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Enantioselective Organocatalytic Conjugate Reduction of β-Azole-Containing α,β-Unsaturated Aldehydes

Thomas J. Hoffman, Jyotirmayee Dash,[†] James H. Rigby,[‡] Stellios Arseniyadis,* and Janine Cossy*

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS, 10 rue Vauquelin, F-75231 Paris Cedex 05, France

stellios.arseniyadis@espci.fr; janine.cossy@espci.fr

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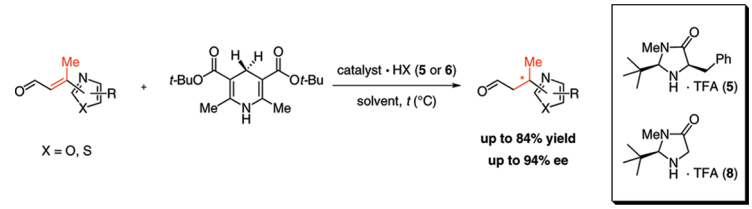
ABSTRACT



β-Azole-containing α,β-unsaturated aldehydes were successfully reduced under highly enantioselective organocatalytic transfer hydrogenation conditions. The products were obtained in good yields and up to 94% optical purity. This simple process was successfully applied to the synthesis of the C7−C14 fragment of ulapualide A, a natural product which exhibits promising antitumor activity.

In recent years, the development of asymmetric hydrogenation processes has been undertaken by several groups in the pursuit of installing chirality onto prochiral alkene scaffolds. In this context, the use of catalytic amounts of transition metals, such as Ru,[1] Rh,[2] or Ir,[3] in conjunction with well-defined chiral ligands, has resulted in a number of attractive and practical protocols, making asymmetric hydrogenation a powerful tool for both industrials and academics. Despite the advantages offered by these processes, they usually suffer from various drawbacks such as the use and storage of hydrogen gas, the need of high catalyst loadings, the toxicity of the catalysts, or the difficulties associated with their removal. With global environmental legislation becoming stricter, sustainable development has been playing an increasingly important role in the strategy of chemical and pharmaceutical industries, allowing enantioselective organocatalysis to emerge as a very promising alternative.[4] Inspired by biological processes which involve specific metalloenzymes that use dihydropyridine-based cofactors, such as nicotinamide adenine dinucleotide (NADH) and flavine adenine dinucleotide ($FADH_2$),[5] to perform highly stereoselective reductions, several research groups have shown that it was possible to replace both the enzymes and the cofactors by small molecule organocatalysts and dihydropyridine analogues.[6] For example, MacMillan et al.[7] showed that

[†] Current address: Department of Chemistry, IISER, Kolkata, India.

[‡] Current address: Department of Chemistry, Wayne State University, Detroit, MI 48202.

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chiral imidazolidinones could, in the presence of Hantzsch esters, catalyze the enantioselective reduction of a wide range of β,β'-disubstituted α,β-unsaturated aldehydes in good yields (up to 95%) and high enantioselectivities (up to 97% ee). Concurrently, List et al.[8] introduced the concept of asymmetric counter anion directed catalysis (ACDC) by developing a highly selective organocatalyst for the asymmetric reduction of enals which consists of an achiral ammonium ion and a chiral phosphate anion derived from 3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (TRIP). Thus, examples of both β,β'-disubstituted enals were reduced in good yields (up to 90%) and excellent enantioselectivities (up to 99% ee).

Interestingly, while these methods have been applied successfully to a wide range of substrates, to our knowledge, there has been no report of an enantioselective organocatalytic transfer hydrogenation applied to β-azole α,β-unsaturated aldehydes of type **I** (Scheme 1). As this motif is present in various natural products of significant biological value, such as myxothiazole Z,[9] calyculin A,[10] and ulapualide A (Figure 1),[11] we were particularly interested in investigating this key transformation which would allow a straightforward access these molecules.

In this paper, we wish to report the results of our endeavor which have led to the first examples of enantioselective organocatalytic transfer hydrogenations applied to β-azole α,β-unsaturated aldehydes (Scheme 1).

This study initially began when synthesizing myxothiazole Z, a secondary metabolite isolated from myxobacteria *Myxococcus fulvus*,[9] which displays interesting antifungal, antibacterial, and anticancer properties.[12,13] Our strategy for the synthesis of myxothiazole Z was similar to the one we have

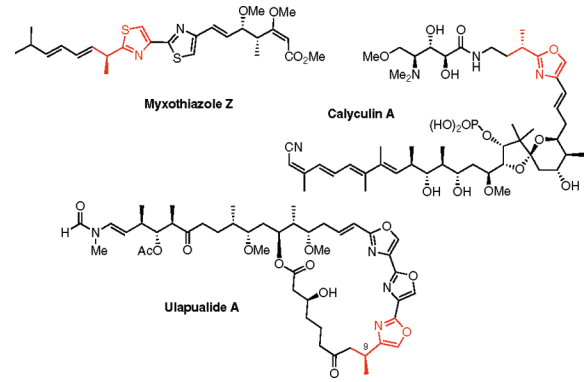
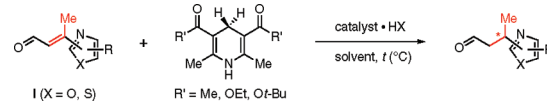


Figure 1. Structure of myxothiazole Z, calyculin A, and ulapualide A.

Scheme 1. Enantioselective Organocatalytic Transfer Hydrogenation of β-Azole-Containing α,β-Unsaturated Aldehydes



previously used to prepare two related natural products: melithiazole C[14] and cystothiazole A.[15] Hence, we planned to employ a cross-metathesis between a vinylthiazole[16] and a β-methoxy acrylate, and a Stille coupling which would allow us to link the two thiazole rings together. Finally, an enantioselective organocatalytic transfer hydrogenation was conceived as a key step to control the stereogenic center at the α-position of the thiazole ring.

With no precedent on such systems, a thorough investigation of the reaction conditions was first undertaken on aldehyde **1**. The results are reported in Table 1.

As depicted, we began by screening two catalysts derived from (*S*)-proline (**3** and **4**). The reactions were typically carried out in $CHCl_3$ at −35 °C using 20 mol % of chiral organocatalyst in combination with 1.2 equiv of either *tert*-butyl or ethyl Hantzsch ester **9** and **10**, or the corresponding methyl ketone **11**, while the selectivities were determined by supercritical fluid chromatography (SFC) analysis after reduction of the aldehyde into the corresponding alcohol with $NaBH_4$.[17]

Our initial attempts using catalysts **3** and **4** resulted, unfortunately, in inefficient and nonselective reductions (Table 1, entries 1−3). In contrast, by switching to imidazolidinone-type

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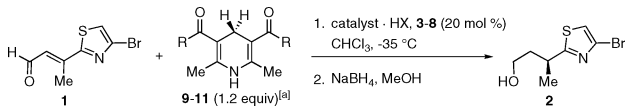
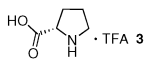
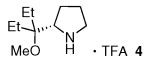
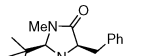
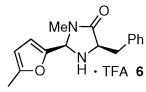
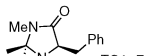
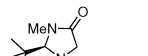
(17) See Supporting Information.

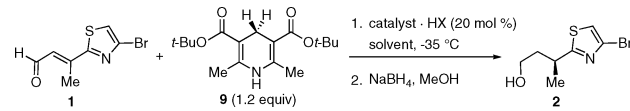
Table 1. Evaluation of the Catalyst on the Enantioselective Organocatalytic Transfer Hydrogenation Reaction

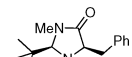
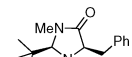
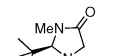
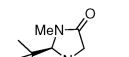
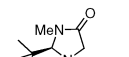
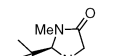


entry	catalyst	hydride donor[a]	time [h]	conversion [%][b]	yield [%][c]	er[d]
1	 · TFA **3**	**9**	24	trace[e]	-	-
2		**9**	24	100[f]	68[f]	57/47[f]
3	 · TFA **4**	**9**	24	NR[e]	-	-
4		**9**	24	trace	-	-
5	 · TFA **5**	**9**	6	100[e]	66[e]	82/18[e]
6		**10**	6	100[e]	88[e]	77/23[e]
7		**11**	24	50[e]	30[e]	65/35[e]
8	 · TFA **6**	**9**	24	NR[e]	-	-
9		**9**	24	100	74	72/28
10	 · TCA **7**	**10**	24	60	21	72/28
11		**11**	24	trace	-	-
12		**9**	12	100	72	92/8
13	 · TFA **8**	**10**	12	100	64	80/20
14		**11**	12	40	24	71/29

[a] Hydride donor: R = O*t*-Bu (**9**), R = OEt (**10**), R = Me (**11**). [b] Conversion determined by crude ^{1}H NMR analysis. [c] Isolated yield. [d] Enantiomeric ratio determined by chiral SFC analysis (ChiralPack AD-H, MeOH). [e] Reaction performed at 0 °C. [f] Reaction performed at rt. TFA = trifluoroacetic acid, TCA = trichloroacetic acid.

Table 2. Evaluation of the Solvent and the Counterion on the Enantioselective Organocatalytic Transfer Hydrogenation Reaction



entry	catalyst	solvent	time [h]	conversion [%][a]	yield [%][b]	er[c]
1	 · TFA **5**	$CHCl_3$[d]	6[d]	100[d]	76[d]	82/18[d]
2		Toluene	48	100	84	97/3
3	 · TCA **12**	Toluene	36	100	80	97/3
4		$CHCl_3$	12	100	72	92/8
5	 · TFA **8**	CH_3CN	24	35	17	72/28
6		THF	12	100	88	86/14
7		CH_2Cl_2	12	100	86	88/12
8		Toluene	12	100	76	89/11
9	 · TFSI **13**	$CHCl_3$	12	100	76	89/11
10	 · (-)-CSA **14**	$CHCl_3$	18	100	84	90/10
11	 · (+)-CSA **15**	$CHCl_3$	18	100	88	88/12

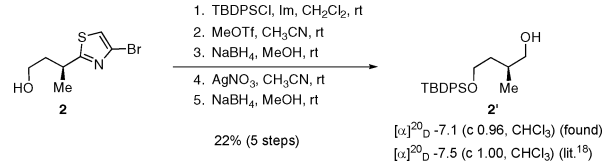
[a] Conversion determined by crude NMR analysis. [b] Isolated yield. [c] Enantiomeric ratio determined by chiral SFC analysis (ChiralPack AD-H, MeOH). [d] Reaction performed at rt. TFSI = trifluoromethanesulfonimide.

catalysts such as **5**, **7**, and **8**, a dramatic increase in both reactivity and selectivity was observed, allowing the isolation of the desired reduced product in high yields and high selectivities (up to 84% ee; Table 1, entry 12). Interestingly, the relative size of the ester moiety on the 3,5-dihydropyridine ring appeared to have a tremendous impact on the selectivity (R = O*t*-Bu, 84% ee; R = OEt, 60% ee; Table 1, entries 12 and 13), while the ketone analogue **11** turned out to be rather inefficient (Table 1, entries 7, 11, and 14). With these promising results in hand, catalysts **5** and **8** were selected for further study.

The influence of the solvent was next examined. As shown in Table 2, catalyst **5** exhibited higher selectivities in toluene (94% ee; Table 2, entry 2) than in $CHCl_3$ (64% ee; Table 2, entry 1), while catalyst **8** appeared to be much more selective in $CHCl_3$ (84% ee; Table 2, entry 4) than in CH_3CN (44% ee; Table 2, entry 5), THF (72% ee; Table 2, entry 6), CH_2Cl_2 (76% ee; Table 2, entry 7), or toluene (78% ee; Table 2, entry 8). In addition, changing the counterion from trifluoroacetate to trichloroacetate or trifluoromethanesulfonimidate did not improve the selectivity (Table 2, entry 2 vs 3 and entry 4 vs 9) nor did the use of a chiral counterion such as (+)- or (−)-camphorsulfonate which, it is worth noting, both led to the isolation of the same major enantiomer (Table 2, entries 10 and 11).

The absolute configuration of **2** was confirmed by converting the latter into a known compound **2′** and by comparing their optical rotation (Scheme 2).[18]

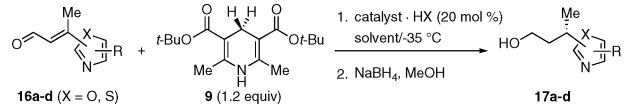
Scheme 2. Assignment of the Absolute Configuration of **2**



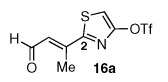
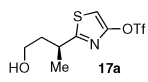
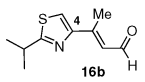
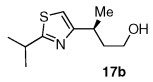
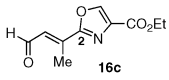
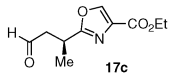
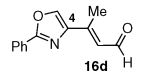
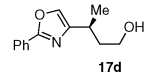
The substrate scope was then examined, and the results are summarized in Table 3. Hence, the analogous 4-trifluoromethylsulfonate derivative **16a** was subjected to the enantioselective organocatalytic transfer hydrogenation conditions (i.e., 20 mol % of chiral organocatalyst **5** or **8** in combination with 1.2 equiv of *tert*-butyl Hantzsch ester **9** in either toluene or $CHCl_3$ at −35 °C). To our delight, the corresponding alcohol **17a** was obtained in good yield and excellent enantioselectivity (81% yield, 92% ee; Table 3, entry 2). Similarly, thiazole **16b**, which exhibits

(18) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691.

Table 3. Scope of the Enantioselective Organocatalytic Transfer Hydrogenation Reaction



16a-d (X = O, S) **9** (1.2 equiv) **17a-d**

entry	substrate	product	catalyst	solvent	yield [%][a]	er[b]
1	 **16a**	 **17a**	**8**	$CHCl_3$	73	91/9
2			**5**	Toluene	81	96/4
3	 **16b**	 **17b**	**8**	$CHCl_3$	52[c]	88/12
4[d]	 **16c**	 **17c**	**5**	Toluene	76	95/5
5	 **16d**	 **17d**	**8**	$CHCl_3$	55[e]	90/10
6			**5**	Toluene	Traces	-

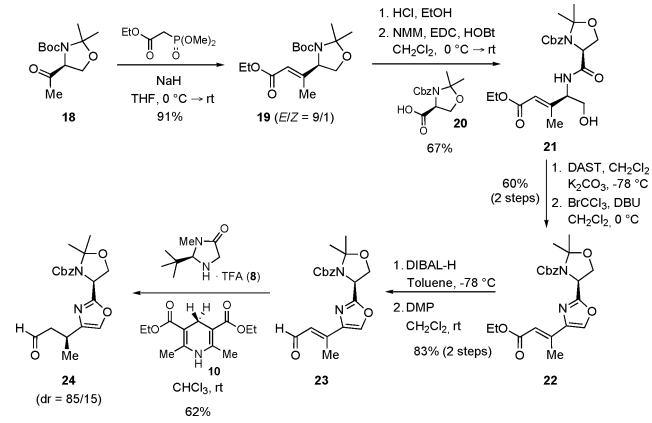
[a] Isolated yield. [b] Enantiomeric ratio determined by chiral SFC analysis (ChiralPack AD-H, MeOH). [c] 57% conversion after 36 h in step 1. [d] $NaBH_4$ reduction was not performed on this substrate. [e] 70% conversion after 48 h in step 1.

an enal motif at the 4-position of the ring, was reduced using catalyst **8** in fair yield and good selectivity (78% yield, 76% ee; Table 3, entry 3). Surprisingly, however, very little conversion was observed when using catalyst **5** in toluene under otherwise identical conditions. Oxazole derivatives also appeared as suitable substrates, as 2- and 4-enal-substituted oxazoles **16c** and **16d** were both reduced with high enantioselectivity (**16c**: 76% yield, 90% ee, Table 3, entry 4; **16d**: 55% yield, 80% ee, Table 3, entry 5) using catalysts **5** and **8**, respectively. However, as observed previously for the 4-enal-substituted thiazoles, catalyst **5** failed to convert the analogous oxazole substrate **16d**. Hence, as a general trend, comparable reactivities, yields, and selectivities were observed between oxazoles and thiazoles bearing similar substitution patterns.

Finally, in order to demonstrate the synthetic utility of this enantioselective organocatalytic transfer hydrogenation, we undertook a synthesis of the C7−C14 fragment of ulapualide A, which contains the requisite C9 stereogenic center α to the oxazole ring (Scheme 3).

The synthesis began with a Horner−Wadsworth−Emmons olefination between ketone **18**[19] and commercially available ethyl dimethylphosphonoacetate, which provided the corresponding α,β-unsaturated ester **19** in 91% isolated yield (*E*/*Z* = 9/1). Removal of the acetonide and the *t*-butyl carbamate in an HCl/EtOH solution, followed by peptide coupling with acid **20**[20] using standard conditions [EDC·HCl, HOBt, NMM, CH_2Cl_2],[21] resulted in the formation of β-hydroxy amide **21** in 67% yield. The latter was then cyclodehydrated using DAST,

Scheme 3. Application of the Enantioselective Organocatalytic Transfer Hydrogenation to the Synthesis of the C7−C14 Fragment of Ulapualide A



and the oxazoline intermediate was immediately aromatized to the corresponding oxazole **22** using the conditions developed by Williams et al. [$BrCCl_3$, DBU, CH_2Cl_2, 60% yield over 2 steps].[22] The ester moiety was then reduced with DIBAL-H to the β,β′-disubstituted α,β-unsaturated aldehyde **23**; however, as over-reduction to the allylic alcohol was also observed, subsequent oxidation using Dess−Martin periodinane allowed us to isolate the desired aldehyde **23** in 83% overall yield. Finally, aldehyde **23** was subjected to the enantioselective organocatalytic transfer hydrogenation conditions using ethyl Hantzsch ester **10** and catalyst **8** to provide **24** in 62% yield and an 85:15 diastereomeric ratio.

In summary, we have demonstrated that enal-substituted oxazoles and thiazoles can be readily reduced in a highly enantioselective fashion using organocatalytic transfer hydrogenation conditions with ee up to 94%. In all the cases studied, the 4-enal-substituted azoles proved less reactive and gave lower selectivities than their 2-enal-substituted counterparts. We suspect that the difference in reactivity is related to the electron-withdrawing character of the azole ring when substituted by an enal moiety at the 2-position. The 4-enal-substituted azoles are, on the other hand, much less reactive and therefore require higher temperatures, which lead to slightly lower selectivities. This key transformation is currently being applied in the total syntheses of myxothiazole Z and ulapualide A, which will be reported in due course.

Acknowledgment. We would like to thank the Ministère de l'Enseignement Supérieur et de la Recherche for financial support to T.J.H.

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

OL900893E

(19) Compound **18** was prepared in four steps and 70% yield. See: (a) Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716. (b) Mckillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synthesis* **1994**, 31. (c) Cambell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Synthesis* **1998**, 1707.

(20) (a) Shin, C.; Ito, A.; Okumura, K.; Nakamura, Y. *Chem. Lett.* **1995**, *1*, 45. (b) Yamada, T.; Okumura, K.; Yonezawa, Y.; Shin, C. *Chem. Lett.* **2001**, *2*, 102.

(21) Chattopadhyay, S. K.; Biswas, S.; Gosh, S. K. *Synthesis* **2008**, 1029.

(22) (a) Williams, D. R.; Lowder, P. D.; Gu, Y.-G.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.