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Stereoselective thia-Michael 1,4-Addition to Acyclic 2,4-Dienones and 2-En-4-ynones

Rafał Kowalczyk[a,*] and Przemysław J. Boratyński[a]

[a] Department of Organic Chemistry, Wrocław University of Technology, 50-370 Wrocław, Poland
Fax: (+48)-713202427; Phone: +4871 3203302; e-mail: rafal.kowalczyk@pwr.wroc.pl

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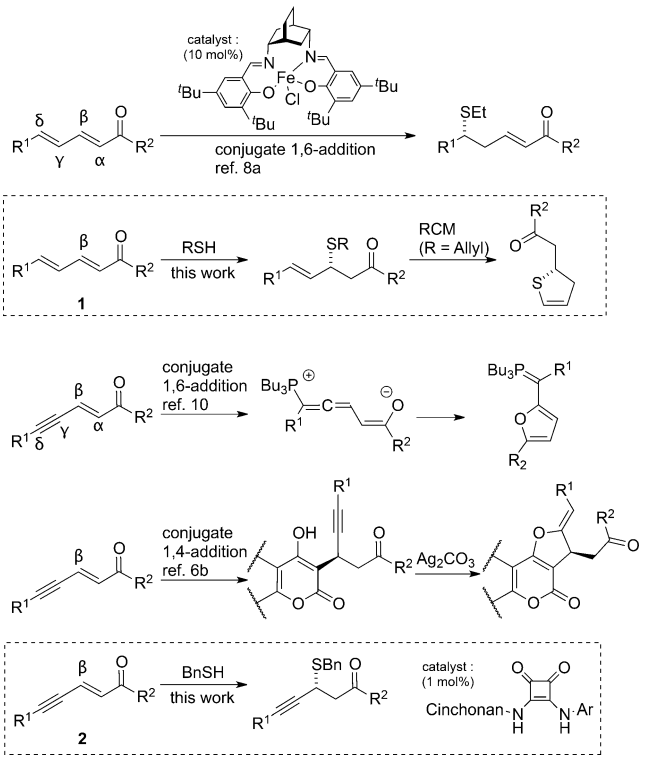
Abstract: Organocatalyzed highly stereoselective 1,4-thia-Michael addition of mercaptans to linear 2,4-dienones and 2-en-4-ynones was developed using *Cinchona* alkaloid-based squaramides. Application of only 0.5–1 mol% loading afforded products in up to 98:2 e.r. and above 99:1 after a single recrystallization. The adducts of allyl mercaptan can be conveniently further transformed to new chiral 2-substituted 2,5-dihydrothiophenes by ring-closing metathesis.

Keywords: conjugate addition; dienones; enynones; organic catalysis; squaramides; thia-Michael addition

Introduction

The enantioselective thia-Michael reaction, that is, addition of thiols to α,β-unsaturated carbonyl compounds, is one of the most valuable synthetic methods in organosulfur chemistry.[1] Products of this transformation include many biologically active compounds and top-selling medicines.[2] Although the use of simple Michael acceptors is now well-established,[3] the reactions of multiply functionalized analogues remain challenging.[4] For example, additions to α,β,γ,δ-diunsaturated carbonyl compounds are expected to produce allylic sulfides[5] that could serve as attractive intermediates in targeted synthesis (Scheme 1). Nevertheless, there are few reported applications of such reactions.[6] The extension of the π-system of the Michael acceptor with an additional double or triple bond comes at the cost of ambiguous regioselectivity, and may be beyond the scope of asymmetric catalysts routinely used for simple acceptors.

In acyclic conjugated dienone **1**, the presence of a substituent at the end of the π-system (i.e., R^1 is different than a hydrogen atom in Scheme 1) generally renders 1,6-addition unfavorable.[7] It was only recently shown, that the use of a specially tailored iron(III)-salen complex could provide such regioselectivity.[8] On the other hand, conjugated ynenone **2** was shown to react with strongly nucleophilic thiophenol[9] or even phosphines[10] at the end of the conjugated system, despite the substitution (Scheme 1). Also possible is a non-selective reaction producing an undesired mixture of regioisomers. So far there are no reported examples of enantioselective 1,4-additions of thiols to either **1** or **2**.



Scheme 1. Conjugate 1,4- and 1,6-Michael additions to **1** and **2** and subsequent reactions of the products.

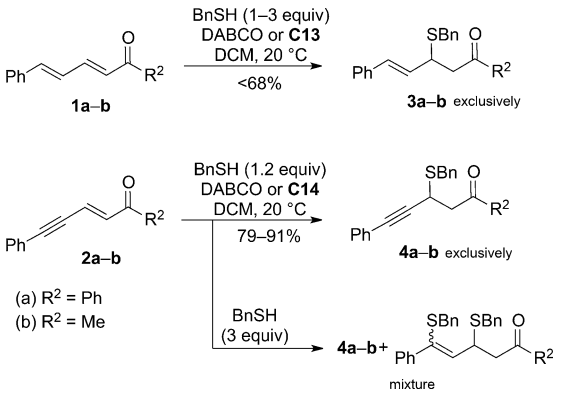
In this paper we describe organocatalyzed Michael 1,4-addition to carbonyl compounds of extended conjugate π-systems **1** and **2**. Also we aim to prove the utility of the adducts of allyl mercaptan to **1** in further modifications.

Results and Discussion

Additions of benzyl thiol to Michael acceptors with two conjugated double bonds (**1**) or a triple and double bonds (**2**) were studied. Initial experiments showed that reactions of both acceptors catalyzed either by simple bases or bifunctional organocatalysts proceeded solely toward 1,4-addition. However, the two extended Michael acceptor classes **1** and **2** differ significantly in terms of reactivity. Diene **1a** is much less reactive than simple acceptors. In a competitive experiment the transformation of **1a** was approximately 5 times slower than that of chalcone. Also the conversion of **1a** was never complete, and in a typical reaction an excess of thiol was required to obtain an acceptable yield. In contrast, the yn-ene **2a** was significantly more reactive providing consistently near complete conversions.

In a competitive experiment monitored by NMR, an equimolar mixture of **1a** and **2a** was treated with a half equivalent of benzyl mercaptan in the presence of a bifunctional squaramide catalyst. Nearly exclusive addition to **2a** was observed within 24 h.[11] The addition to **1a** remaining in the mixture was observed after applying an excess of thiol. The differences in site selectivity between Michael acceptors **1** and **2** were also demonstrated in response to a varying excess of benzyl mercaptan. Less active dienone **1** reacted in a 1,4-mode regardless of the amount of nucleophile, while the outcome of addition to ynenone **2**[9] was strongly dependent on the quantity of thiol (Scheme 2). When used in three-fold excess, the mercaptan reacts unselectively,[12] forming an inseparable mixture of mono and di-addition products as confirmed by NMR and ESI-MS. Nevertheless, at lower excess of the mercaptan the reaction remained highly selective, and only the 1,4-adduct was formed. The preferential attack of benzyl mercaptan at the β-position (double bond) but not at the δ-position (triple bond) in **2** may be ascribed to the differences in polarizability between these units. The alkene is more polarizable compared to the alkyne, and the proximity of the alkene to the carbonyl group results in greater inductive activation.

Several chiral organic catalysts were screened in the reaction. Chalcones as well as cyclic dienones undergo addition of benzylthiol with high enantioselectivity using covalent catalysis (iminium ion catalysis).[13] However, this strategy provided only poor enantioselectivity for the transformations of both **1** and **2**. Nevertheless, much better stereocontrol was achieved for bifunctional catalysts possessing both a hydrogen-bond donor and tertiary amine. Out of the assayed catalysts (Figure 1, Table 1) the *Cinchona* alkaloid-derived squaramides[14] were particularly effective for both additions to **1** and **2**. The structurally related thioureas as well as catalysts of a different chiral scaffold were less selective. However, variation in the achiral amide residue in squaramides **C7**–**C10** did not influence the stereochemical outcome of the reaction leading to almost the same enantioselectivity as **C6**. This was confirmed for both electron-rich and



Scheme 2. Base and organocatalyzed conjugate addition to **1** and **2**

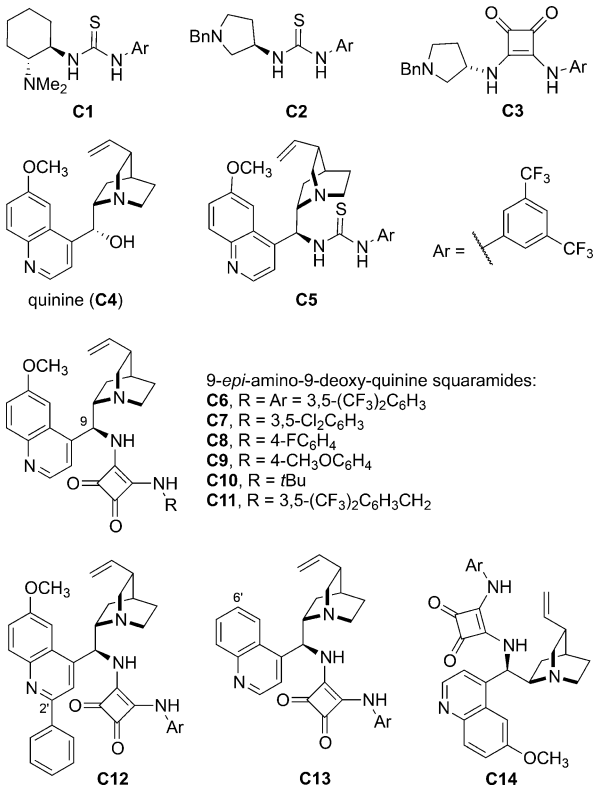
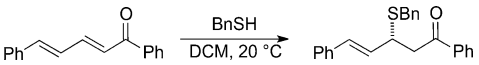


Figure 1. Organocatalysts

Table 1. Catalyst screening for addition of benzyl mercaptan to **1** and **2**[a]

Entry	Catalyst	Loading	Yield (%)[b]	e.r.[c]
				
1	**C1**	10 mol%	88	26:74[d]
2	**C2**	10 mol%	14	55:45
3	**C3**	10 mol%	n.d.[e]	79:21[d]
4	**C4**	20 mol%	89	42:58[d]
5	**C5**	10 mol%	n.d.[e]	70:30
6	**C6**	1 mol%	82	93:7
7	**C7**	1 mol%	54	94:6
8	**C8**	2 mol%	40	93:7
9	**C9**	2 mol%	47	93:7
10	**C10**	2 mol%	51	93:7
11	**C11**	5 mol%	n.d.[e]	50:50
12	**C12**	2 mol%	61	88:12
13	**C14**	1 mol%	68	7:93
14	**C13**	5 mol%	61	95:5
15	**C13**	1 mol%	70	96:4
				
16	**C1**	5 mol%	99	70:30
17	**C5**	5 mol%	81	70:30
18	**C6**	5 mol%	43	22:78
19	**C6**	1 mol%	92	13:87
20	**C7**	5 mol%	90	11:89
21	**C8**	5 mol%	85	11:89
22	**C9**	5 mol%	99	13:87
23	**C10**	5 mol%	99	14:86
24	**C11**	5 mol%	92	37:63
25	**C12**	5 mol%	99	16:84
26	**C13**	5 mol%	84	7.5:92.5
27	**C14**	5 mol%	99	94:6
28	**C14**	1 mol%	90	94:6
29	**C14**	1 mol%	86	97.5:2.5[d]

[a] Reaction was performed in a 0.3–0.25 mmol scale applying 1.2–1.5 equiv of benzyl mercaptan in dichloromethane (0.1 M) for 20 h at r.t.
[b] After column chromatography.
[c] Determined by HPLC.
[d] Reaction run in toluene.
[e] Not determined.

electron-poor aryls, as well as a *tert*-butyl group. Nevertheless, with one particular flexible residue (3,5-bistrifluoromethylbenzylamine) in **C11**, the reactions gave racemic or nearly racemic products.

Modification of the *Cinchona* alkaloid residue at the 2′-position of quinoline ring was previously reported to improve catalyst efficiency.[15] However, such modification in **C12** only deteriorated the enantioselectivity in the reactions of **1** and **2**.

Both antipodes of addition products were obtainable through proper choice of catalyst diastereomer. Application of quinidine- and quinine-based catalysts **C14** and **C6** gave different enantiomers of products in similar enantioselectivity.

The enantioselectivities of the reactions of **2** were more affected by small variations in the structure of catalyst than that of **1**. The highest *ee* in addition to **2** was achieved with the catalyst **C14** having a quinidine core. On the other hand, reaction of **1** was best catalyzed by a cinchonidine-derived **C13**.

The influence of catalyst loading was examined for the two most effective catalysts **C13** and **C14**. The model reaction of benzyl mercaptan and diene **1a** catalyzed by **C13** revealed that 1 mol% of the catalyst in dichloromethane led to the product in good yield and 92% *ee*. Surprisingly, an increase in loading led to worse results. Interestingly, 0.5 mol% of squaramide **C13** gave adduct **3a** with better *ee* (93%), at the cost of fairly diminished yield (56%). Further decrease in loading to 0.2 mol% resulted in a decline of both the yield (30%) and *ee* (86%).[11] Also, lowering the temperature to −20 °C led to an unexpected deterioration of stereoselectivity down to 66% *ee* and seriously affected the yield (23–29%). Similar effects of catalyst loading on the stereochemical outcome of reaction were noted for acceptor **2a**.

In general, the use of 1 to 2 mol% of catalysts **C13** and **C14** provided optimum results in terms of yield and *ee*. The observation that higher catalyst concentrations induced deterioration of their efficiency suggests significant self-association of the catalyst. However, it turned out that the reactions were affected by the choice of solvent only to a minor extent. Among several tested solvents, the best results were achieved by application of dichloromethane for **1a** and toluene for **2a** (Table 1, entry 29, Tables S1-S2, SI).

The optimized conditions were used to evaluate the scope of sulfur nucleophiles in the Michael addition to acceptors **1a** and **2a** (Figure 2). Several benzyl mercaptans and allyl thiol reacted with diene **1a** and afforded products in good yield and enantiomeric ratios close to 95:5. The highest selectivity (97% *ee*) was achieved for *tert*-butylbenzyl mercaptan. Substitution of the benzene ring in the mercaptan did not interfere with the yield or stereochemical outcome through steric interactions, as exemplified by the reactions of a few *ortho*-substituted benzyl mercaptans. On the other hand, the presence of electron-donating substituents, such as in 4-methoxybenzyl mercaptan led to a significant decrease in the yield, but not enantioselectivity (91% *ee*). These results suggest that the retro-addition of electron rich mercaptans to **1a** may be a serious limitation. Also, no product was isolated in the reaction of **1a** and lauryl mercaptan. On the other hand, the use of aromatic thiols was detrimental for the enantioselectivity. Thiophenol and **1a** gave addition products in e.r. of up to 73:27. It is noteworthy that other *Cinchona* alkaloids and their dimeric ethers, provided even lower degree of enantioselectiv-

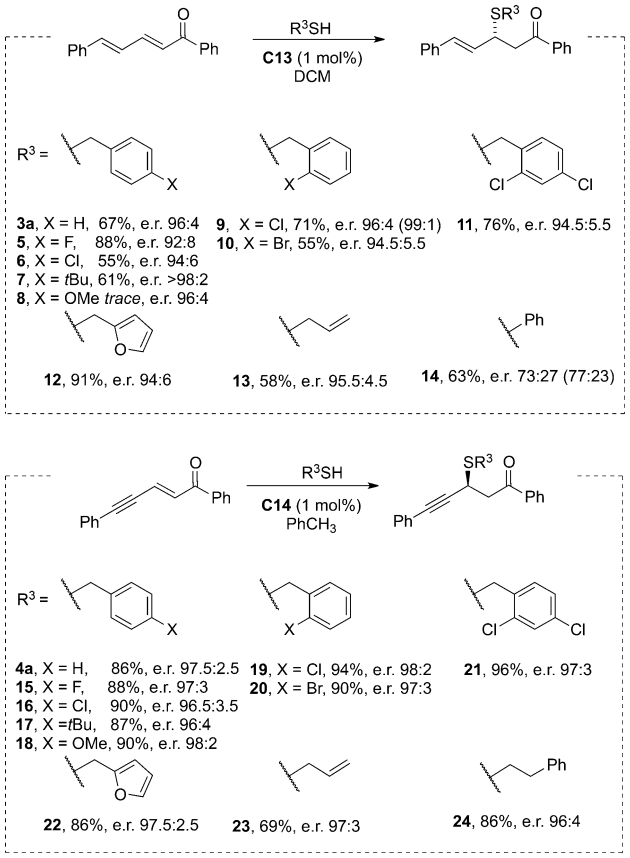


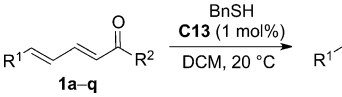
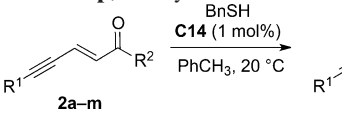
Figure 2. Scope of the thiols in the reaction with acceptors **1a** and **2a** catalyzed by **C13** and **C14**, respectively. Values in parentheses correspond to e.r. after a single recrystallization.

ity (up to 34:66 e.r. for the $(DHQ)_2AQN$), despite their successful applications in addition of thiophenol to simple chalcones.[16] In contrast the reaction of this thiol with more reactive acceptors **2** resulted in nearly racemic products (9% *ee* for **2d**). The marked differences in enantioselectivity obtained for aliphatic mercaptans and aromatic thiols were reported previously for other types of Michael acceptors as well.[17]

In general, the thia-Michael reaction of the tested mercaptans with acceptor **2a** occurred with high enantioselectivity regardless of the nucleophile's structure. The greater reactivity of this acceptor resulted in efficient transformations even using mercaptans unreactive with **1a**, that is, 4-methoxybenzyl mercaptan and 2-phenylethane thiol. Also, better yields of the adducts were obtained in comparison to the corresponding reactions of dienone **1a**. However, the lower yields achieved for acceptors **1** are to some extent attributable to the difficulty in separating the products from unreacted starting material.

In an attempt to better understand the nature of the interactions between the Michael acceptor and the catalyst, a series of analogues of **1** and **2** were obtained with different groups at the ends of the π-systems, that is, at the carbonyl group and at the δ-positions. The acceptors were tested in the addition of benzyl mercaptan under previously optimized conditions for **1a** and **2a** (Table 2). In all the studied cases only the 1,4-addition products were formed. The nature of the substituent at the δ-position had no noticeable effect on the reaction outcome. Small but

Table 2. Scope of Michael acceptors[a]

Entry	Acceptor, R^1, R^2		Yield (%)[b]	e.r.[c]
	 **1a–q**	BnSH, **C13** (1 mol%), DCM, 20 °C → **3a–q**		
1	**1a**, Ph	Ph	67	96:4
2	**1c**, Ph	4-FC_6H_4	51	93:7
3	**1d**, Ph	4-ClC_6H_4	59	97:3
4	**1e**, Ph	4-$CH_3C_6H_4$	51	97:3
5	**1f**, Ph	4-$MeOC_6H_4$	57	91:9
6	**1g**, Ph	4-PhC_6H_4	51	97:3(99:1)
7	**1h**, Ph	2-naphthyl	73	96:4(99:1)
8	**1i**, Ph	3-$NO_2C_6H_4$	65	95:5
9	**1j**, Ph	2-$NO_2C_6H_4$	61	89:11
10	**1k**, Ph	2-ClC_6H_4	44	92:8
11	**1l**, Ph	2-BrC_6H_4	77[d]	90:10
12	**1m**, Ph	2-thienyl	64	95:5
13	**1b**, Ph	CH_3	15[e]	90:10
14	**1n**, 4-ClC_6H_4	Ph	81	95.5:4.5
15	**1o**, 2-$NO_2C_6H_4$	Ph	73	92:8
16	**1p**, 2-furyl	Ph	88[d]	95:5
	 **2a–m**	BnSH, **C14** (1 mol%), $PhCH_3$, 20 °C → **4a–m**		
17	**2a**, Ph	Ph	86	97.5:2.5
18	**2c**, Ph	4-FC_6H_4	92	98:2
19	**2d**, Ph	4-ClC_6H_4	95	98:2
20	**2e**, Ph	4-BrC_6H_4	99	96:4
21	**2f**, Ph	4-$NO_2C_6H_4$	74	96:4
22	**2g**, Ph	4-$MeOC_6H_4$	72	97:3
23	**2b**, Ph	CH_3	43[f]	22:78
24	**2h**, 4-FC_6H_4	Ph	94	98:2
25	**2i**, 4-ClC_6H_4	Ph	94	98:2
26	**2j**, 2-ClC_6H_4	Ph	54	96.5:3.5
27	**2k**, 2-naphthyl	Ph	99	98:2
28	**2l**, 2-thienyl	Ph	97	96:4
29	**2m**, *n*Bu	Ph	88	97:3

[a] Reaction was performed using 1 mol% of catalysts in a 0.25–0.3 mmol scale applying 1.2–1.5 equiv of benzyl mercaptan for 20 h at r.t.
[b] After column chromatography.
[c] Determined by HPLC. Values in parentheses correspond to e.r. after single recrystallization.
[d] Reaction run with 3-fold excess of thiol.
[e] Catalyzed by **C6**.
[f] Performed using 5 mol% of **C6**.

visible differences were observed for compounds with differently substituted aryl groups adjacent to the carbonyl. Poorer enantioselectivities were obtained for *ortho*-substituted derivatives of **1**. However, particularly worse results in terms of both the yield and enantioselectivity were obtained for alkyl-substituted carbonyl derivatives **1b** and **2b**.

Interestingly, no deterioration of stereoselectivity was observed when a mixture of isomers (*Z* and *E*) of Michael acceptor **2** was applied, compared to purely *E* material. Notably, reaction of (*E*)-**2f** gave the product with 92% *ee*, while the mixture of isomers (*E*/*Z* 9:1 by NMR) subjected to an analogous reaction led to the same product with identical yield and 94% *ee*. These results most likely stem from the reversibility of the addition. The stereoconvergence of the reaction alleviates the need for the isomeric purity of Michael acceptors, and makes the transformation practical even for reactants for which isomers are too difficult to separate (e.g., **2m**). In contrast, the additions of mercaptans to unsymmetrically substituted fumarate and maleate gave enantioenriched and racemic products, respectively.[4b]

A single recrystallization of some adducts resulted in an enhancement of optical purity, providing samples of e.r. close to 99:1. As a further extension of the studied reactions, we developed an alternative protocol for the reactions of dienones. The troublesome purification step *via* column chromatography was replaced with a brief filtration through a plug of silica gel to remove catalyst, and subsequent recrystallization from methanol. For compound **3g**, the crystalline product was obtained in 99:1 e.r. and 78% yield. However, the same reaction mixture processed through standard column chromatography (requiring careful separation from unreacted starting material) gave the product in only 51% yield and 97:3 e.r.

The structures of all the products were confirmed in NMR experiments. The crystals of **3g** (obtained using catalyst **C13**) undergo reversible phase transition observed in DSC between 17 and 21 °C. In an X-ray study at 300 K the asymmetric unit of $P2_1$ space group contained one molecule in the asymmetric part. At a lower temperature the crystals changed and the unit cell volume nearly quadrupled. Based on the X-ray diffraction data at 300 K the (*R*)-configuration for the product **3g** was assigned unequivocally (Figure 3) with an appropriate value of Flack parameter (−0.04(8)). Tentatively, the same configuration was ascribed to all the dienone adducts, and the (*S*)-configuration to the en-ynones adducts catalyzed by the pseudoenantiomeric catalyst **C14**.

The configuration observed in the X-ray structure is consistent with the stereochemical outcomes observed for simple Michael acceptors and similar catalysts. The catalyst most likely forms hydrogen bonds with the ketone group of the Michael acceptor while

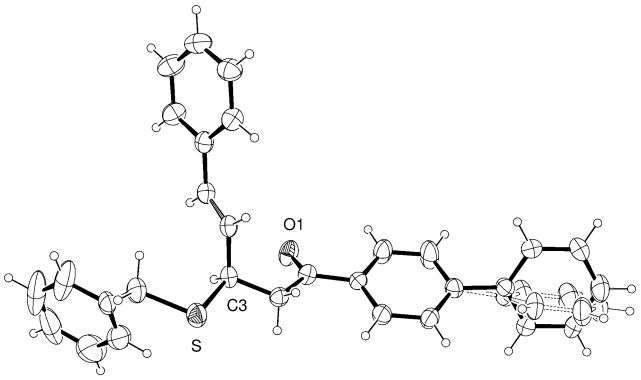


Figure 3. X-ray structure of **3g**. Ellipsoids are set at 30% probability, the terminal ring of biphenyl group is disordered equally between two positions.[18]

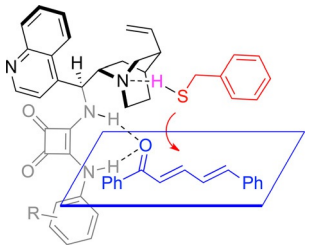


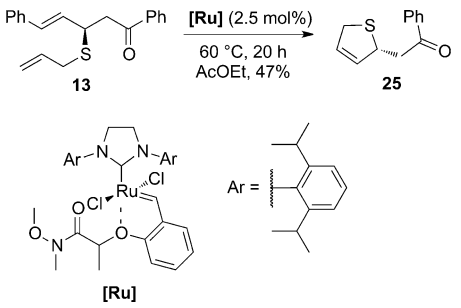
Figure 4. Plausible approach of the nucleophile to **1a** (for a computational approach, see Figure S3, SI)

the basic center of the quinuclidine directs the approach of the nucleophile (Figure 4).[14]

The products of stereoselective monoadditions to acceptors **1** and **2** have a remaining double or triple bond. Extra functionalities could be introduced with a proper choice of nucleophile. Also, the nucleophilic sulfur atom in sulfides is known to coordinatively promote ruthenium-catalyzed metathesis reaction[19] and is tolerated in palladium-catalyzed transformations.[20] As a result the products are prone to further modifications. Consequently, the synthetic utility of obtained allyl sulfides was exemplified in an intramolecular ring-closing methathesis reaction. The adduct of allyl mercaptan was transformed to a chiral 2-substituted dihydrothiophene[19b,21] in modest yield (Scheme 3). Among the tested RCM catalysts, a modified Hoveyda–Grubbs catalyst (Green-cat)[22] offered the best yield of the cyclic product. The reaction operated in commercial grade, non-degassed ethyl acetate with full substrate conversion. The catalyst was easy to remove from the crude reaction mixture.

Conclusions

We have developed catalytic systems for asymmetric 1,4-thia-Michael addition of mercaptans to challeng-



Scheme 3. RCM reaction of adduct **13**

ing acceptors such as electron poor, conjugated dienones and en-ynones. Bifunctional catalysis based on *Cinchona* alkaloid squaramides facilitated the reaction of dienones by hydrogen-bonding, but also assured regioselectivity in the addition to ynenones leading exclusively to β-adducts. As little as 0.5–1 mol% of squaramide catalysts provided very good enatioselectivity at room temperature. Moreover, a single recrystallization of a few solid products led to further enantiomeric enrichment. Together with iron(III)-salen complexes,[8a] squaramides **C13** and **C14** offer access to all possible adducts to linear dienones in a highly regio- and stereoselective manner. The obtained products, still possessing reactive unsaturated bonds, can undergo further transformations including ring-closing metathesis.

Experimental Section

A solution of catalyst **C13** or **C14** (1.0 mol%) and acceptor **1** or yn-enone **2** (0.3 mmol for **1** and 0.25 mmol for **2**) in dichloromethane or toluene (0.1 M) was stirred at r.t. for 15–20 min. Then a solution of thiol (1.2–1.5 equiv) in the same solvent (0.6 M) was added dropwise and the resulting homogenous mixture was stirred for 20 h at r.t. The reaction mixture was then diluted with about an equal volume of chloroform and passed through a plug of silica gel (5–10 g). Elution by a total volume of 100 mL chloroform afforded crude product, which was further purified using column chromatography (silica gel, hexanes/AcOEt, 15:1, v/v). Enantiomeric excess was determined using HPLC on chiral stationary phase (AD-H, OD-H).

Acknowledgements

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