high

level of stereinduction observed, the authors proposed a transition state where the catalyst binds to the alkylidene barbituric acid through hydrogen bonding thanks to the thiourea moiety while the tertiary amine part deprotonates the isothiocyanate **65** (Scheme 17c).

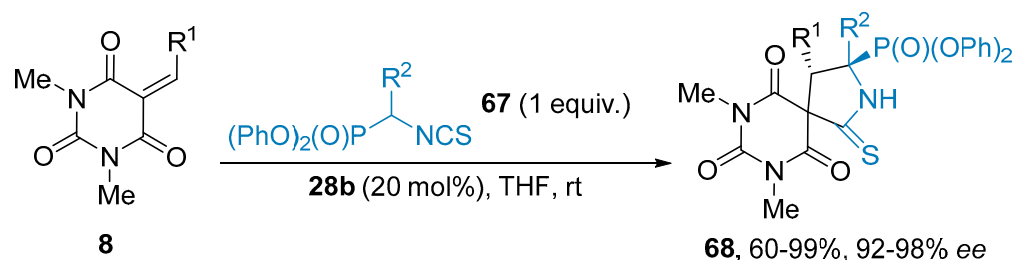


Scheme 16. Organocatalytic synthesis of dispirobarbiturates from 3-isothiocyanato oxindoles and alkylidenes barbituric acid.

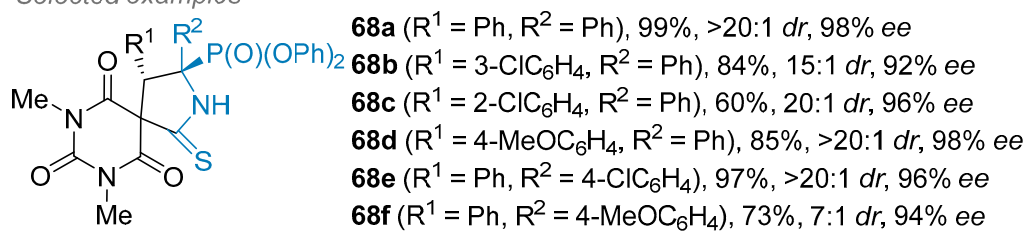


Scheme 17. Enantioselective synthesis of spiranic 2-pyrrolidinethiones from amino acid isothiocyanate derivatives and alkylidene barbituric acids. (a) General conditions. (b) Scope and limitations. (c) Proposed transition state.

Eventually, the Albrecht group envisioned the use of isothiocyanato α -aminophosphonates **67** for the synthesis of spirobarbiturates **68** (Scheme 18) [40]. By switching the solvent from toluene to THF, the diphenyl derivative **68a** was obtained in 99% yield and 98% *ee*. Albrecht and co-workers then modified the R^1 substituent. Various aryl substituted moieties were tolerated without showing a significant impact on the enantiomeric excesses of the reaction, as exemplified with 3-ClC₆H₄ and 2-ClC₆H₄ derivatives **68b–68c** together with 4-MeOC₆H₄ derivative **68d** providing almost the same *ees* (92%, 96% and 98%, respectively). Finally, the same trend was observed for the R^2 substituents on isothiocyanate nucleophile **67** as underlined by the excellent level of enantioselection obtained either for the 4-ClC₆H₄ derivative **68e** or the 4-MeOC₆H₄ derivative **68f** (96% *ee* and 94% *ee*, respectively).

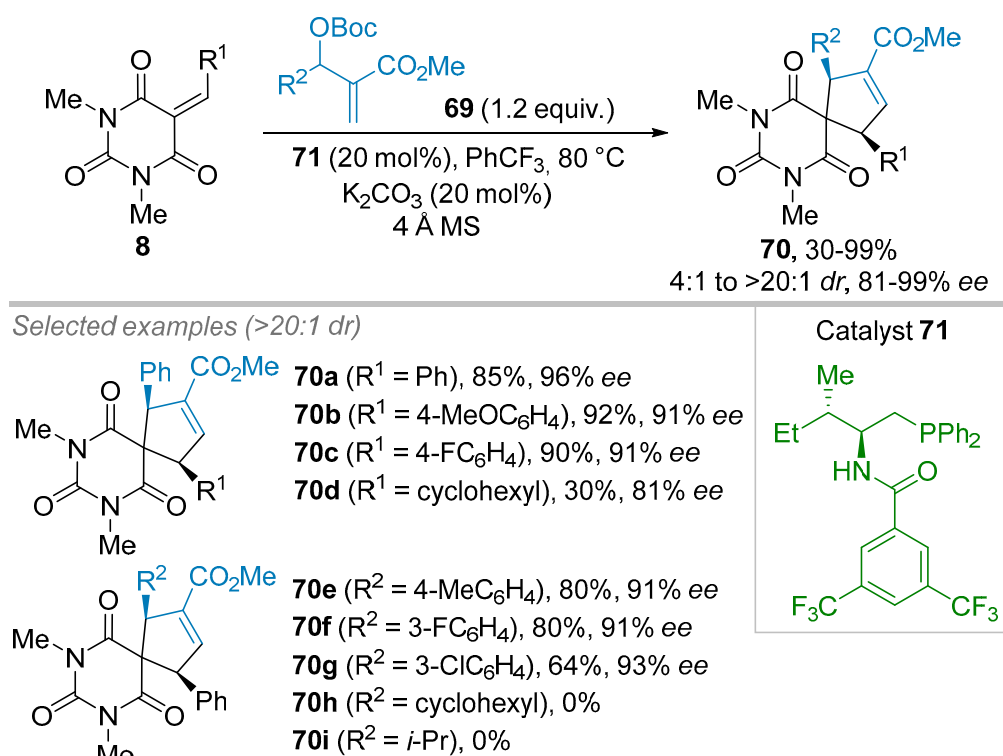


Selected examples



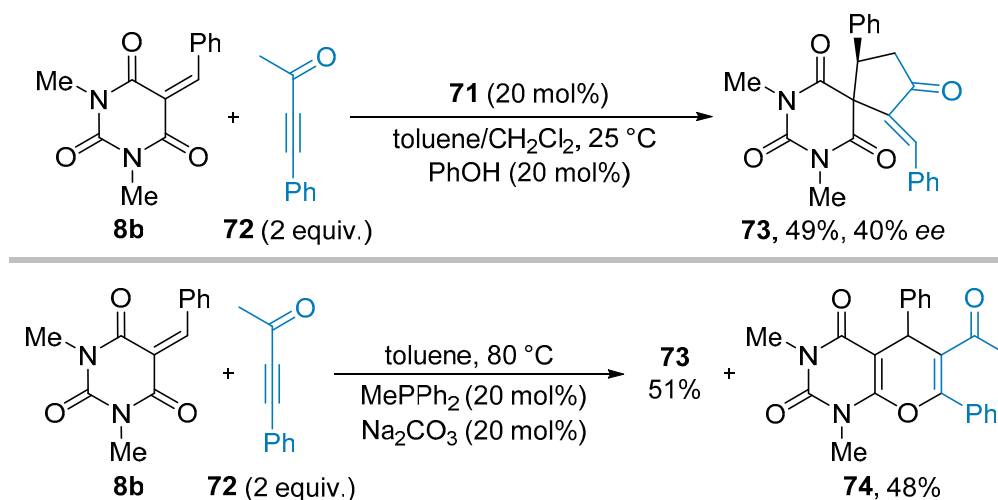
Scheme 18. Enantioselective spirobarbiturates synthesis from phosphonate isothiocyanate derivatives.

MBH adducts have also been used in (3+2) cycloaddition reaction with alkylidenes barbituric acids **8** as dipolarophile partners. In this reaction, the phosphine catalyst reacts with the MBH adducts **69** to furnish a transient 1,3-dipole giving rise to a (3+2) cycloaddition with the alkylidene barbiturate **8** (Schemes 15b and 19) [41]. In this vein, Guo et al. described in 2016 the first enantioselective phosphine-catalyzed (3+2) annulation of alkylidene barbiturates **8** with MBH adducts **69** leading to spirobarbiturates **70** in excellent diastereoselectivities (>20:1 *dr*) and high to excellent enantiomeric excesses of 81 to 99% *ees* (Scheme 19) [41]. Optimization of the catalyst showed that bifunctional phosphine catalyst **71** afforded the best balance between yield and *ee* of product **70a** for instance (76% yield and 93% *ee* in PhCF₃). It was also noted that the addition of molecular sieves along with 20 mol% of K₂CO₃ increased the yield of **70a** from 76 to 85% while *ee* reached 96%. It is believed that K₂CO₃ facilitates the formation of the reactive phosphonium zwitterion (See Scheme 15b). Thereafter, the scope of benzylidene barbituric acids **8** was studied, and it was found that aromatic substituents were, in general, well tolerated and gave rise to the formation of products **70** with 60–98% yields and 91–99% *ee*. However, the use of a cyclohexyl moiety ($R^1 = \text{cyclohexyl}$) on the corresponding alkylidene barbituric acid **70d** instead of an aromatic ring decreased the yield of product **70d** significantly to 30%, while still affording 81% *ee*. Guo et al. also showed that the MBH precursors **69** including aromatic substituents ($R^2 = \text{Ar}$) furnished a wide range of cycloaddition products **70** in excellent yields (64–99%) and enantioselectivities (85–93% *ee*), independently of the electronic properties of the substituent on the phenyl ring. However, one should note that the yield decreases when R^2 is 3-ClC₆H₄ (**70g**, 64%) and that the presence of an aliphatic group (either a cyclohexyl for **70h** or an *iso*-propyl for **70i**) on the MBH adduct completely inhibits the reaction.



Scheme 19. (3+2) Cycloaddition between Morita-Baylis-Hillman adducts and alkylidene barbiturates.

In 2017, Guo and colleagues described a (3+2) cycloaddition with alkylidene barbituric acids involving an ynone as dipole precursor (see Scheme 15c) which upon reaction with the phosphine catalyst provides the reactive 1,3-dipole [42]. In their publication, the authors only provided one example of an asymmetric (3+2) cycloaddition between ynone **72** and benzyldiene barbituric acid **8b** using the chiral phosphine catalyst **71** (Scheme 20). The expected product **73** was, thus, obtained in 49% yield and 40% ee [42]. Remarkably, during the screening of the reaction parameters in racemic fashion, the authors found that using Na₂CO₃ as a Brønsted base additive (20 mol%) allowed the formation of the expected (3+2) cycloaddition adduct **73** along with equal amount of the (4+2) cycloaddition product **74**.

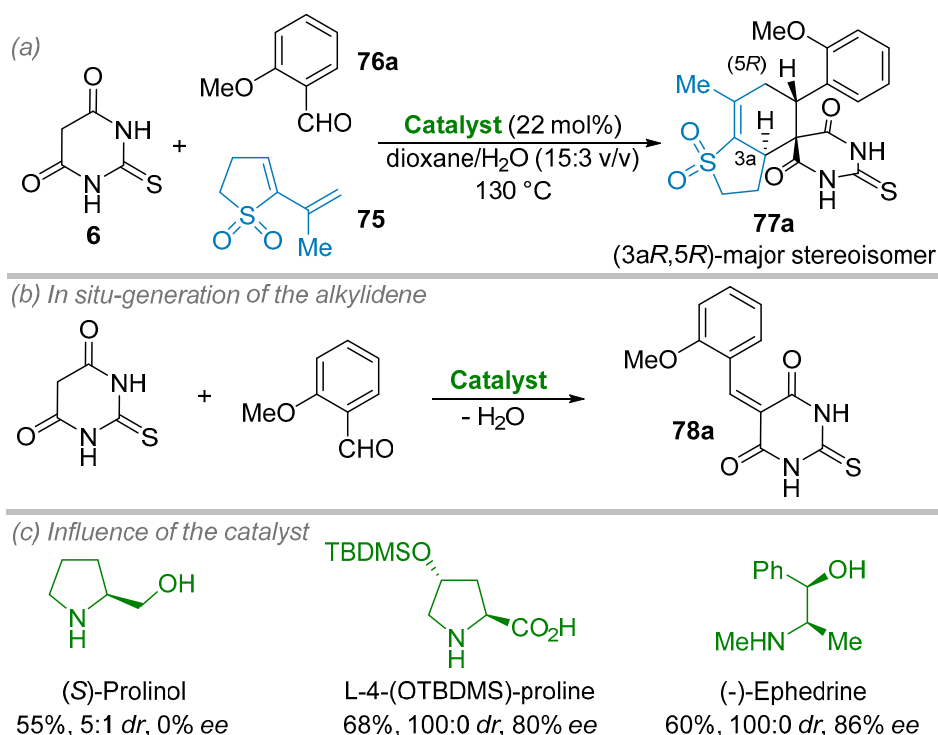


Scheme 20. Phosphine-catalyzed (3+2) cycloaddition between ynones and alkylidene barbituric acids.

Guo's team is not the only research group to have studied (4+2) cycloadditions involving alkylidene barbituric acids. Others have published their work on asymmetric (4+2) cycloadditions, the details of which will follow in the next part of this Section.

3.2. (4+2) Cycloaddition Reactions

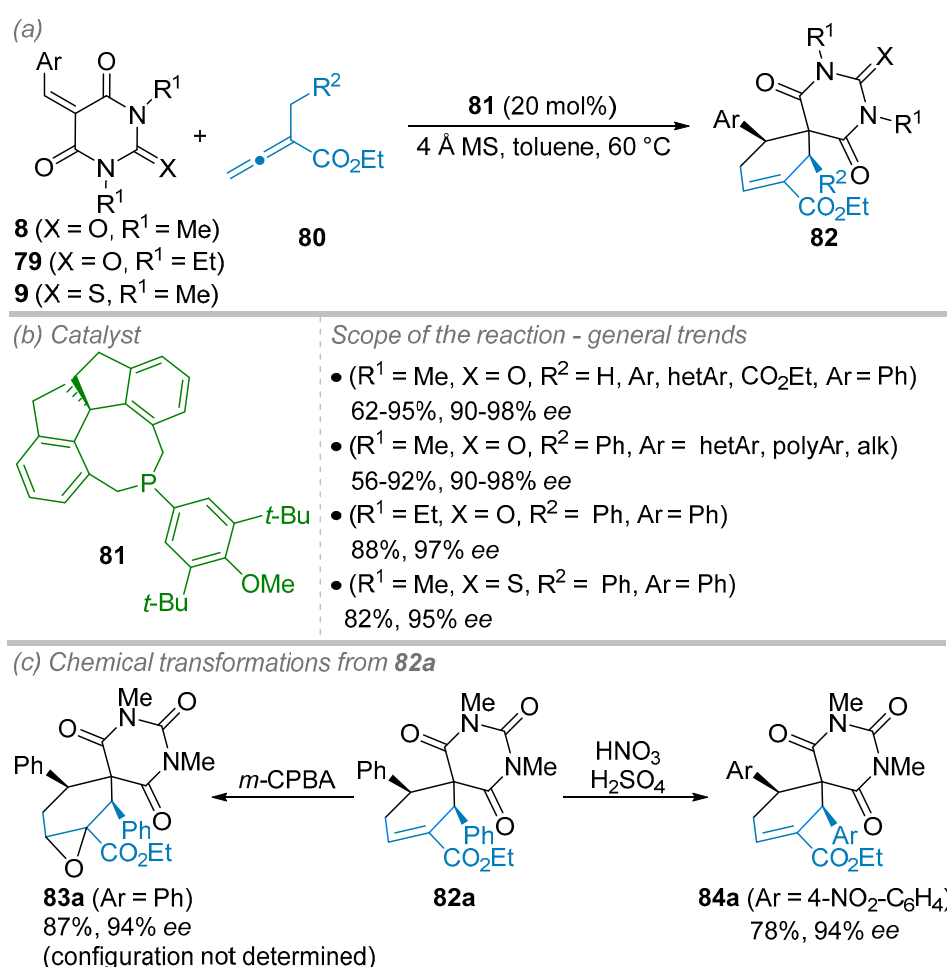
Enantioselective Diels–Alder reaction involving alkylidene dienophile intermediates, such as **78a**, derived from barbituric acid **6**, was first tackled by Tolstikov and colleagues in 2009 (Scheme 21a,b) [43]. Indeed, several chiral Diels–Alder adducts **77** were obtained using cyclic sulfone **75** as diene in the presence of chiral amino-acid or amino-alcohol organocatalysts. While several enantioselective examples (based upon optical rotation measurement) were reported in the publication, the enantiomeric excesses were only provided for the product **77a**. Accordingly, several chiral catalysts were evaluated for the reaction between cyclic sulfone **75** and benzylidene **78a**, generated in situ from thiobarbituric acid **6** and 2-methoxybenzaldehyde **76a** in dioxane–water (15:3 v/v) at 130 °C to afford the spiranic adduct **77a** (Scheme 21c). Whereas (*S*)-prolinol provided the cycloaddition product **77a** under a racemic form as a 5:1 mixture of diastereoisomer, the use of L-4-(*tert*-butyldimethylsiloxy)-proline (L-4-(OTBDMS)-proline) or (–)-ephedrine resulted in a spectacular improvement of the enantiomeric excesses (up to 80% *ee* and 86% *ee*, respectively) while affording acceptable isolated yields (68 and 60%, respectively) in **77a**, which was obtained as a single stereoisomer. The absolute configuration of the cycloadduct **77a** was ascertained by X-ray diffraction analysis.



Scheme 21. Enantioselective Diels–Alder reaction involving in situ-generated alkylidene barbituric acid as dienophile. (a) General conditions. (b) Formation of the alkylidene barbituric acid intermediate. (c) Catalysts evaluation.

In 2016, Guo, Zhou and co-workers have reported on a (4+2) annulation reaction between alkylidene barbituric acid **8**, **9** or **79** and allenoates **80** in the presence of a chiral phosphine **81** as a nucleophilic organocatalyst. Chiral spirocycloalkenes **82** were, thus, provided even though architectures are difficult to obtain through regular Diels–Alder reaction (Scheme 22) [44]. Among all the conditions and chiral phosphines tested, the ones displaying a spiranic architecture and more particularly **81**, previously reported by the same authors, gave the best level of diastereo-

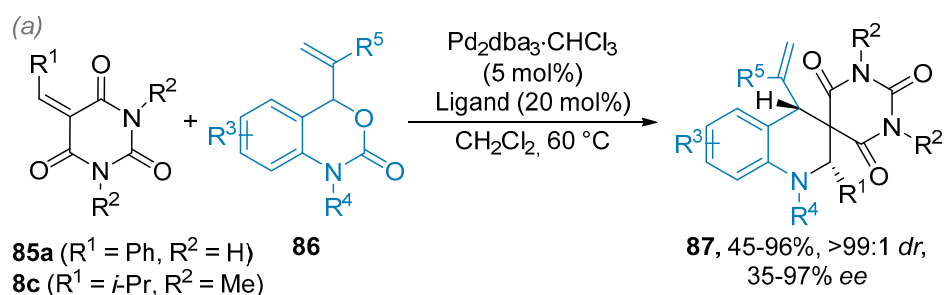
enantioselectivity and yields providing that 4 Å molecular sieves (MS) were used as an additive (Scheme 22b). The organocatalyst **81** (20 mol%) was elected to study the scope and limitations of this methodology (4 Å MS, toluene, 60 °C). Both substitutions on allenolate **80** and alkylidene **8** partners were evaluated. Generally speaking, excellent *ees* (above 90%) along with high isolated yields were obtained for a wide range of functional groups covering simple hydrogen atom to diversely substituted aromatic or heteroaromatic rings. Even other alkylidene barbituric acid derivatives **79** and **9** possessing an *N,N'*-diethyl barbituric acid ($R^2 = \text{Et}$, $X = \text{O}$) or *N,N'*-dimethyl thiobarbituric acid ($R^2 = \text{Me}$, $X = \text{S}$) moiety, respectively, were successfully engaged providing also excellent enantiomeric excesses (97% *ee* and 95% *ee*, respectively). To underline the synthetic utility of the spirocyclohexene products **82**, the authors performed two chemical transformations starting from enantioenriched **82a** ($R^1 = \text{Ph}$, $R^2 = \text{Me}$, $R^3 = \text{Ph}$, $X = \text{O}$, 94% *ee*, Scheme 22c). These encompassed an epoxidation of the double bond of the cyclohexene part to give **83a** (87%, 94% *ee*) and a nitration reaction of the aromatic ring to furnish **84a** (78%, 94% *ee*) without racemization event.



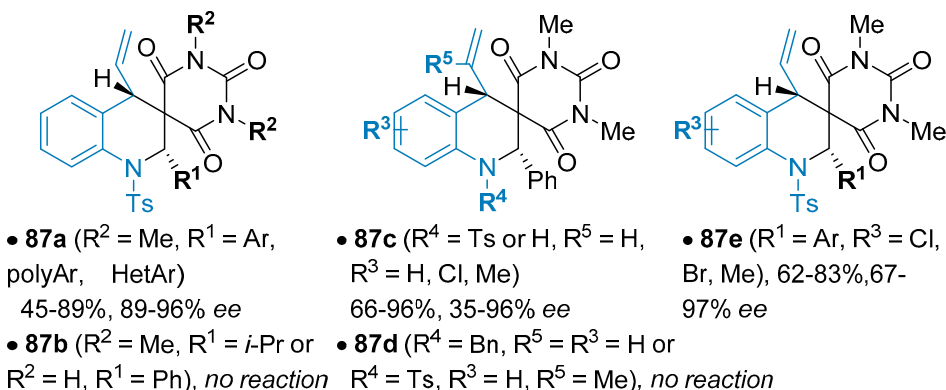
Scheme 22. Enantioselective (4+2) Cycloaddition Reaction. (a) General conditions. (b) Scope and limitations. (c) Synthetic transformations.

Another application of alkylidene barbituric acids in (4+2) cycloaddition reaction was reported recently by Zhao and colleagues during the synthesis of barbiturate-fused spiro-tetrahydroquinolines **87** from vinyl benzoxazinanes **86** in the presence of chiral palladium(0)-ligand complex (Scheme 23) [45]. Thus, a chiral ligand (20 mol%) derived from BINOL in association with $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (5 mol%) as Pd(0) source in a 4:1 ratio in CH_2Cl_2 at room temperature were selected as the best conditions to obtain optimal levels of *ee* and yields (Scheme 23b,c). By applying the above-mentioned conditions, the scope and limitations of the reaction were investigated. By using simple *N*-Ts lactam **86a** ($R^3 = R^5 = \text{H}$),

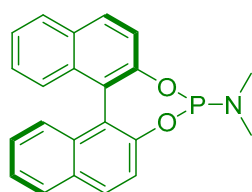
high level of *ee* ranging from 89% to 96% was observed for a wide range of mono- or poly-substituted phenyl rings and hetero- or poly-aromatic rings along with variable isolated yields (45–89%). Of note, no reaction was detected with benzylidene barbituric acid having NH moiety (**85a**, R¹ = Ph, R² = H) or alkylidene barbituric acid having an NR moiety (**8c**, R¹ = *i*-Pr, R² = Me). The substitution of the vinyl benzoxazinanone partner **86** was also possible providing that R⁵ substituent remains a hydrogen atom and R⁴ substituent a tosyl group. In this case, however, somewhat lower *ees* were obtained (35–96% *ee*). Finally, the best results in terms of *ee* were obtained by introducing substituents on both aromatic parts of the benzylidene barbituric acid **85** and vinyl benzoxazinanones **86**, thus, providing the corresponding spirotetrahydroquinolines **87** in up to 97% *ee*. It should be mentioned that all the spirotetrahydroquinolines **87** were obtained as a single diastereoisomer where vinyl and R¹ group exhibited a *cis* relationship. To account for this excellent diastereoselectivity, the authors proposed a plausible reaction intermediate where Ts and R¹ groups are *pseudo-trans* to each other to avoid a steric clash in the intermediate resulted from a reversible aza-Michael addition of **88** to **85** or **8c** (Scheme 23d). Then, the intramolecular addition of the carbanion of the barbiturate occurs at the *Si*-face of the π -allyl-palladium-ligand complex to provide the *cis*-adduct. This cyclisation step was proposed as the rate-limiting and enantio-determining step.



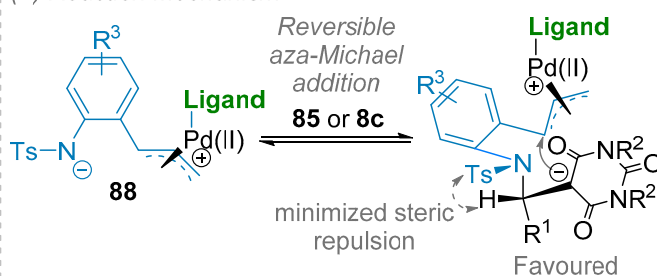
(b) Scope of the reaction: general trends (>99:1 *dr*)



(c) **Ligand**

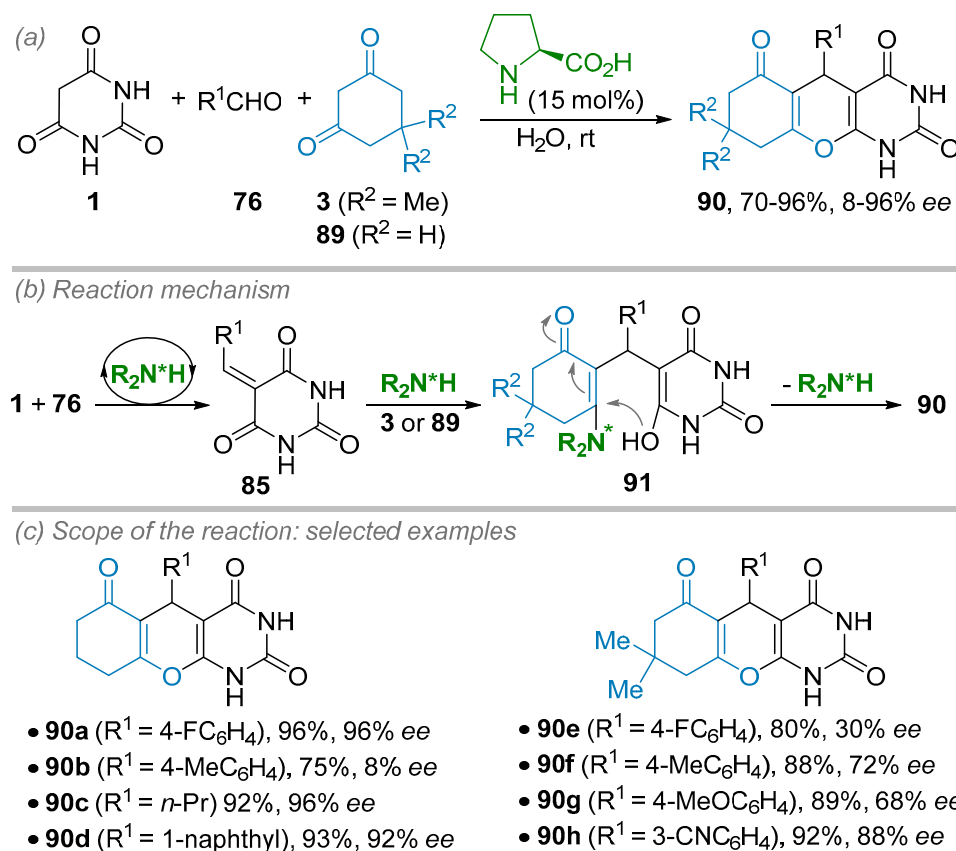


(d) Reaction mechanism



Scheme 23. Enantioselective palladium-catalyzed (4+2) cycloaddition reaction between vinyl benzoxazinanones and benzylidene *N,N'*-dimethyl barbituric acids. (a) General conditions. (b) Scope and limitations. (c) Ligand structure. (d) Proposed reaction mechanism.

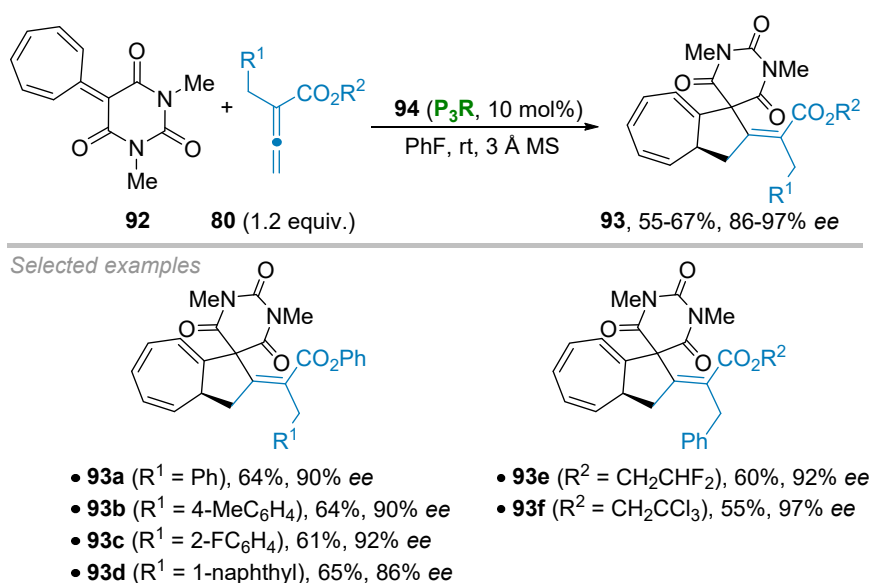
In 2017, the Myrboh group studied the multi-component reaction involving aromatic aldehydes **76**, 1,3-cyclohexanediones **89** and barbituric acid **1** catalyzed by simple L-proline catalyst (15 mol%) to afford chromano[2,3-*d*]pyrimidine-triones **90** in high yields (70–96%) and low to excellent enantiomeric excesses (8–96% *ee*, Scheme 24) [46]. The strength of this methodology relies on the user- and the eco-friendly protocol. Indeed, water was used as a solvent at room temperature and pure products **90** were obtained after a simple filtration and recrystallization in ethanol. With these conditions in hand, the authors studied the scope and limitations of this reaction (Scheme 24c). Regarding the 1,3-dione partners, both dimedone (**3**, $R^2 = \text{Me}$) or 1,3-cyclohexanedione (**89**, $R^2 = \text{H}$) were tested; the latter providing slightly better results in terms of *ee*. Nevertheless, this *gem*-dimethyl substituent seems to have a strong, erratic impact on the stereoinduction, but this phenomenon was not explained. For example, 4-fluoro benzaldehyde gave excellent results (96% yield, 96% *ee*) when reacting with 1,3-cyclohexanedione **89** whereas its reaction with dimedone **3** resulted in a dramatic drop in efficacy (80% yield, 30% *ee*). The opposite trend could be observed when 4-methyl benzaldehyde was used (88% yield, 72% *ee* with dimedone vs 75% yield, 8% *ee* with 1,3-cyclohexanedione). Regarding the aldehyde partner **76**, most successful examples involve aromatic aldehydes (substituted by electron-withdrawing or -donating groups at different positions) tested while only two examples in the aliphatic or heteroaromatic series were reported with high *ee* (propanal, 96% *ee* and 1-naphthaldehyde, 92% *ee*, respectively). The authors proposed a mechanism where the first step is the formation of the alkylidene barbituric acid **85** catalyzed by proline (Scheme 24b). These Michael acceptor species then react with the enamine formed in situ between the catalyst and the 1,3-diketones **3** or **89** to give the intermediate **91** that cyclizes to provide the desired chromano[2,3-*d*]pyrimidine-triones **90** thanks to an oxa-Michael addition along with the regeneration of the catalyst.



Scheme 24. (S)-Proline-catalyzed multicomponent synthesis of chromano [2,3-*d*]pyrimidine-triones from aldehydes, 1,3-cyclohexanediones and barbituric acid. (a) General conditions. (b) Proposed reaction mechanism. (c) Scope and limitations.

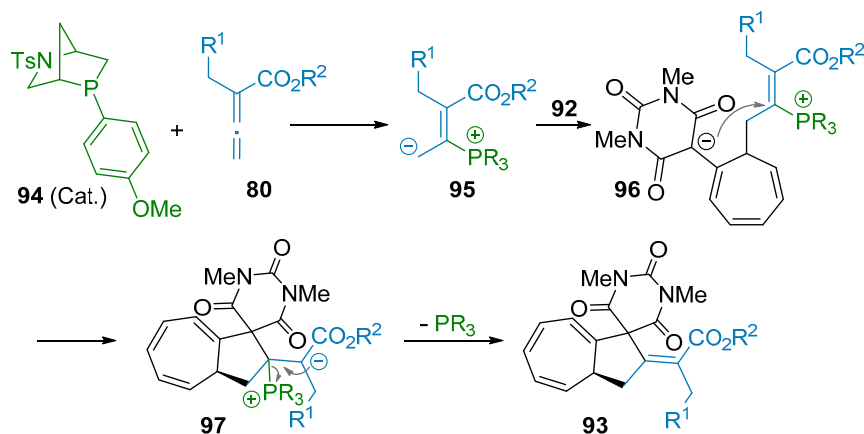
3.3. Other Cycloaddition Reactions

Guo and colleagues recently tackled the challenging higher-order cycloaddition reactions both in racemic and enantioselective fashion starting from a heptafulvene barbituric acid platform **92** and functionalized allenoates **80** (Scheme 25) [47]. Upon phosphine catalysis a formal (8+2) cycloaddition process occurred to furnish the corresponding bicyclo [5.3.0] decanes **93** with excellent *ees* ranging from 86% to 97%. The authors observed that a rather activated ester moiety on allenoate **80** was required to secure a good reactivity with sterically hindered chiral phosphine catalyst **94**. Thus, for examples, the allylic esters **93a–93d** were obtained with high stereinduction (86–92% *ee*) and isolated yields ranging from 61% to 65%, together with derivatives **93e–93f** having either a fluorinated (**93e**, 92% *ee*) or chlorinated (**93f**, 97% *ee*) alkyl substituents on the ester moiety.



Scheme 25. Phosphine-catalyzed (8+2) annulation of barbituric acid heptafulvenes.

Actually, a screening of chiral phosphines revealed that the best results were achieved using Kwon's endo phosphine **94** (Scheme 26). Regarding the mechanism, the authors proposed a formal (8+2) cycloaddition triggered by the addition reaction of the phosphine organocatalyst **94** to the allenoate **80** to form the phosphonium betaine intermediate **95**. Then, an addition reaction takes place to the heptafulvene barbituric acid **92** to give **96**, giving rise to a cyclization process that leads to the transient cyclopentane **97**. This charged intermediate undergoes the final elimination event allowing the formation of product **93** along with the concomitant regeneration of phosphine organocatalyst **94**.



Scheme 26. Proposed mechanism of the (8+2) Annulation reaction.

4. Conclusions

Despite the long-standing interest in barbituric acid derivatives as useful building blocks for the elaboration of both bio-relevant products or architectures having interesting properties in material science, the enantioselective catalytic synthesis of chiral non-racemic barbiturates-derived products slowly emerged in the 1990s. The marked Brønsted acidity of barbituric acid derivatives or electrophilicity of alkylidene counterparts have required the development of specific catalysts or catalytic approaches to manage these unique properties. Furthermore, as far as non-symmetrical barbituric acid scaffolds are concerned, the challenging stereo-differentiation of rather similar functionality on both nitrogen atoms required ingenious methodological approaches to be carried out. Nonetheless, both metal- and organic catalysts are currently able to engage barbituric derivatives into highly enantioselective addition and cycloaddition reactions to provide original chiral linear, fused, and spiro-bicyclic architectures. The panel of enantioselective reactions carried out on barbituric acids remains, however, rather limited and many opportunities to develop new processes still exist. By giving an overview of the state-of-the-art of catalytic enantioselective transformations, we hope this review will provide a springboard to elicit new developments in this field of research.

Author Contributions: writing—original draft preparation, C.S., A.L., V.L., S.O., J.-F.B.; supervision, J.-F.B.

Acknowledgments: This work has been partially supported by INSA Rouen, Rouen University, CNRS, EFRD, Labex SynOrg (ANR-11-LABX-0029) and region Normandie (CRUNCH network). This work was also supported by the French National Research Agency (ANR) as part of the ANR-16-CE07-0011-01 project.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

BINOL	1,1'-Bi-2-naphthol
DMSO	dimethyl sulfoxide
HPLC	High Performance Liquid Chromatography
THF	tetrahydrofuran
TS	Transition state

References

1. Baeyer, A. Mittheilungen aus dem organischen Laboratorium des Gewerbeinstitutes in Berlin: Untersuchungen über die Harnsäuregruppe. *Justus Liebigs Ann. Chem.* **1864**, *130*, 129–175. [[CrossRef](#)]
2. Fischer, E.; von, M. New class of narcotics. *Ther. Ggw.* **1903**, *44*, 97–101.
3. Moussier, N.; Bruche, L.; Viani, F.; Zanda, M. Fluorinated Barbituric Acid Derivatives: Synthesis and Bio-activity. *Curr. Org. Chem.* **2003**, *7*, 1071–1080. [[CrossRef](#)]
4. Bojarski, J.T.; Mokrosz, J.L.; Barton, H.J.; Paluchowska, M.H. Recent progress in barbituric acid chemistry. *Adv. Heterocycl. Chem.* **1985**, *38*, 229–297. [[CrossRef](#)]
5. Sans, R.G.; Chozas, M.G. Historical aspects and applications of barbituric acid derivatives. A review. *Pharmazie* **1988**, *43*, 827–829.
6. Nikoofar, K.; Khademi, Z. Barbituric Acids in Organic Transformations, An Outlook to the Reaction Media. *Mini-Rev. Org. Chem.* **2017**, *14*, 143–173. [[CrossRef](#)]
7. Bialer, M. How did phenobarbital's chemical structure affect the development of subsequent antiepileptic drugs (AEDs)? *Epilepsia* **2012**, *53*, 3–11. [[CrossRef](#)]
8. Renard, A.; Lhomme, J.; Kotera, M. Synthesis and Properties of Spiro Nucleosides Containing the Barbituric Acid Moiety. *J. Org. Chem.* **2002**, *67*, 1302–1307. [[CrossRef](#)] [[PubMed](#)]
9. Kim, S.-H.; Pudzianowski, A.T.; Leavitt, K.J.; Barbosa, J.; McDonnell, P.A.; Metzler, W.J.; Rankin, B.M.; Liu, R.; Vaccaro, W.; Pitts, W. Structure-based design of potent and selective inhibitors of collagenase-3 (MMP-13). *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1101–1106. [[CrossRef](#)]
10. Fessenden, R.J.; Larsen, J.G.; Coon, M.D.; Fessenden, J.S. Silicon Heterocyclic Compounds. III. Silicon-Substituted Spirobarbiturates. *J. Med. Chem.* **1964**, *7*, 695–698. [[CrossRef](#)]

11. Duan, J.J.W.; Chen, L.; Lu, Z.; Jiang, B.; Asakawa, N.; Sheppeck, J.E.; Liu, R.-Q.; Covington, M.B.; Pitts, W.; Kim, S.-H.; et al. Discovery of low nanomolar non-hydroxamate inhibitors of tumor necrosis factor- α converting enzyme (TACE). *Bioorg. Med. Chem. Lett.* **2007**, *17*, 266–271. [[CrossRef](#)] [[PubMed](#)]
12. Ingle, V.N.; Gaidhane, P.K.; Dutta, S.S.; Naha, P.P.; Sengupta, M.S. Synthesis of Novel Galactopyranosyl-Derived Spiro Barbiturates. *J. Carbohydr. Chem.* **2006**, *25*, 661–671. [[CrossRef](#)]
13. Hese, S.V.; Meshram, R.J.; Kamble, R.D.; Mogle, P.P.; Patil, K.K.; Kamble, S.S. Antidiabetic and allied biochemical roles of new chromeno-pyrano pyrimidine compounds: Synthesis, in vitro and in silico analysis. *Med. Chem. Res.* **2017**, *26*, 805–818. [[CrossRef](#)]
14. Kalaria, P.N.; Satasia, S.P.; Raval, D.K. Synthesis, characterization and biological screening of novel 5-imidazopyrazole incorporated fused pyran motifs under microwave irradiation. *New J. Chem.* **2014**, *38*, 1512–1521. [[CrossRef](#)]
15. Gomes, R.F.A.; Coelho, J.A.S.; Afonso, C.A.M. Synthesis and Applications of Stenhouse Salts and Derivatives. *Chem. Eur. J.* **2018**, *24*, 9170–9186. [[CrossRef](#)] [[PubMed](#)]
16. Mohammadi Ziarani, G.; Aleali, F.; Lashgari, N. Recent applications of barbituric acid in multicomponent reactions. *RSC Adv.* **2016**, *6*, 50895–50922. [[CrossRef](#)]
17. Schade, A.; Schreiter, K.; Rüffer, T.; Lang, H.; Spange, S. Interactions of Enolizable Barbiturate Dyes. *Chem. Eur. J.* **2016**, *22*, 5734–5748. [[CrossRef](#)] [[PubMed](#)]
18. Shaker, R.M.; Ishak, E.A. Barbituric acid utility in multicomponent reactions. *Z. Naturforsch. B J. Chem. Sci.* **2011**, *66*, 1189–1201. [[CrossRef](#)]
19. Bojarski, J. Chiral barbiturates: Synthesis, chromatographic resolutions, and biological activity. *Chem. Anal. (New York)* **1997**, *142*, 201–234.
20. Brunner, H.; Deml, I.; Dirnberger, W.; Nuber, B.; Reißer, W. Enantioselective Palladium-Catalysed Allylation of 1,5-Dimethylbarbituric Acid. *Eur. J. Inorg. Chem.* **1998**. [[CrossRef](#)]
21. Brunner, H.; Fürst, J. Enantioselective allylation of 1,5-dimethylbarbituric acid with Pd catalysts and new optically active PN ligands. *Inorg. Chim. Acta* **1994**, *220*, 63–66. [[CrossRef](#)]
22. Brunner, H.; Deml, I.; Dirnberger, W.; Ittner, K.-P.; Reißer, W.; Zimmermann, M. Synthesis of the Stereoisomers of Methohexital by Palladium-Catalyzed Allylation. *Eur. J. Inorg. Chem.* **1999**. [[CrossRef](#)]
23. Brunner, H.; Rückert, T. Enantioselective Katalyse, 121. Mitt. [1]: Chirale Phosphanliganden mit zusätzlichen Sauerstofffunktionalitäten. *Monatshefte Chem./Chem. Mon.* **1998**, *129*, 339–354. [[CrossRef](#)]
24. Bordwell, F.G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988**, *21*, 456–463. [[CrossRef](#)]
25. Pair, E.; Cadart, T.; Levacher, V.; Brière, J.-F. Meldrum's Acid: A Useful Platform in Asymmetric Organocatalysis. *ChemCatChem* **2016**, *8*, 1882–1890. [[CrossRef](#)]
26. Dumas, A.M.; Fillion, E. Meldrum's Acids and 5-Alkylidene Meldrum's Acids in Catalytic Carbon–Carbon Bond-Forming Processes. *Acc. Chem. Res.* **2009**, *43*, 440–454. [[CrossRef](#)]
27. Bug, T.; Mayr, H. Nucleophilic Reactivities of Carbanions in Water: The Unique Behavior of the Malodinitrile Anion. *J. Am. Chem. Soc.* **2003**, *125*, 12980–12986. [[CrossRef](#)]
28. Schade, A.; Tchernook, I.; Bauer, M.; Oehlke, A.; Breugst, M.; Friedrich, J.; Spange, S. Kinetics of Electrophilic Alkylations of Barbiturate and Thiobarbiturate Anions. *J. Org. Chem.* **2017**, *82*, 8476–8488. [[CrossRef](#)]
29. Seeliger, F.; Berger, S.T.A.; Remennikov, G.Y.; Polborn, K.; Mayr, H. Electrophilicity of 5-Benzylidene-1,3-dimethylbarbituric and -thiobarbituric Acids. *J. Org. Chem.* **2007**, *72*, 9170–9180. [[CrossRef](#)]
30. Trost, B.M.; Schroeder, G.M. Palladium-Catalyzed Asymmetric Allylic Alkylation of Barbituric Acid Derivatives: Enantioselective Syntheses of Cyclopentobarbital and Pentobarbital. *J. Org. Chem.* **2000**, *65*, 1569–1573. [[CrossRef](#)]
31. del Pozo, S.; Vera, S.; Oiarbide, M.; Palomo, C. Catalytic Asymmetric Synthesis of Quaternary Barbituric Acids. *J. Am. Chem. Soc.* **2017**, *139*, 15308–15311. [[CrossRef](#)]
32. Trost, B.M.; Van Vranken, D.L. Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev.* **1996**, *96*, 395–422. [[CrossRef](#)]
33. Rombola, M.; Sumaria, C.S.; Montgomery, T.D.; Rawal, V.H. Development of Chiral, Bifunctional Thiosquaramides: Enantioselective Michael Additions of Barbituric Acids to Nitroalkenes. *J. Am. Chem. Soc.* **2017**, *139*, 5297–5300. [[CrossRef](#)]

34. Liu, Y.; Zhang, Y.; Duan, H.-X.; Wanyan, D.-Y.; Wang, Y.-Q. Enantioselective organocatalytic Michael additions of *N,N'*-dialkylbarbituric acids to enones. *Org. Biomol. Chem.* **2017**, *15*, 8669–8679. [CrossRef]
35. Zhang, J.; Yin, G.; Du, Y.; Yang, Z.; Li, Y.; Chen, L. Michael–Michael Addition Reactions Promoted by Secondary Amine–Thiourea: Stereocontrolled Construction of Barbiturate-Fused Tetrahydropyrano Scaffolds and Pyranocoumarins. *J. Org. Chem.* **2017**, *82*, 13594–13601. [CrossRef]
36. Zhu, Y.; Wang, Z.; Zhang, J.; Yu, J.; Yan, L.; Li, Y.; Chen, L.; Yan, X. An Organocatalytic Synthesis of Chiral Pyrano[2,3-*d*]pyrimidines through [3 + 3] Annulation of 1,3-Dimethyl-barbituric Acid with 2-(1-Alkynyl)-2-alken-1-ones. *Eur. J. Org. Chem.* **2018**, *2018*, 347–354. [CrossRef]
37. Reddy Chidipudi, S.; Burns, D.J.; Khan, I.; Lam, H.W. Enantioselective Synthesis of Spiroindenes by Enol-Directed Rhodium(III)-Catalyzed C-H Functionalization and Spiroannulation. *Angew. Chem. Int. Ed.* **2015**, *54*, 13975–13979. [CrossRef]
38. Zhao, H.-W.; Tian, T.; Li, B.; Yang, Z.; Pang, H.-L.; Meng, W.; Song, X.-Q.; Chen, X.-Q. Diastereoselective Synthesis of Dispirobarbiturates through Et₃N-Catalyzed [3 + 2] Cycloaddition of Barbiturate-Based Olefins with 3-Isothiocyanato Oxindoles. *J. Org. Chem.* **2015**, *80*, 10380–10385. [CrossRef]
39. Zhao, H.-W.; Tian, T.; Pang, H.-L.; Li, B.; Chen, X.-Q.; Yang, Z.; Meng, W.; Song, X.-Q.; Zhao, Y.-D.; Liu, Y.-Y. Organocatalytic [3 + 2] Cycloadditions of Barbiturate-Based Olefins with 3-Isothiocyanato Oxindoles: Highly Diastereoselective and Enantioselective Synthesis of Dispirobarbiturates. *Adv. Synth. Catal.* **2016**, *358*, 2619–2630. [CrossRef]
40. Frankowski, S.; Gajda, T.; Albrecht, L. Isothiocyanate Strategy for the Synthesis of Quaternary α -Amino Acids Bearing a Spirocyclic Ring System. *Adv. Synth. Catal.* **2018**, *360*, 1822–1832. [CrossRef]
41. Liu, Y.; Yang, W.; Wu, Y.; Mao, B.; Gao, X.; Liu, H.; Sun, Z.; Xiao, Y.; Guo, H. Asymmetric Construction of Highly Functionalized Spirobarbiturate-Cyclopentenones through Chiral Phosphine-Catalyzed [3 + 2] Annulation of Morita–Baylis–Hillman Carbonates with Barbiturate-Derived Alkenes. *Adv. Synth. Catal.* **2016**, *358*, 2867–2872. [CrossRef]
42. Gao, X.; Li, Z.; Yang, W.; Liu, Y.; Chen, W.; Zhang, C.; Zheng, L.; Guo, H. Phosphine-catalyzed [3 + 2] and [4 + 2] annulation reactions of ynones with barbiturate-derived alkenes. *Org. Biomol. Chem.* **2017**, *15*, 5298–5307. [CrossRef]
43. Shul'ts, E.E.; Andreev, G.N.; Shakirov, M.M.; Komarova, N.I.; Bagryanskaya, I.Y.; Gatilov, Y.V.; Tolstikov, G.A. Diels–Alder reactions with cyclic sulfones: VIII. Organic catalysis in the synthesis of spiro[1-benzothiophene-4,5'-pyrimidine]-2',4',6'-trione 1,1-dioxides and 2'-thioxospiro[1-benzothiophene-4,5'-pyrimidine]-4',6'-dione 1,1-dioxides. *Russ. J. Org. Chem.* **2009**, *45*, 87–101. [CrossRef]
44. Liu, H.; Liu, Y.; Yuan, C.; Wang, G.-P.; Zhu, S.-F.; Wu, Y.; Wang, B.; Sun, Z.; Xiao, Y.; Zhou, Q.-L.; et al. Enantioselective Synthesis of Spirobarbiturate-Cyclohexenes through Phosphine-Catalyzed Asymmetric [4 + 2] Annulation of Barbiturate-Derived Alkenes with Allenates. *Org. Lett.* **2016**, *18*, 1302–1305. [CrossRef]
45. Zhao, H.-W.; Feng, N.-N.; Guo, J.-M.; Du, J.; Ding, W.-Q.; Wang, L.-R.; Song, X.-Q. Diastereoselective and Enantioselective Synthesis of Barbiturate-Fused Spirotetrahydroquinolines via Chiral Palladium(0)/Ligand Complex Catalyzed [4 + 2] Cycloaddition of Vinyl Benzoxazinones with Barbiturate-Based Olefins. *J. Org. Chem.* **2018**, *83*, 9291–9299. [CrossRef]
46. Bhattacharjee, D.; Sutradhar, D.; Chandra, A.K.; Myrboh, B. l-proline as an efficient asymmetric induction catalyst in the synthesis of chromeno[2,3-*d*]pyrimidine-triones, xanthenes in water. *Tetrahedron* **2017**, *73*, 3497–3504. [CrossRef]
47. Gao, Z.; Wang, C.; Zhou, L.; Yuan, C.; Xiao, Y.; Guo, H. Phosphine-Catalyzed [8 + 2]-Annulation of Heptafulvenes with Allenates and Its Asymmetric Variant: Construction of Bicyclo[5.3.0]decane Scaffold. *Org. Lett.* **2018**, *20*, 4302–4305. [CrossRef]

