

5-Mercaptotetrazoles as Synthetic Equivalents of Nitrogen-Containing Functional Groups. The Case of the Organocatalytic Enantioselective aza-Michael Reaction

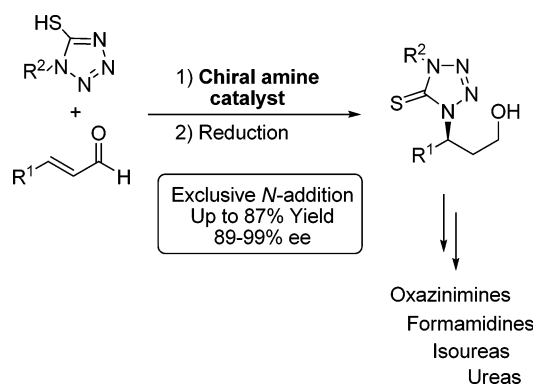
Uxue Uribe, Efraím Reyes, Jose L. Vicario,* Dolores Badía, and Luisa Carrillo

Departamento de Química Orgánica II, Facultad de Ciencia y Tecnología, Universidad del País Vasco/Euskal Herriko Unibertsitatea, P.O. Box 644, E-48080 Bilbao, Spain

jose Luis.vicario@ehu.es

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ABSTRACT



5-Mercaptotetrazoles have been identified as useful and versatile Michael donors in enantioselective amine-catalyzed aza-Michael reactions with α,β -unsaturated aldehydes, showing excellent behavior as N-nucleophiles instead of their usual trend to react as S-nucleophiles. In addition several unprecedented chemical modifications on the tetrazolothione moiety have been carried out leading to the enantioselective preparation of different compounds incorporating nitrogen-containing functionalities such as oxazinimines, formamidines, ureas and isoureas.

The aza-Michael reaction is a fundamental transformation for the stereoselective preparation of nitrogen-containing chiral compounds, and as a consequence of this, many different catalytic enantioselective approaches have been developed,¹ most of them involving metal catalysis.^{1b} Alternatively, a particularly interesting approach is related to the use of chiral amines as catalysts in Michael-type reactions because of their ability to activate α,β -unsaturated aldehydes or ketones toward conjugate addition by the

reversible formation of an iminium ion.² However, while a variety of chiral amine catalysts have been explored for the conjugate addition of different types of nucleophiles to enals or enones, the aza-Michael reaction has remained significantly less developed.³ The main reason for this is associated with the additional chemoselectivity issues that have to be

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controlled in this case because both the catalyst and the Michael donor are primary or secondary amine species. Moreover, the reversibility of the reaction is an additional problem which often leads to the low configurational stability of the final aza-Michael adducts.

In this context, after the first pioneering report by MacMillan involving the use of *N*-silyloxycarbamates as nucleophiles,⁴ only a few number of other amine-catalyzed enantioselective aza-Michael reactions have been reported, most of them integrated into cascade processes, in which a subsequent intramolecular reaction occurs avoiding the retro-addition.⁵ In fact, only a few examples can be found in which a pure intermolecular aza-Michael reaction has been carried out,⁶ which include the one initially developed by MacMillan⁴ and other later examples by Jørgensen,⁷ our group,⁸ and two others⁹ using nitrogen heterocycles as *N*-nucleophiles. However, an important drawback of all the later methodologies is the lack of reactivity of the nitrogen heterocycle incorporated as the nucleophile, which makes the obtained adducts not suitable for their transformation into other chiral building blocks, consequently limiting the applicability of these methodologies in organic synthesis. On the other hand, while *N*-silyloxycarbamates have shown to perform well in this kind of chemistry, these are not commercially available and have to be prepared from the corresponding *N*-protected hydroxylamines.

With all these precedents in mind, we turned our attention to the possibility of employing 5-mercaptotetrazoles as suitable *N*-nucleophiles in enantioselective aza-Michael reac-

tions with α,β -unsaturated aldehydes using a chiral secondary amine as a catalyst (Figure 1). On one hand, it was envisaged

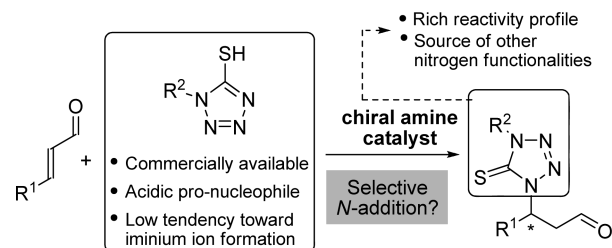


Figure 1. 5-Mercaptotetrazoles as Michael donors in organocatalytic conjugate additions under iminium activation.

that the tetrazolothione moiety incorporated at the final aza-Michael products could show an interesting reactivity profile which would allow its conversion into compounds with different nitrogen-based functionalities by means of an unprecedented process involving reductive N–N bond cleavage, developed in our laboratories and presented herein. In addition, many members of this family of compounds are cheap and commercially available reagents and are also highly acidic compounds which guarantee the formation of a reactive anionic species in the reaction medium under the neutral or slightly basic reaction conditions associated with iminium catalysis.

It should also be noted that the ambident nucleophilic nature of these 5-mercaptotetrazoles might also lead to the formation of two products arising from the *N*- and the *S*-addition pathways and therefore the chemoselectivity of the reaction constitutes a relevant issue to be considered, which implies that conditions had to be found that allowed controlling the selectivity of the addition toward the formation of the desired *N*-addition product vs the undesired *S*-addition pathway, which is on the other hand the usual behavior of 5-mercaptotetrazoles when employed as nucleophiles.

Our studies began with the identification of the best catalyst and reaction conditions for this transformation (Table 1). We also decided to carry out the *in situ* reduction of the aza-Michael adduct in order to prevent racemization during the purification.¹⁰ We started using MacMillan catalyst **3a** under the conditions previously employed by us before,⁸ but no aza-Michael reaction product was observed (entry 1), even though we isolated small amounts of *S*-adduct **5a** (31% yield).¹¹ Running the reaction at $-30\text{ }^{\circ}\text{C}$ resulted in an unselective process with the preferential formation of **5a** and obtaining the minor *N*-adduct **4a** with very low enantioselectivity (entry 2). Alternatively, we evaluated the use of diarylprolinol derivatives **3b–d** as catalysts which, in general, resulted in a highly chemoselective reaction favoring

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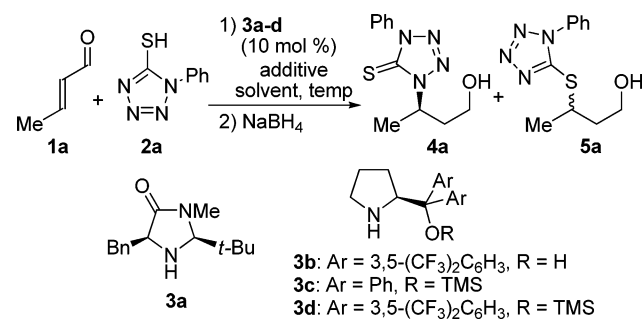
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(10) All aza-Michael products were found to be configurationally unstable, undergoing fast racemization upon standing at rt.

(11) In all cases in which the *S*-adduct **5a** was isolated, it was obtained as a racemic mixture.

Table 1. Screening for the Best Reaction Conditions

entry	catalyst	additive	solvent	temp (°C)	yield 4a 4a/5a ^c	ee 4a (%) ^d
1	3a	TFA ^a	EtCN	-78	n.d. ^e	<5
2	3a	TFA ^a	EtCN	-30	1:1.5	35
3	3b	PhCO ₂ H ^b	Toluene	-30	>10:1	45
4	3c	PhCO ₂ H ^b	Toluene	-30	>10:1	57
5	3d	PhCO ₂ H ^b	Toluene	-30	>10:1	76
6	3d	PhCO ₂ H ^b	Toluene	-40	>10:1	78

^a 10 mol % of TFA was used. ^b 20 mol % of PhCO₂H was used. ^c Determined by NMR analysis of crude reaction mixture. ^d Calculated by chiral HPLC analysis (see Supporting Information). ^e n.d.: not determined.

the *N*-addition pathway (entries 3–6). For this kind of catalysts, PhCO₂H was used as a Brønsted acid cocatalyst to assist the formation of the intermediate iminium ion. The use of OH-containing catalyst **3b** led to **4a** in moderate yield and low ee (entry 3), while the reaction using the *O*-TMS derivative **3c** provided the addition product in better yield and with improved enantioselectivity (entry 4). Importantly, a more enantioselective reaction was observed using catalyst **3d** which incorporates bulkier aryl substituents (entry 5). Finally, the enantioselectivity of the process could be further improved up to 91% by carrying out the reaction at a slightly lower temperature (entry 6).

Having established the best protocol for the reaction, we extended this methodology to a series of α,β -unsaturated aldehydes and 5-mercaptotetrazoles with different substituents (Table 2). As Table 2 indicates, the reaction showed to have a broad substrate scope regarding the substituent both at the α,β -unsaturated aldehyde and at the mercaptotetrazole reagent, obtaining a wide variety of reduced aza-Michael compounds **4a–u** with excellent yields and, remarkably, as single regioisomers in all the cases. In addition, the reaction proceeded with excellent enantioselectivity for all substrates tested, furnishing the final compounds **4a–u** as highly enantioenriched compounds.

It is to be noted that β -aryl substituted enals could also be used as substrates furnishing excellent levels of enantiocontrol, although in these cases yields were highly dependent on the electronic nature of this β -aryl substituent (entries 19–21). The use of these particular α,β -unsaturated aldehydes required a lower temperature (–60 °C) in order to achieve high enantiocontrol and also the use of the more reactive LiBH₄ for the subsequent reduction step. It is to be

Table 2. Scope of the Reaction^a

entry	compd	R ¹	R ²	yield(%) ^b	ee(%) ^c
1 ^d	4a	Me	Ph	78	91
2	4b	Et	Ph	79	90
3	4c	<i>n</i> -Pr	Ph	76	94
4	4d	<i>i</i> -Pr	Ph	74	94
5	4e	<i>n</i> -Bu	Ph	77	90
6	4f	<i>n</i> -C ₅ H ₁₁	Ph	78	90
7	4g	<i>n</i> -C ₆ H ₁₃	Ph	77	89
8	4h	<i>n</i> -C ₈ H ₁₇	Ph	67	90
9	4i	Z-EtCH=CHCH ₂ CH ₂	Ph	50	92
10	4j	CO ₂ Et	Ph	67	89
11	4k	Me	PMP	74	92
12	4l	Et	PMP	74	95
13	4m	<i>n</i> -Bu	PMP	73	94
14	4n	<i>n</i> -C ₆ H ₁₃	PMP	77	94
15	4o	CO ₂ Et	PMP	81	94
16	4p	Et	Me	71	97
17	4q	<i>n</i> -Bu	Me	87	98
18	4r	CO ₂ Et	Me	51	92
19 ^e	4s	Ph	PMP	51	94
20 ^e	4t	<i>p</i> -NO ₂ C ₆ H ₄	PMP	39	99
21 ^e	4u	<i>p</i> -FC ₆ H ₄	PMP	53	96

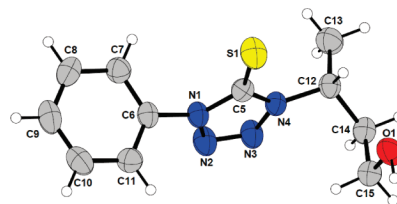
^a Reactions were carried out in a 0.5 mmol scale of **1** using 10 mol % of catalyst **3d** and 20 mol % of PhCOOH in 2.0 mL of toluene. ^b Isolated yield; only formation of the *N*-addition product was observed in all cases.

^c Determined by chiral HPLC (see Supporting Information for details).

^d Reaction was carried out at –40 °C. ^e Reaction was carried out at –60 °C and LiBH₄ was used as reducing agent.

noted that β -aryl substituted enals have been found to be elusive substrates in other reported amine-catalyzed enantioselective aza-Michael reactions.^{4,7–9}

For compound **4a**, which had been obtained in 91% ee, we were also able to grow crystals suitable for single-crystal X-ray analysis (Figure 2).¹² This allowed us to establish the

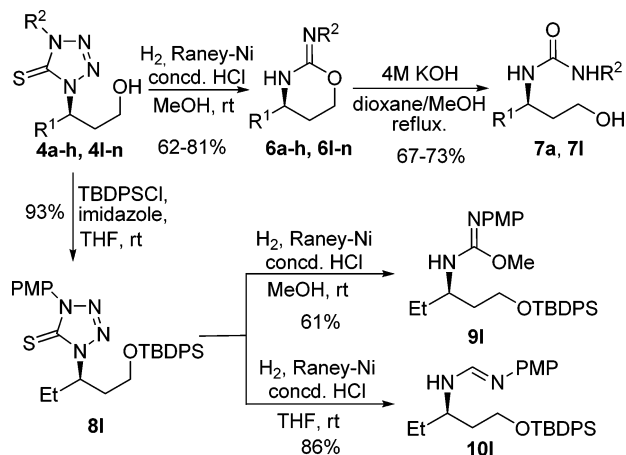
**Figure 2.** X-ray structure of compound **4a**.

absolute configuration for the stereocenter that had been generated in the conjugate addition reaction as **3R** in **4a**. According to the stereostructure obtained for this compound, the configuration of all other adducts **4b–u** was established by analogy. This absolute configuration is in good agreement

with the sense of enantioinduction exerted by catalyst **3d** and related ones in other conjugate addition reactions to α,β -unsaturated aldehydes.¹³

The ability of the tetrazolothione substructure to undergo chemical modification was next surveyed (Scheme 1). In this

Scheme 1. Survey of Transformations Carried out on Adducts **4**



context, we initially found that treating a representative family of adducts **4** with H_2 in the presence of Raney-Nickel and HCl led to the formation of 1,3-oxazin-2-imines **6** in good yields (see Scheme 1 and Supporting Information). This unprecedented reaction consisted of the hydrogenolytic cleavage of the tetrazole moiety leading most likely to the formation of a thiourea intermediate, which subsequently would be ready to undergo intramolecular reaction with the free OH group. This transformation exhibited a remarkable substrate scope, proceeding smoothly with a variety of differently substituted representative substrates. We could also access ureas **7a** ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) and **7l** ($R^1 = \text{Et}$, $R^2 = \text{PMP}$) from 1,3-oxazinimines **6a** and **6l** respectively by simple base-promoted hydrolysis. In addition, we also

explored other possible transformations to be carried out on these adducts **4** in order to illustrate their potential applications as chiral building blocks in organic synthesis. For example, using adduct **4l** as a model substrate, we found that isourea **9l** was obtained when the hydrogenolytic cleavage was carried out under the same reaction conditions but after protection of the primary alcohol moiety, as a result of the intermolecular reaction of the intermediate generated during the reductive cleavage with the solvent. Moreover, and in a noteworthy transformation, when *O*-protected derivative **8l** was treated with H_2 in the presence of Raney-Ni but using THF as solvent, the clean formation of chiral formamidine **10l** was observed, which was explained in terms of the initial formation of the already mentioned intermediate thiourea after the reductive cleavage of the heterocycle, which in this case was unable to undergo the intra- or intermolecular reaction that led to the formation of cyclic oxazinimines **6** or acyclic isourea **9l** and therefore could remain in solution for a sufficient time to participate in a reductive desulfuration process exerted by Raney-Ni.

In summary, we have developed a new procedure for carrying out enantioselective aza-Michael reactions to a wide range of α,β -unsaturated aldehydes using a chiral secondary amine catalyst and 5-mercaptotetrazoles as *N*-nucleophiles. Interesting features of the methodology are (1) the high yields and enantioselectivities obtained, (2) the fact that all reagents employed are commercially available, (3) the exceptional selectivity shown by the mercaptotetrazol reagents to undergo *N*-addition rather than their usual behavior as *S*-nucleophiles, and (4) the ability of the tetrazolothione moiety incorporated at the aza-Michael adducts to undergo an unprecedented reductive ring cleavage which, under different conditions has led to the enantioselective preparation of important reagents in organic and medicinal chemistry such as oxazinimines, formamidines, ureas and isoureas.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) CCDC 782265 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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