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Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines†

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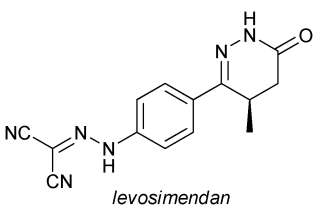
We have developed an efficient procedure for the easy and straightforward preparation of functionalized dihydropyridazines as highly enantiopure materials by reaction of pyruvaldehyde 2-tosyl hydrazone with a variety of α,β-unsaturated aldehydes using a chiral secondary amine as catalyst. The overall process consists of a cascade reaction involving an initial aza-Michael reaction, in which the stereocentre is installed, followed by an intramolecular aldol reaction/dehydration step.

Pyridazines belong to a family of heterocyclic compounds that possess remarkable pharmaceutical activities and have also shown important applications in materials science. For example, several members of this class of compounds have been utilised in the development of therapeutic agents that have been employed as analgesic and anti-inflammatory,[1] antibacterial,[2] antihypertensive,[3] antidiabetic[4] or antihistaminic[5] agents and have also been incorporated into semi-conductor materials as well as in substances with non-linear optical properties.[6] Among this wide range of different applications and activities displayed, chirality also plays a crucial role, which is exemplified with the case of levosimendan (Fig. 1), an inotropic commercial drug with vasodilatory activity in which only the (*R*) enantiomer is pharmacologically active.[7]

In this context, and as part of the continuing efforts of our group directed towards the development of new synthetic methodologies for the preparation of chiral heterocycles, we have found that the pyridazine framework can be easily accessed from α,β-unsaturated aldehydes and a functionalized hydrazone of type **2** by means of a cascade reaction consisting



levosimendan

Fig. 1 The structure of the pharmacologically active enantiomer of pyridazine-containing drug Simendan.

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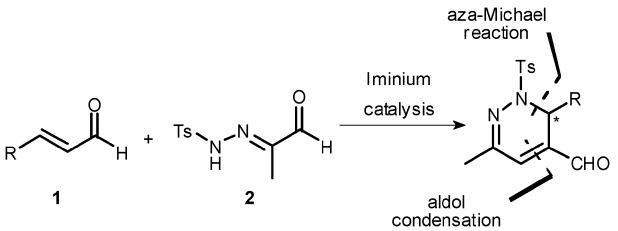
† Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, copies of ^{1}H and ^{13}C-NMR spectra and chiral HPLC traces. CCDC 855796. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17370k

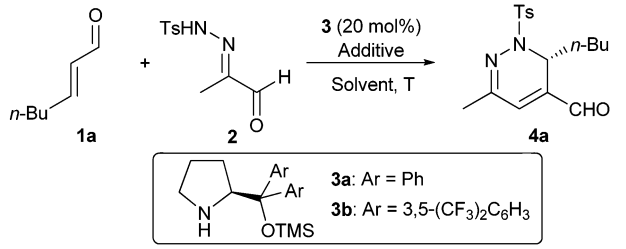


Scheme 1 Organocatalytic enantioselective synthesis of 2,3-dihydropyridazines by aza-Michael reaction/aldol condensation cascade through iminium/enamine activation.

of an initial aza-Michael reaction followed by intramolecular aldol condensation (Scheme 1). Moreover, we have also investigated generation of the target compounds in an enantioselective manner by using the iminium/enamine activation manifold,[8] thus employing a chiral secondary amine as catalyst for this transformation. In this context, the chiral catalyst would play a crucial role in the initial aza-Michael reaction step proceeding under iminium activation by providing the desired stereocontrol. The subsequent enamine-mediated intramolecular aldol reaction/dehydration step would provide the required driving force for the reaction to proceed to completion, pushing forward all of the equilibriums participating in the catalytic cycle and avoiding the problems associated with the inherent reversible character of the aza-Michael reaction, which would eventually lead to low conversions and/or lack of enantiocontrol.[9]

According to this reaction design, we decided to use the tosyl hydrazone **2** assuming that this compound would have an enhanced profile (compared to alternative protecting groups) to undergo the initial aza-Michael reaction step, since the high acidity of the NH moiety would presumably favour its deprotonation under the neutral or slightly basic conditions associated with iminium catalysis.[10] It should be pointed out that even though the use of aza-Michael/aldol condensation cascades exploiting the iminium/enamine manifold for the construction of different classes of nitrogen heterocycles is well documented in the literature,[11] there are no examples that explore the use of functionalized hydrazones in cascade reactions. Moreover, there is only one example in which hydrazones were used as nitrogen-centered pro-nucleophiles for the aza-Michael reaction with enones, using a chiral Brønsted base catalyst.[12] Therefore, this is the first example demonstrating that hydrazones can be successfully employed as nitrogen-centered nucleophiles for the enantioselective conjugate addition reaction under iminium catalysis.

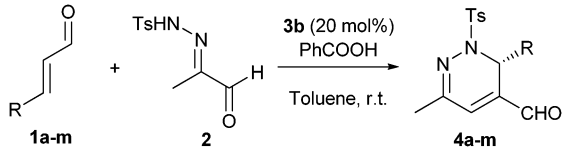
Table 1 Screening for the best experimental conditions using the reaction between **1a** and **2** as a model system[a]



Entry	Catalyst	Additive	Solvent	T/°C	Yield[b] (%)	ee[c] (%)
1	**3a**	PhCOOH	Toluene	rt	54	82
2	**3b**	PhCOOH	Toluene	rt	60	98
3	**3b**	4-$(NO_2)C_6H_4COOH$	Toluene	rt	31	n.d.[d]
4	**3b**	AcOH	Toluene	rt	42	98
5	**3b**	$(Ph)_2CHCOOH$	Toluene	rt	48	98
6	**3b**	DABCO	Toluene	rt	—	—
7	**3b**	PhCOOH	$CHCl_3$	rt	24	94
8	**3b**	PhCOOH	CH_2Cl_2	rt	30	94
9	**3b**	PhCOOH	THF	rt	13	n.d.[d]
10	**3b**	PhCOOH	EtOH	rt	18	n.d.[d]
11[e]	**3b**	PhCOOH	Toluene	rt	84	96

[a] Reactions performed on a 0.3 mmol scale of **1a** and **2** using 20 mol% of catalyst in 3.0 mL of solvent. [b] Isolated yield. [c] Determined by HPLC (see ESI). [d] Not determined. [e] Reaction carried out using **2** equiv. of **2** in 6.0 mL of toluene.

Table 2 Scope of the reaction[a]



Entry	Aldehyde	R	Product	Yield[b] (%)	ee[c] (%)
1	**1a**	*n*-Bu	**4a**	84	96
2	**1b**	Me	**4b**	91	89
3	**1c**	Et	**4c**	74	96
4	**1d**	*n*-Pr	**4d**	72	96
5	**1e**	n-C_8H_{17}	**4e**	63	97
6	**1f**	Z-EtCH=$CH(CH_2)_2$	**4f**	68	97
7	**1g**	$CH(OMe)_2$	**4g**	61	97
8	**1h**	$BnOCH_2$	**4h**	69	96
9	**1i**	Ph	**4i**	19	86
10[d]	**1i**	Ph	**4i**	49	89
11[d]	**1j**	*p*-$(NO_2)C_6H_4$	**4j**	52	95
12[d]	**1k**	*p*-$(MeO)C_6H_4$	**4k**	60	85
13[d]	**1l**	*p*-$(CN)C_6H_4$	**4l**	72	94
14[d]	**1m**	5-(NO_2)-Furyl	**4m**	55	90

[a] Reactions performed on a 0.6 mmol scale of **2** and 0.3 mmol scale of **1** using 20 mol% of catalyst **3b** in 6.0 mL of toluene. [b] Isolated yield. [c] Determined by HPLC on a chiral stationary phase (see ESI). [d] Reactions performed on a 0.6 mmol scale of **1** and 0.3 mmol scale of **2**.

With these precedents in mind, we started our work by surveying the viability of the projected cascade process using the reaction between 2-heptenal (**1a**) and tosylhydrazone **2**, the later being synthesized by direct condensation of commercially available pyruvic aldehyde and tosylhydrazine,[13] as a representative model system (Table 1). We first tested diarylprolinol derivatives **3a** and **3b** as chiral secondary amine catalysts, which have already demonstrated their performance in many other examples of conjugate addition reactions under iminium activation,[14] working in toluene at room temperature. We incorporated benzoic acid as Brønsted acid co-catalyst since its ability to accelerate the formation of the activated iminium ion intermediate is also well known. In this context, *O*-trimethylsilyl protected diphenylprolinol **3a** delivered the desired product **4a** in moderate isolated yield albeit with high enantiocontrol. When the bulkier catalyst **3b** was employed, enantioselectivity improved significantly and also a slight increase in the yield of the process was observed (entries 1 and 2). Once a catalyst that provided high enantiocontrol had been identified (**3b**), we directed our efforts to the improvement of the yield of the reaction, first studying the role of the Brønsted acid co-catalyst by testing carboxylic acids of different acidity. However, the incorporation of additives with higher or lower pK_a compared to $PhCO_2H$ led to a considerable loss in the yield of the desired compound **4a** (entries 3–5), although enantioselectivities remained intact. The incorporation of a base as a co-catalyst was also surveyed but in this case formation of the desired product was not observed (entry 6).

We next studied the influence of the solvent (entries 7–10) and, as shown in Table 1, toluene appeared to be the most efficient one in terms of both conversion and enantioselectivity. Slightly more polar solvents like chloroform or dichloromethane yielded the desired adduct still in high enantioselectivities but with an accentuated drop in isolated yield (entries 7 and 8), while the incorporation of strongly polar solvents like THF or EtOH resulted in very poor conversion after the same reaction time (entries 9 and 10). Finally, we succeeded in improving the yield of the reaction by increasing the amount of hydrazone reagent, reaching an 84% yield of dihydropyridazine **4a** and a 96% ee (entry 11).

Once the best protocol for the reaction had been established, we next proceeded to extend the reaction to the use of α,β-unsaturated aldehydes with different substitution patterns in order to determine the scope of the reaction and its performance for the preparation of differently substituted 2,3-dihydropyridazines. From the results summarized in Table 2 we observed that the hydrazone **2** reacted in a satisfactory way in most of the cases studied, furnishing the adducts **4a–m** in moderate to very good yields and excellent enantioselectivities. The reaction tolerates well the use of different β-substituted α,β-unsaturated aldehydes containing linear alkyl chains of different length and size (entries 1–5), also observing that the yield of the process became only moderately affected when the size of the chain was considerably increased (entry 5). Furthermore, functionalized α,β-unsaturated aldehydes such as **1f**, **1g** or **1h** also performed well, furnishing the final adducts in good yield and very high stereocontrol (entries 6–8).

On the other hand, cinnamaldehyde **1i** showed a remarkably lower reactivity and slightly decreased enantiocontrol under the same reaction conditions (entry 9). This led us to survey modified reaction conditions in order to improve this result and, after several attempts, it was found that the reaction proceeded more efficiently by simply changing the proportion of reagents from using excess of hydrazone reagent to employing

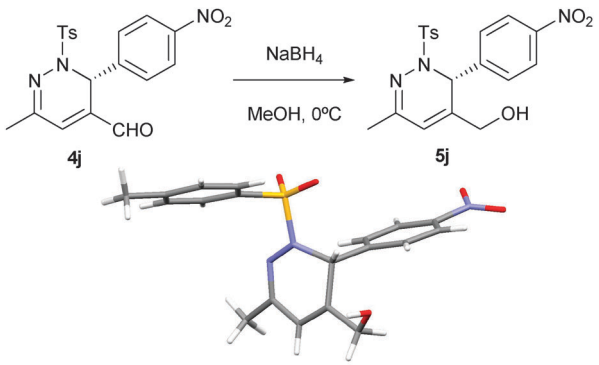


Fig. 2 Synthesis of compound **5j** and its crystal structure.

an excess of enal (entry 10). These conditions were further extended to other β-aryl substituted α,β-unsaturated aldehydes leading to the formation of the corresponding adducts in moderate to good yields and high enantioselectivities (entries 11–14).

The absolute configuration of the cycloadducts obtained in this cascade process was assigned by X-ray analysis of primary alcohol **5j** obtained after sodium borohydride reduction of **4j** (Fig. 2). This compound provided monocrystal structures suitable for single-crystal X-ray analysis (see ESI†) showing an (3*R*) absolute configuration. The absolute stereochemical outcome for the rest of the adducts **4a–m** synthesized was established by analogy, assuming an identical configuration based on mechanistic analogy for the reaction in all the cases. This configuration is also in good agreement with the sense of the chirality induction provided by catalyst **3b** in other conjugate addition reactions in which this catalyst has been employed.[14]

In conclusion, we have demonstrated that hydrazone **2** can efficiently be employed as a bifunctional reagent in the reaction with α,β-unsaturated aldehydes in the presence of a chiral secondary amine as catalyst in a cascade reaction operating through the iminium/enamine manifold. This compound is able to first behave as a N-nucleophile, initiating the process with an aza-Michael-type reaction, in which the stereochemical information is installed with very high stereocontrol. Secondly, the enamine intermediate reacts intramolecularly with the remaining formyl moiety through an aldol condensation. According to the recent classification of organocatalytic cascade/one-pot reactions made by Jørgensen,[15] this reaction can be classified as a TypeA-1-1C1X process with a Y_{PBF} (yield per bond formed) of 70–95%, a Y_{PMO} (yield per manual operation) of 49–91% and a P_f (purification factor) of 0. As far as we know this is the first example of the use of a hydrazone as a nitrogen-based pro-nucleophile in conjugate addition reactions under iminium activation and also the first case of a hydrazone reagent that is able to react bifunctionally in an enantioselective manner in a cascade process under iminium/enamine activation. This procedure also represents an efficient way for building up the pyridazine scaffold, a heterocyclic architecture of remarkable interest for medicinal chemists. Moreover, this simple protocol allows the preparation of chiral derivatives as highly enantiopure materials which incorporate different functionalities with potential for further manipulations, therefore anticipating the synthetic utility of the methodology.

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Notes and references

1 (*a*) M. Gökçe, S. Utku and E. Küpeli, *Eur. J. Med. Chem.*, 2009, **44**, 3760; (*b*) M. Y. Y. Khan and A. A. Siddiqui, *Indian J. Chem., Sect. B*, 2000, **39**, 614; (*c*) F. Rohet, C. Rubat, P. Coudert and J. Couquelet, *J. Bioorg. Med. Chem.*, 1997, **5**, 655.
2 M. Sönmez, I. Berber and E. Akbas, *Eur. J. Med. Chem.*, 2006, **41**, 101.
3 S. Demirayak, A. C. Karaburun and R. Beis, *Eur. J. Med. Chem.*, 2004, **39**, 1089.
4 I. G. Rathish, K. Javed, S. Bano, S. Ahmad, M. S. Alam and K. K. Pillai, *Eur. J. Med. Chem.*, 2009, **44**, 2673.
5 M. Gyoten, H. Nagaya, S. Fukuda, Y. Ashida and Y. Kawano, *Chem. Pharm. Bull.*, 2003, **51**, 122.
6 Y. Cheng, B. Ma and F. Wudl, *J. Mater. Chem.*, 1999, **9**, 2183.
7 For some reviews: (*a*) A. A. Rognoni, A. A. Lupi, M. M. Lazzero, A. S. A. Bongo and G. G. Rognoni, *Recent Pat. Cardiovasc. Drug Discovery*, 2011, **6**, 9; (*b*) D. J. Milligan and A. M. Fields, *Anesthesiol. Clin.*, 2010, **28**, 753; (*c*) W. G. Toller and C. Stranz, *Anesthesiology*, 2006, **104**, 556.
8 For some reviews about organocatalytic cascade reactions see: (*a*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*b*) A.-N. Alba, X. Companyo, M. Viciano and R. Rios, *Curr. Org. Chem.*, 2009, **13**, 1432; (*c*) X. Yu and W. Wang, *Org. Biomol. Chem.*, 2008, **6**, 2037; (*d*) D. Enders, C. Grondal and M. R. M. Huettl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570. For pioneering reports: (*e*) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 6964; (*f*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051; (*g*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710.
9 For reviews about catalytic enantioselective aza-Michael reactions see: (*a*) L.-W. Xu and C.-G. Xia, *Eur. J. Org. Chem.*, 2005, 633; (*b*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058.
10 When other hydrazones related to **2** incorporating different *N*-substituents were tested either the reaction did not take place or, when it occurred, only a minor amount of the desired pyridazine adduct was isolated.
11 (*a*) S.-J. Lee, S.-H. Youn and C.-W. Cho, *Org. Biomol. Chem.*, 2011, **9**, 7734; (*b*) J.-Y. Bae, H.-J. Lee, S.-H. Youn, S.-H. Kwon and C.-W. Cho, *Org. Lett.*, 2010, **12**, 4352; (*c*) L. Hong, W. Sun, C. Liu, L. Wang and R. Wang, *Chem.–Eur. J.*, 2010, **16**, 440; (*d*) D. Enders, C. Wang and G. Raabe, *Synthesis*, 2009, 4119; (*e*) Y. Yoshitomi, H. Arai, K. Makino and Y. Hamada, *Tetrahedron*, 2008, **64**, 11568; (*f*) H. Li, J. Wang, H. Xie, L. Zu, W. Jiang, E. N. Duesler and W. Wang, *Org. Lett.*, 2007, **9**, 965; (*g*) H. Sundén, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Córdova, *Adv. Synth. Catal.*, 2007, **349**, 827.
12 D. Perdicchia and K. A. Jørgensen, *J. Org. Chem.*, 2007, **72**, 3565.
13 N. De Kimpe, *Pyruvaldehyde 2-Phenylhydrazone*, in *e-EROS: Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons, New York, 2001, DOI: 10.1002/047084289X.rp305.
14 (*a*) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res.*, 2011, DOI: 10.1021/ar200149w; (*b*) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen and K. A. Jørgensen, *Chem. Commun.*, 2010, **47**, 632; (*c*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*d*) C. Palomo and A. Mielgo, *Angew. Chem., Int. Ed.*, 2006, **45**, 7876.
15 L. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492.

