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FULL PAPER

Stereoselectivity Enhancement During the Generation of Three Contiguous Stereocenters in Tetrahydrothiophenes

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Abstract: Application of carefully designed Cinchona alkaloid based squaramides resulted in the formation of three contiguous stereocenters in enantio- and diastereoselective Sulfa-Michael/intramolecular aldol reactions cascade. Increase of the temperature to 333 K in reaction of mercaptoacetic aldehyde and various en-ynones allowed the rise of the reaction rate while not affecting the enantioselectivity nor diastereoselectivity. Stereoselectivity was dependent on the structure of the hydrogen-bonding unit, thus revealing the importance of weak interactions in the formation of the multifunctional tetrahydrothiophenes. Kohn-Sham Density Functional Theory results suggest that a perfect fit of the electrophile and squaramide via tailored (+)N-H hydrogen bonding and π-π stacking interactions were the main factors of the chirality transfer.

Introduction

Chiral tetrahydrothiophenes are valuable scaffolds exhibiting various biological activities.[1] The importance of such a structural motif is demonstrated by a variety of synthetic approaches to the formation of the tetrahydrothiophene ring. Among them, an application of the dithiane diol as a source of low-weight building block covering nucleophilic and electrophilic functionalities deserves particular attention.[2] Decomposition of the stable dimer of mercaptoacetaldehyde by a base or heating was the pillar of the elaborated cascade Sulfa-Michael/aldol reaction or aldol condensation resulting in the formation of the multi-decorated tetrahydrothiophenes in a highly stereoselective fashion.[3] The majority of transformations involve an initial addition to simple Michael acceptors. However, the application of electrophiles with additional π-electron conjugated system in β or δ position of polyene may result in reaction at remote positions.[4] Hence, the addition at either 4- or 6-position could afford the synthesis of the chiral tetrahydrothiophenes bearing additional reactive function in the molecule, thus enabling further transformations into complex structures (eg. **3** and **5**, Scheme 1). The highly stereoselective formation of such heterocycles is limited to the addition of 2-mercaptocarbonyl nucleophiles (**1,** Scheme 1) rarely bearing aldehyde functionality. Therefore, in this contribution we focus on the development of organocatalytic strategy for the functionalization of variably decorated Michael acceptors with additional double or triple bonds and another electron-withdrawing group (**Acc 1-3**, Scheme 1) by applying a convenient source of mercaptoaldehyde. The acceleration of the reaction of 1,4-dithiane-2,5-diol (**6**) in the aqueous system by the formation of hydrogen bonds or its decomposition by a base indicates the bifunctional character of hydrogen bonding systems, with the basic unit as the potential catalyst to the effective formation of the sulfur-containing heterocycles. Hence, we also studied the nature of the hydrogen bonding unit and its impact on stereoselectivity of the transformation in which three contiguous stereocenters were formed.

Results and Discussion

The effective synthesis of the functionalized molecules with a few stereocenters is prone to diastereoselection issues. The initial reactions of dithiane diol **6** and enynone **11a**[5], as a model acceptor, suffered from the low selectivity when DABCO (4:1 d.r) or chiral quinine (1:1 d.r.) were applied (Scheme 2), seriously affecting the analysis of the reaction mixture. The essential increase of the diastereomers ratio was noted when thiourea **C1** was used, albeit the product **9a** was formed with low enantioselectivity. With the assumption that the stronger N-H donor might be responsible for the diastereoselection improvement, several squaramides were tested.[6]

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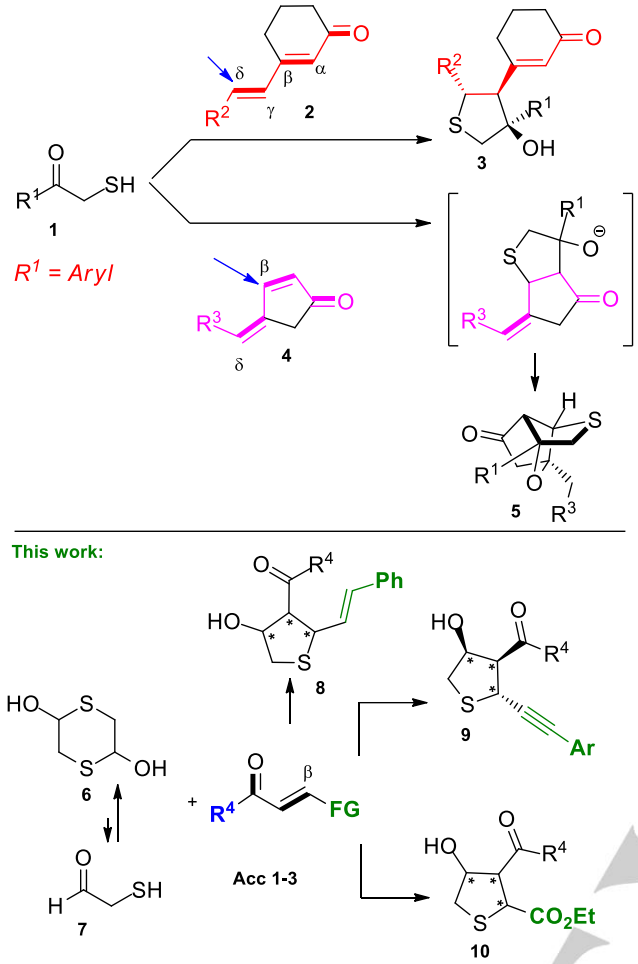
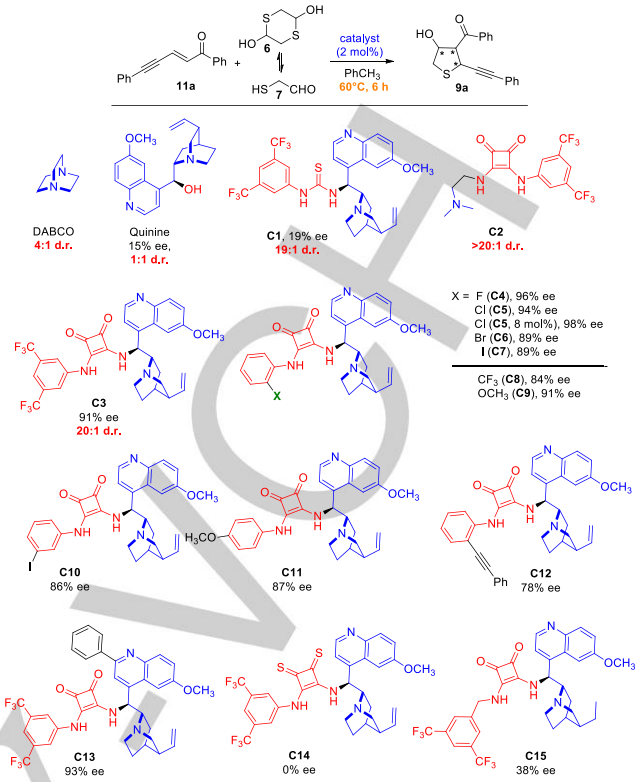


Scheme 1. Addition of mercaptocarbonyls to functionalized enone-based π-conjugated systems.

Achiral **C2** offered the product with a bit higher d.r. than thiourea **C1**. However, the application of chiral squaramide **C3** led to the product with high d.r. and 91% ee. Additional improvement was observed for the reaction catalyzed by Cinchona-alkaloid based squaramide **C4,** application of which led to the chiral tetrahydrothiophene **9a** with 96% ee and 20:1 d.r. Further studies on the catalyst's structure-stereoselectivity of the product revealed that as low as 2 mol% of squaramide **C4** could efficiently promote the studied reaction. The importance of the hydrogen-bonding was demonstrated by the impact of the solvent (see SI for details). The reaction catalyzed by **C4** led to enantioselectivities exceeding 90% only when chlorinated alkanes and aromatics were applied, while the usage of 2-propanol afforded adduct with only 40% of ee. No additional improvement was observed for the congeners of **C4** bearing chlorine (**C5**), bromine (**C6**) or iodine (**C7**) atom in place of fluorine, thus excluding the impact of the halogen-lone pair interaction with carbonyl group in enynone.[7] Although product with up to 98% ee was formed with the assistance of **C5,** it required four times more of catalyst (8 mol% vs 2 mol%). In the case of large substituents as in **C6** and **C7**, the introduction of both trifuoromethyl (**C8**) and methoxy (**C9**) groups instead of fluorine resulted in lowered enantioselectivities. This was even more evident for catalyst **C12,** that catalyzes the reaction but with only 78% of ee.



Scheme 2. Catalyst screen. For the **C4**-**C15** 20:1 d.r. was noted. Ees are given for the crude product due to changes of enantiomeric composition affected by column chromatography.

Among the tested, 3-iodo (**C10**) and 4-methoxy (**C11**) catalysts provided the product but with lower ees than **C4.** Also, the changes of the *Cinchona* core as 2'-phenyl-substituted catalyst **C1** had no distinct impact on stereoselectivity leading to an adduct with 93% ee. Surprisingly, modification of the squaramide unit into the more acidic analog of **C3** like in thiosquaramide **C14**[8] resulted in total loss of stereoselectivity. A flexible amine unit present in squaramide **C15** was also a probable factor of the lowering enantioselectivity of the product. Besides providing the effective chirality transfer, the role of the catalyst begins with the decomposition of the stable 1,4-dithiane-2,5-diol (**6**) into the reactive thiol **7**[9] that is promoted also by the temperature increase to 333 K.[3d] The amine unit is responsible for the generation of dithiane anion, which then becomes unstable and undergoes decomposition to thiolate. This process requires energy for activation but provides a low concentration of nucleophile formed upon the protonation. Reaction performed at 298 K required 48 h instead of only 6 h at 333 K. Although enantioselectivity was satisfactory, such conditions led to irreproducible results. Our KS-DFT calculations of a system containing catalyst **C3** and **6** indicate a readily accessible molecular pathway allowing for the formation of the neutral and activated nucleophile (mercaptoacetaldehyde **7**). The decomposition process is initiated by a proton abstraction from dithiane diol by the basic unit of catalyst **C3.** This step, characterized by a free energy barrier of 4.2 kcal/mol (cf. inset **1**-dithiane diol which is stabilized by three hydrogen bonds between the oxygen atom of the anion and three N-H sites of **C3** (the structures of the relevant molecules are shown in the SI). Our

calculations performed on the isolated anionic dithiane diol indicate that it may decompose (cf. right panel of Figure 1).

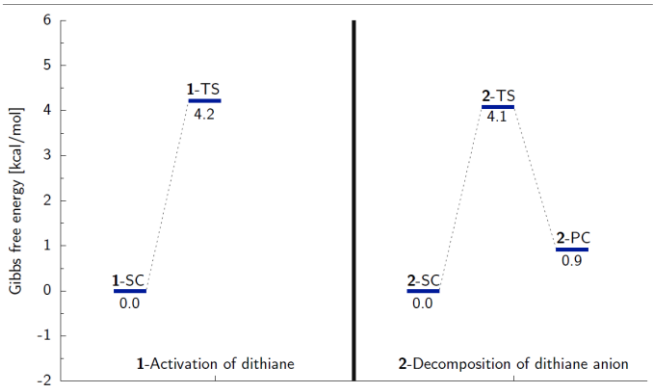


Figure 1. The computed Gibbs energy profile for the catalyst-supported decomposition of **6** to mercaptoacetaldehyde **7** in the presence of **C3** catalyst. In the left panel the profile for proton abstraction is shown, leading to an anion of dithiane diol, and in the right panel the profile for its decomposition is shown, computed for isolated anion.. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC products.

Subsequently, a proton transfer from hydroxyl group to the sulfur atom induces a C-S bond rupture (cf. Figure 2, **2**-TS), that leads to the formation of neutral and anionic forms of mercaptoacetaldehyde (cf. Figure 2, **2**-PC). The rate-limiting step in the formation of nucleophile seems to be the release of an anion of dithiane diol from the complex. A higher temperature of the system should facilitate breaking of the hydrogen bonds between anion of dithiane diol and **C3** catalyst. Hence, at lower temperatures, the aldehyde remained unconsumed and followed self-condensation leaving Michael acceptor unreacted. The results of our KS-DFT calculations are thus consistent with the observed rates of performed reactions, which required elevated temperature to be efficient. The complete mechanism elucidated by KS-DFT calculations is summarized in Figure 2, whereas in Figure 3 the corresponding Gibbs energy profile is shown. The stationary points were located at the ωB97X-D/PCM(toluene)/def2-SVP level and the corresponding Gibbs energies were computed assuming def2-TZVP basis set. Only in the case of dithiane anion decomposition we employed B2PLYP/PCM(toluene)/ma-def2-TZVP approach (cf. SI for details).[10] According to our calculations the next step after release of dithiane diol anion leads to mercaptoacetaldehyde addition to en-ynone in the presence of **C4** catalyst. The latter starts with a deprotonation of mercaptoacetaldehyde by the amine unit of chiral squaramide **C4.** This step (cf. Figure 3, **3-Activation**) seems to be readily available due to a low free energy barrier of 4.4 kcal/mol. The activation process leads to the formation of activated nucleophile (anion of mercaptoacetaldehyde, cf. **3**-TS in Figure 2 and 3) having excess negative charge located on the sulfur atom (reaching -0.54 e in the **3**-TS structure and -0.65 e in the **3**-PC, Figure 2). Hence, it is assumed that reaction underwent according to the specific base catalysis. Moreover, our calculations indicate that the aldehyde group forms hydrogen bonds with the squaramide unit which thus assumes the appropriate position to attack the acceptor (2.48 Å). According to the previous model involving organocatalyzed addition to Michael acceptor[11], the ketone is believed to interact with the protonated amine. In the alternative orientation of the ketone, that would result in formation of the opposite stereogenic center, the electron poor double bond is away of the reaction center and thus becomes unreachable for the C-S bond formation. Our KS-DFT results indicate that the **4-TS** transition state is formed, in which the nucleophile's and en-ynone's double bonds are aligned with the assistance of advantageous aryl-aryl stacking interactions (cf. **4**-**TS**, Figure 2). Hence, the formed nucleophile can attack the positively charged (+0.26 e) β-carbon atom of en-ynone approaching the Si-face of the double bond and leading to the formation of negatively charged intermediate (cf. Figure 3, **4**-PC). The free energy barrier for the addition step is merely 7.3 kcal/mol (cf. Figure 3, **4-Addition**).

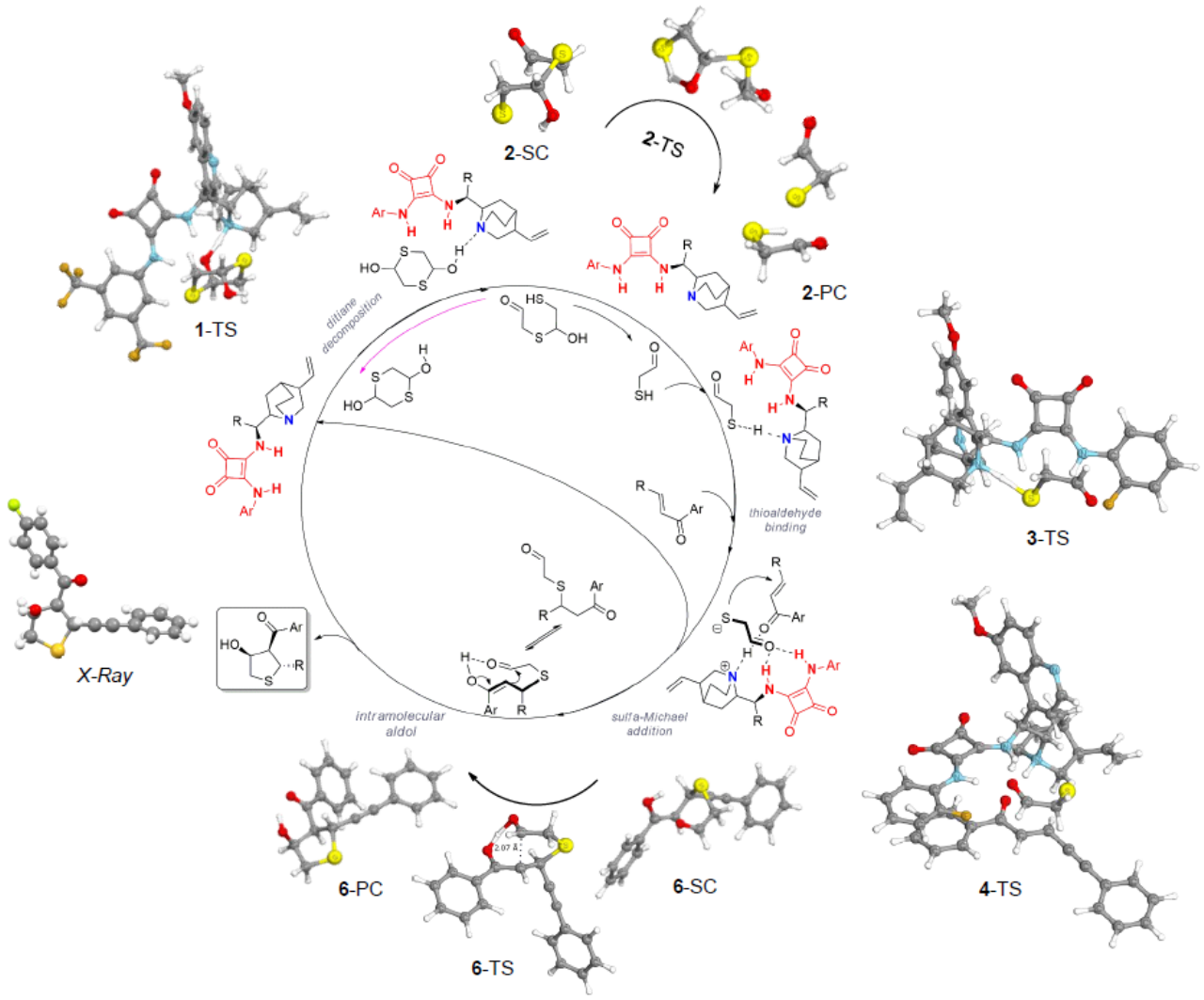


Figure 2. The plausible reaction path including sulfa-Michael addition, intramolecular aldol reaction, the formation of the final product and X-ray of the product **9g**

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Then, the excess proton located in the basic unit of **C4** catalyst is spontaneously detached by the carbonyl group of the anionic intermediate in a barrierless manner (cf. Figure 3, **5-Proton Transfer**), forming a neutral product and releasing the catalyst thus providing a sulfa-Michael adduct. At this stage the topology and stereochemistry of the final product is already established.

Further enolization of ketone generates a C-centered nucleophile that could adopt the conformation in which both reactive centers remain in proximity, separated by only 2.07 Å (cf. Figure 2, **6-TS**). The mutual orientation of the enol and aldehyde is organized by the configuration of the C-S bond and an intramolecular hydrogen bond, that enables formation of the next C-C bond in a highly stereoselective manner. According to our KS-DFT calculations, in which we assumed dissociation of en-ynone (requiring additional 29.6 kcal/mol) what is consistent with the use of elevated temperature, the intramolecular aldol reaction resulted in formation of the final product in a cyclization process (cf. **6**-TS inset in Figure 2), marked by the free energy barrier of 16.2 kcal/mol (cf. Figure 3, **6-Cyclization**). Although the intermolecular cyclization appears to be the overall rate limiting step this is also a highly exoergic process, leading to the formation of (1*S*, 2*S*, 3*R*)-tetrahydrothiophene (cf. **6**-PC inset in Figure 2) without the assistance of a chiral catalyst and with high stereoselectivity. Thus, the KS-DFT predictions are consistent with the observed stereoselectivity of the investigated reaction (96% ee and >20:1 d.r.).

The absolute configuration observed in the final product was supported by the X-ray analysis of the product **9g**.[12] The chemical absolute configuration of the compound was determined on the grounds of the Flack parameter equal to 0.010(15) and was assigned by analogy to other adducts **9a**-**9w** (cf. Table 1). According to the plausible mechanism revealed by our calculations (Figure 2), only the precise arrangement of both partners allows the activation of the electrophile, followed by the stereoselective addition of sulfur nucleophile. The assumption that only aromatic congeners of squaramides **C3**-**C7** allow for the

weak but crucial interactions with the aromatic unit of electrophile could also be supported by a low yield and small enantioselectivity when **C15** was used instead (56%, 38% ee).

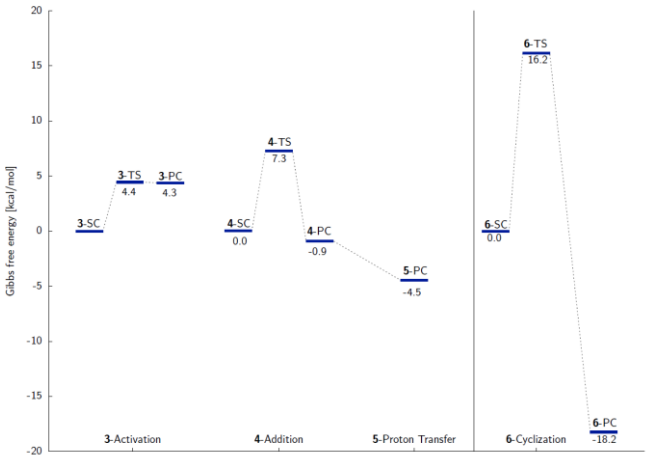


Figure 3. The Gibbs energy profile for the sulfa-Michael addition of mercaptoacetaldehyde to en-ynone in the presence of chiral squaramide **C4** calculated at the ωB97xD/PCM(Toluene)/def2-TZVP level. The abbreviations refer to -SC substrate complex, -TS transition state, and -PC product complex. Furthermore, the profile for cyclization step calculated assuming earlier dissociation of en-ynone is shown separately For further details, see SI.

The minimum energy structures of both **C3** and **C14** catalysts located in our KS-DFT calculations are shown in Figure 4. A comparison of the structural features of these two squaramides led to the conclusion that the aromatic unit of **C14** could occupy two conformations. Hence, on the contrary to **C3**, substitution of the oxygen atom by sulfur does not allow to adopt the co-planar alignment in **C14**. Therefore, in the latter the aromatic rings of the acceptor are not able to fit nearby the hydrogen bond donor.[13]

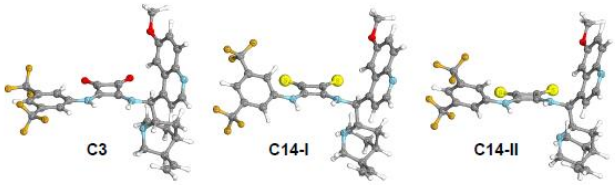


Figure 4. The ground-state minimum energy structures of **C3** and the two located conformers of **C14** (**C14-I** and **C14-II**) obtained using ωB97xD/PCM(Toluene)/def2-SVP method.

Further studies revealed that the formation of the tetrahydrothiophene ring catalyzed by **C4** performed well for a variety of Michael acceptors **11** (Table 1). However, the structure of the electrophile turned out to be crucial for the stereoselectivities achieved. 2-Substituted ketones as in cases of **11b** and **11c** were transformed to products **9b** and **9c**, respectively (Table 1), with poor to moderate enantioselectivities. This observation is consistent with the proposed mechanism (Figure 2) in which the formation of a hydrogen bond with protonated amine and ketone (N-H and O=C) could be less effective and thus allowing the reaction to occur without the control of the catalyst. On the contrary, 3- and 4-substitution patterns in Michael acceptors had a modest impact on enantioselectivity (products **9d**-**9g** and **9i**-**j**, 89-99% ee) except 4-nitro-derivative (**9h**, 78% ee). The effects caused by the surrounding of the triple bond in studied en-ynones to stereoselectivities were found to be minor (Table 1, entries 12-22) and only the 2-tiophene-derivative reacted to give the product **9u** with 77% ee albeit >20:1 d.r.

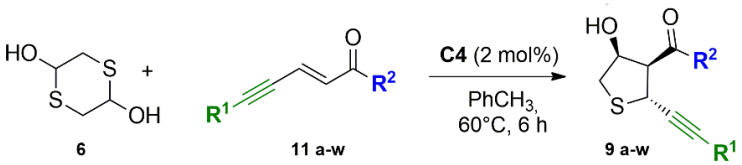


Table 1. Influence of the substitution of en-ynone system in acceptors **11a**-**11w** on the stereoselectivity[a]

Entry	R^1	R^2	Adduct	Yield [%][b]	ee [%][c]	d.r.[d]
1	Ph	Ph	**9a**	62	96	20:1
2	Ph	2-ClC_6H_4	**9b**	76	68	20:1
3	Ph	2-BrC_6H_4	**9c**	67	76	13:1
4	Ph	3-FC_6H_4	**9d**	69	94	20:1
5	Ph	3-Cl_6H_4	**9e**	71	89	13:1
6	Ph	4-BrC_6H_4	**9f**	67	93	20:1
7	Ph	4-FC_6H_4	**9g**	74	94	20:1
8	Ph	4-$NO_2C_6H_4$	**9h**	52	78	8:1

9	Ph	4-MeOC$_6$H$_4$	**9i**	73	95	20:1
10	Ph	4-PhC$_6$H$_4$	**9j**	77	99	18:1
11	Ph	2-Npht	**9k**	90	93	20:1
12	2-FC$_6$H$_4$	Ph	**9l**	90	94	20:1
13	2-ClC$_6$H$_4$	Ph	**9m**	84	93	20:1
14	3-FC$_6$H$_4$	Ph	**9n**	83	94	20:1
15	3-ClC$_6$H$_4$	Ph	**9o**	83	90	20:1
16	3-BrC$_6$H$_4$	Ph	**9p**	81	91	15:1
17	3-NO$_2$C$_6$H$_4$	Ph	**9q**	61	93	20:1
18	4-ClC$_6$H$_4$	Ph	**9r**	99.5	93	20:1
19	2,4-Cl$_2$C$_6$H$_4$	Ph	**9s**	72	94	20:1
20	1-Npht	Ph	**9t**	92	94	17:1
21	2-Tiophene	Ph	**9u**	78	77	20:1
22	4-NO$_2$C$_6$H$_4$	Ph	**9v**	84	92	20:1
23[e]	Ph	CH_3	**9w**	52	70	20:1

[a] Unless otherwise stated, reactions were performed using 2 mol% of **C4** in toluene at 60°C for 6h.

[b] Yield of isolated product. [c] Determined by HPLC on chiral stationary phases.

[d] Determined using ^{1}H NMR. [e] Reaction was performed for 24h.

In general, products **9a**, **9d-v** (excluding **9h** and **9u**) were formed with stereoselectivities ranged from 90 to 94% with little dispersion of the ee values and regardless of structural variations in the substrate. The aryl groups attached to triple bond in the source en-ynones remained far apart from the reaction center and did not affect the nucleophile's approach. However, reaction applying aliphatic en-ynone (R^1 = 1-hexyne, Scheme in Table 1) provided only a trace amount of product (up to 10% of yield). Even more drastic impact on the reactivity was noted in case of reaction involving acceptor (*Z*)-**11a**, that transformation in the optimized conditions resulted in recovery of starting material without changes of the double bond configuration. On the contrary, methyl-ketone **11w** reacted giving a product, with 52% of yield and diminished enantioselectivity (up to 70%, Table 1, entry 23) in comparison to aromatic ketones. In addition, reaction required 24h to proceed.

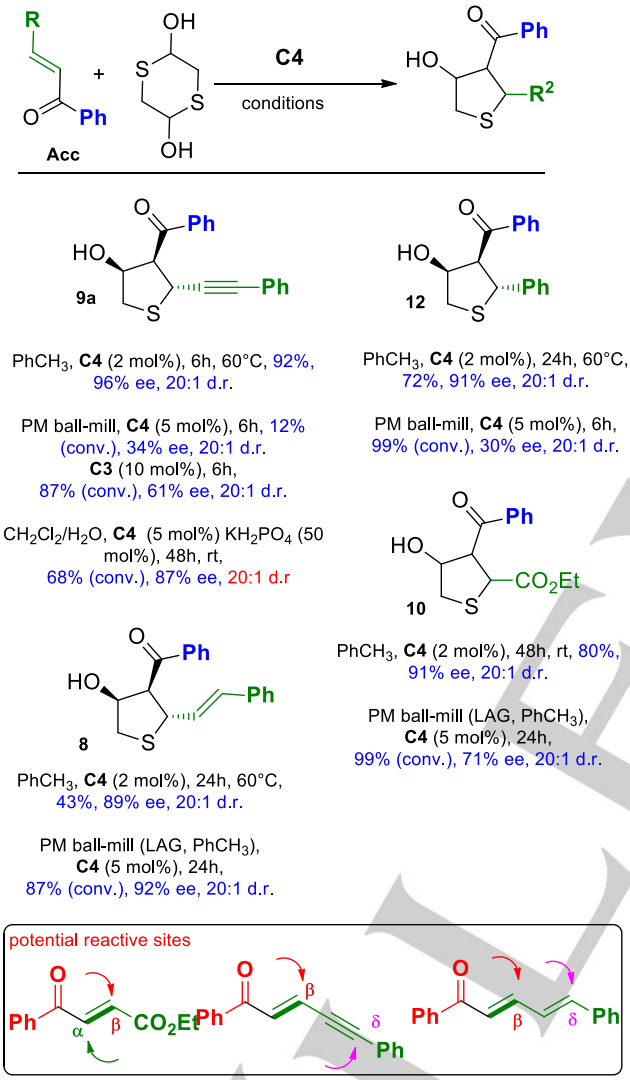
Extension of the catalyst's system based on squaramide **C4** to the transformation of different Michael acceptors (Scheme 3) provided tetrahydrothiophenes with enantioselectivities close to 91% in essentially one diastereomeric form. The studied acceptors offered two potential paths of addition (Scheme 3, framework). Due to construction of the unsaturated electron poor system, the sulfa-Michael addition could potentially occur at the end of conjugated system of en-ynones **11**[14] and dienone **Acc-2**[15] or both positions of benzylidene acrylate **Acc-1**.[16] However, mercaptoaldehyde **7** reacted at the β-position of the π-systems with accordance to the reported sulfa-Michael additions to acyclic system of this type. Thus, formation of tetrahydrothiophenes **8**, **9a**, **10** and **12** was both stero- and regioselective. Bearing in mind that the reaction outcome in terms of stereoselectivity was strongly dependent on the conditions, including catalysts structure, solvent, and temperature, some transformations were also performed using mechanochemistry. However, application of ball-milling as the technique to promote hydrogen-bonding catalysis and thus to improve stereoselectivity of the transformation[17] resulted in divergent conclusions. Among the tested substrates, reactions performed in solution led to generally better enantioselectivities than those obtained using mechanochemistry in all tested transformations (Scheme 3) except for dienone (**8**, 89% vs. 92% ee). The reaction performed in the biphasic (toluene/water) system led to product **9a** with lowered enantioselectivity in comparison to standard conditions (toluene, 6h, 60°C). Moreover, this transformation required 48h to reach 68% conversion.

Some attempts of further oxidative transformations of the product **9a** were performed[18], but with no success. However, the catalytic system based on **C4** proved that reaction was scalable, resulting in the formation of the desired product with slightly lower enantioselectivities.

Conclusion

The carefully designed hydrogen-bond donor with tertiary amine unit in Cinchona-alkaloid based squaramides provided the effective catalytic system for the sulfa-Michael addition of the reactive mercaptoaldehyde. Stereoselective addition of the mercaptane to form a sulfide, followed by the intramolecular aldol reaction, allowed for the synthesis of chiral tetrahydrothiophenes in up to 99% ee and 20:1 d.r. Generation of the three contiguous stereocenters required only 2 mol% of chiral bifunctional squaramide. The reaction worked well for a variety en-ynones and other Michael acceptors until the benzoyl moiety allowed a suitable formation of the hydrogen bond with catalyst, limiting the usage of sterically encumbered ketones. The KS-DFT

calculations indicate the multiple functions of the catalyst elucidating the plausible mechanism of chirality transfer and explaining the observed stereochemical outcome. In particular, the basic amine unit in the bifunctional catalyst **C4** was found to be responsible for the generation of a low concentration of reactive thiol from the easily available 2,5-ditianediol. Thus, the catalyst was involved in the formation of reactive nucleophile (mercaptoaldehyde). The latter upon deprotonation, forms hydrogen bonds via oxygen lone pairs of aldehyde and directs the thiol to form C-S bond stereoselectively.



Scheme 3. Formation of tetrahydrothiophenes with three stereocenters applying various Michael acceptors in reactions catalyzed by **C4**.

The corresponding transition state (**4-TS**) revealed the importance of the weak π-stacking interactions of the substituents of the Michael acceptor and catalyst to achieve the favorable orientation of the reagents. Hence, it was concluded that the sulfa-Michael addition was a crucial step determining the overall stereoselectivity, in which generation of the C-S bond in a selective manner greatly influenced the further aldol reaction, with the assistance of intramolecular hydrogen bond between enol and the aldehyde. Our KS-DFT calculations also helped to decipher the factors hampering the stereoselectivity of the reaction applying thiosquaramide **C14.** Based on the elaborated stereochemical model it was devised that the application of the latter in a catalytic cycle essentially reduces the interactions of the catalyst with the ketone and directs the reaction to perform without the assistance of catalyst.

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Keywords: Organocatalysis • Asymmetric catalysis • Tetrahydrothiophenes • Squaramides • Density functional calculations

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[18] The oxidation of the sulfur into the sulfoxide performed and attempts to the gentle synthesis of sulfoximine in A. Tota, M. Zenzola, S. J. Chawner, S. St John-Campbell, C. Carlucci, G. Romanazzi, L. Degennaro, J. A. Bull, R. Luisi, *Chem. Comm.* **2017**, *53*, 348–351, fizzled out. It was assumed that the triple bond present in the final adduct nearby the sulfur atom was the main reason for the failure.

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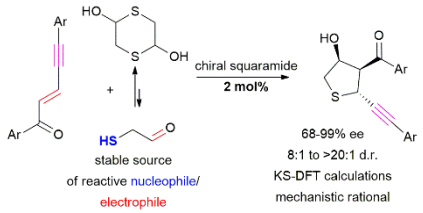

Tetrahydrothiophenes with three contiguous stereocenters and contained three reactive functionalities were formed with high stereoselectivities in sulfa-Michael/intramolecular aldol reactions cascade