Tetrahedron Letters 53 (2012) 5323–5326

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Organocatalyzed stereoselective construction of *N*-formylpiperidines via a Michael-aza-Henry-hemiaminalization reaction cascade

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ARTICLE INFO

Article history:
Received 19 June 2012
Revised 18 July 2012
Accepted 22 July 2012
Available online 27 July 2012

Keywords:
Organocatalysis
Piperidines
Nitroalkenes
Stereoselective synthesis
Cascade reactions

ABSTRACT

An efficient asymmetric synthesis of *N*-formylpiperidines via an organocatalytic Michael-aza-Henry-hemiaminalization reaction cascade of an aldehyde, a nitroalkene, and an *N*-arylideneformamide is reported. The reaction is triggered by diphenylprolinol trimethylsilyl ether and creates two C–C and one C–N bonds leading to the formation of highly enantio-enriched *N*-formylpiperidines with five contiguous chiral centers in a one-pot operation.

Organocatalysis has become a thriving area of general concepts and has contributed greatly to the past decade's advances in synthetic organic chemistry.[1] One of its impressive and current applications is in the construction of cyclic molecules via domino/cascade reactions.[2] In our earlier investigations on organocascade reactions, we have reported the synthesis of cyclic systems with up to five stereocenters.[3] A study on further potential of organocascade reactions via the enamine activation employing the same class of pyrrolidine-based catalysts to generate variously substituted piperidine ring system appears an interesting area of research.[4–7] The ubiquitous molecular skeleton of a piperidine ring with one or more substituents finds important application in the construction of natural products and pharmaceuticals. Efficient new approaches for the preparation of chemically and biologically relevant piperidines are of great significance in chemical research, especially those with an intriguing mechanism and good stereoselectivity. Hence, such a framework has attracted the attention of synthetic chemists tremendously over the recent years.[4–7]

Although a number of methods for the synthesis of polysubstituted piperidines are known,[5–7] only a few reports on their chiral versions are available in the literature.[2g,7,8] The previously reported methods are lengthy, whereas the recently reported one-pot asymmetric organocascade reaction approaches employ *N*-sulfonylimines for incorporating the nitrogen atom into the piperidine ring. *N*-sulfonylimines are relatively unstable compounds and their reactions, in most of the cases, are carried out in dry solvents and under inert atmosphere. In order to present an alternative to such procedures, we decided to employ *N*-(α-tosylaryl)formamides in place of *N*-sulfonylimines for the organocatalyzed stereoselective construction of the piperidine skeleton. *N*-(aryl(tosyl)methyl)formamides are stable, readily accessible substrates which can undergo elimination of sulfinic acid to afford an *N*-arylideneformamide under very mild conditions.[9] In fact, *N*-arylideneformamides are not only potential substitute for *N*-sulfonylimines but they also offer an additional advantage of synthesizing substituted *N*-formylpiperidines. Most of the available synthetic methods for *N*-formylpiperidines are tedious and require harsh conditions.[10] To the best of our knowledge, *N*-formylpiperidines have never been prepared using *N*-(aryl(tosyl)methyl)formamides in conjunction with enamine catalysis.

The *N*-formylpiperidines are valuable compounds as their CHO group can be utilized for the direct synthesis of various analogs. For example, *N*-formylpiperidines can be either thionized with Lawesson's reagent to *N*-CHS piperidines or selenized with P/Se or Woollins' reagent to *N*-CHSe piperidines.[11] *N*-methyl compounds can be also easily obtained from *N*-formyl derivatives.[12] All of these analogs show useful biological activities such as excellent antifungal, herbicidal, insecticidal, bactericidal, anti-inflammatory, antihistaminic, hypotensive, anticancer, CNS stimulant and depressant, and nerve activities.[10,11] Furthermore, *N*-formylpiperidine moiety is used for the synthesis of drugs for treatment of neurological disorders.[13]

The literature survey reveals that the synthesis of numerous compounds bearing multiple stereogenic centers involves organocatalysis.[7,8] In the context of our continued investigations on new

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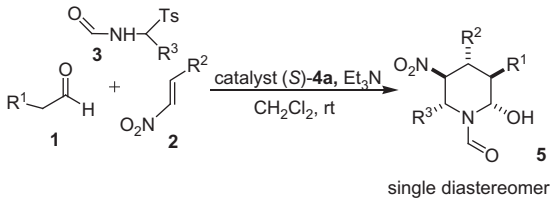
http://dx.doi.org/10.1016/j.tetlet.2012.07.097



Scheme 1. Synthesis of *N*-formylpiperidines.

organocatalytic strategies for the synthesis of chiral heterocycles,[3] we herein disclose the first chiral amine-triggered cascade reaction that allows the construction of highly enantio-enriched *N*-formylpiperidines with five contiguous chiral centers (Scheme 1).

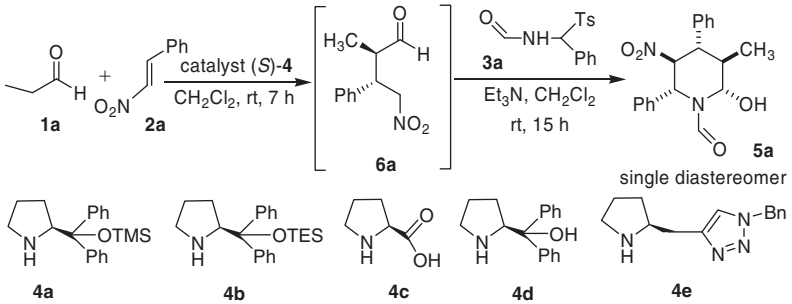
The feasibility of the proposed synthesis was examined using propionaldehyde **1a**, *trans*-β-nitrostyrene **2a**, *N*-(phenyl(tosyl) methyl)formamide **3a**, and a range of pyrrolidine-based organocatalysts along with Et_3N in varying solvents. Our initial endeavor was to evaluate appropriate conditions for the Michael addition of propionaldehyde **1a** to nitrostyrene **2a** and to screen a range of catalysts **4** and solvents.

Thus, we first focused on the search for an efficient catalyst for the one-pot three-component reaction. Interestingly, the desired product **5a** was obtained in excellent diastereo- and enantioselectivities apparently depending upon the catalyst used. The results of this assessment are summarized in Table 1. The conditions that gave the best result in terms of yield and stereoselectivity, used 20 mol % of catalyst **4a** at room temperature (Table 1, entry 2). On lowering the catalyst loading from 20 mol % to 15 mol %, there was considerable decrease in the yield and stereoselectivity (Table 1, entries 2 and 3). Moreover, an increase in catalyst loading from 20 mol % to 25 mol % neither improved the yield nor stereoselectivity (Table 1, entries 1 and 2). Gratifyingly, the use of 20 mol % of catalyst **4a** gave the best results and was used as the catalyst in the following exploration. With optimal catalyst in hand, different organic solvents were screened to investigate their effect on the reaction. As recorded in Table 1, the efficiency of solvents was of overwhelming distinction. An inference has been drawn that polar aprotic solvents give good results (Table 1, entries 2 and 8–14) in terms of yield and stereoselectivity. Thus, among CH_2Cl_2, THF, DCE, 1,4-dioxane, and acetonitrile, the best solvent was CH_2Cl_2 (Table 1, entry 2) to carry out the reaction.

Consequently, considering the overall effects of catalyst, solvent, and catalyst loading, finally the synthetic strategy was established and applied to the present study to transform a series of substrates to the corresponding products.[14] Further studies on the exploration of substrate scope and limitations were carried out. As shown in Table 2, regardless of the presence of an electron-withdrawing or -donating group in the aryl rings at *ortho*, *meta*, or *para* positions almost similar reactivity and selectivity in the formation of **5** were observed (Table 2).

A tentative mechanism for the formation of *N*-formylpiperidines is depicted in Scheme 2. In the first step, the catalyst trimethylsilyl ether **4a** activates aldehyde **1** by enamine formation, which then selectively adds to nitroalkene **2** in a Michael type reaction. The addition takes place through the transition state **8** as proposed by Hayashi et al.[1e] The following in situ hydrolysis forms nitroalkane **6** and liberates the catalyst to complete the catalytic cycle of the first step (Michael reaction). The subsequent aza-Henry reaction followed by hemiaminalization furnishes the product **5**. The present reaction cascade forms a single diastereomer with a high enantioselectivity. The main reason for the high stereoselectivity is the chiral diphenylprolinol trimethylsilyl ether (*S*)-**4a** catalyzed Michael addition, which is known to proceed with high

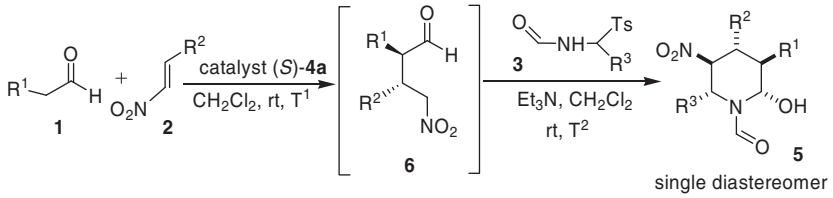
Table 1
Optimization of the reaction conditions[a]



S. No.	Catalyst (mol %)	Solvent	Yield[b] (%)	ee[c] (%)
1	**4a** (25)	CH_2Cl_2	91	97
2	**4a** (20)	CH_2Cl_2	91	97
3	**4a** (15)	CH_2Cl_2	84	90
4	**4b** (20)	CH_2Cl_2	73	92
5	**4c** (20)	CH_2Cl_2	62	86
6	**4d** (20)	CH_2Cl_2	69	88
7	**4e** (20)	CH_2Cl_2	65	89
8	**4a** (20)	CH_3CN	81	90
9	**4a** (20)	DCE	79	94
10	**4a** (20)	THF	69	96
11	**4a** (20)	1,4-Dioxane	71	96
12	**4a** (20)	*n*-Hexane	85[d]	99[d]
13	**4a** (20)	Isooctane	78[d]	96[d]
14	**4a** (20)	Toluene	80[d]	95[d]

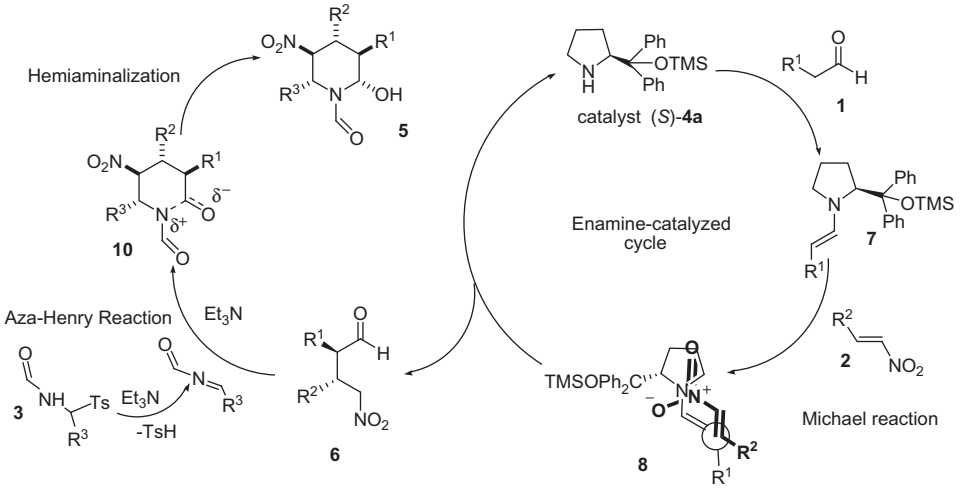
[a] For the experimental procedure, see Ref. 14.
[b] Isolated yield of the product **5a**.
[c] Determined by HPLC analysis on a chiral Eurocel column (250 × 4.6 mm, 5 μ).
[d] Yield and ee of compound **6a**, product **5a** was formed only in traces. The HPLC data of **6a**, determined with a OD-H column at 237 nm (2-propanol/hexane = 1:10) and 1.0 mL/min flow rate, are in agreement with those reported in the literature,[1e] which confirm its absolute configuration (2*R*, 3*S*).

Table 2
Scope of the synthesis of *N*-formylpiperidines[a]



S. No.	R^1	R^2	R^3	T^{1b} (h)	T^{2b} (h)	Product	Yield[c,d] (%)	ee[e] (%)
1	Me	Ph	Ph	7	15	**5a**	91	97
2	Me	*p*-MeOPh	*p*-ClC_6H_4	8	15	**5b**	90	95
3	Me	*p*-BrC_6H_4	Ph	7	17	**5c**	88	95
4	Me	*o*-ClC_6H_4	*p*-ClC_6H_4	6	16	**5d**	88	96
5	Me	2-Furyl	Ph	10	19	**5e**	74	90
6	Me	*p*-MeC_6H_4	Ph	10	20	**5f**	80	93
7	Me	*m*-$MeOC_6H_4$	Ph	9	20	**5g**	86	88
8	Et	Ph	Ph	6	17	**5h**	85	92
9	Et	*p*-BrC_6H_4	*p*-ClC_6H_4	8	15	**5i**	87	89
10	Et	2-Furyl	Ph	10	18	**5j**	72	85
11	*i*Pr	*p*-MeOPh	*p*-ClC_6H_4	9	17	**5k**	83	91
12	*i*Pr	*o*-ClC_6H_4	Ph	9	16	**5l**	81	94
13	$PhCH_2$	*p*-ClC_6H_4	Ph	7	18	**5m**	89	90
14	$PhCH_2$	*p*-MePh	*p*-ClC_6H_4	8	19	**5n**	85	84

[a] For the experimental procedure, see Ref. 14.
[b] Time taken (T^1) for the generation of **6** and the time elapsed (T^2) for the synthesis of products **5.**
[c] Isolated yield of the product **5**.
[d] All compounds gave C, H, N analyses within ±0.35% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR, and EIMS) data.
[e] Determined by HPLC analysis on a chiral Eurocel column (250 × 4.6 mm, 5 μ).



Scheme 2. Tentative mechanism for the synthesis of *N*-formylpiperidines **5**.

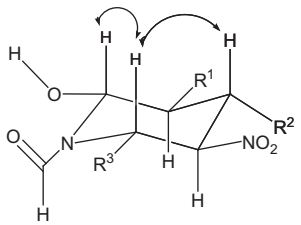


Figure 1. Selected NOE.

diastereo- and enantioselectivities; clearly this selectivity is kept or enhanced in the subsequent steps probably owing to the chirality of **6** along with a sterically favorable interaction between the in situ generated *N*-arylideneformamide from *N*-(aryl(tosyl) methyl)formamide **3** and the nitroalkane **6** followed by intramolecular hemiaminalization to afford **5**. The possibility of controlling the absolute configuration up to five contiguous stereocenters on the piperidine ring offers a useful methodology for a short synthesis of several differently substituted piperidine derivatives with excellent yields and high diastereo- and enantioselectivities.

The relative stereochemistry of **5** was determined by NOE experiments and coupling constants (Fig. 1). Strong NOE between 2-H and 6-H; 4-H and 6-H shows that 2-H, 4-H, and 6-H are on the same face of the molecule. The coupling constants (J = 10.4–11.9 Hz) of these protons clearly indicate that they occupy axial (ax) positions, hence the other substituents at positions 2, 4, and 6 must be equatorial (eq). A significant NOE between 3-H and hydroxylic proton shows that they are *cis* to each other, which

confirms the *trans*-stereochemistry at all the vicinal carbons of the piperidine ring in products **5** as shown in Scheme 2.

In summary, we have developed the first one-pot chiral amine-triggered asymmetric synthesis of highly substituted *N*-formylpiperidines via a [2+2+2]-annulation of an aldehyde, a nitroalkene, and an *N*-(aryl(tosyl)methyl)formamide. The merit of this method is highlighted by its efficiency to install five contiguous chiral centers into the piperidine structure. No by-product formation, operational simplicity, ambient temperature, and high stereoselectivity are the salient features of the present protocol, which would encourage chemical and pharmaceutical applications of *N*-formylpi peridines.

Acknowledgments

We sincerely thank the DST, Govt. of India, for financial support (DST File No. SR/S1/OC-22/2010) and the SAIF, Punjab University, Chandigarh, for providing microanalyses and spectra.

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14. *General procedure for the synthesis of N-formylpiperidines* ***5***: Diphenylprolinol trimethylsilyl ether **4a** (0.2 mmol) was added to a solution of nitroalkene **2** (1 mmol) and aldehyde **1** (1.2 mmol) in CH_2Cl_2 (2 mL) at 23 °C under nitrogen atmosphere and the mixture was stirred for 6–10 h at rt. Then, *N*-(aryl(tosyl)methyl)formamide **3** (1.2 mmol) and triethylamine (2 mmol) in CH_2Cl_2 (4 mL) were added to the reaction mixture at rt under nitrogen atmosphere. The resulting mixture was stirred for 15–20 h at rt, then, quenched with saturated aqueous citric acid, and extracted three times with ethyl acetate. The combined organic layer was washed with water followed by saturated aqueous sodium chloride, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc-hexane; 1:9 as eluent) to afford an analytically pure sample of *N*-formylpiperidines **5**. Characterization data of representative compounds **5**. Compound **5a**: Yellow liquid, yield 91%. IR (KBr) ν_{max} 3444, 2963, 1660, 1554, 1450, 1330, 1154, 1021, 924, 813, 704, 676 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) δ: 1.05 (d, J = 6.9 Hz, 3H), 1.68 (bs, exch. D_2O, 1H), 2.42–2.51 (m, 1H), 2.82 (dd, J = 11.8, 8.5 Hz, 1H), 3.43 (t, J = 11.8 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 5.46 (dd, J = 10.8, 2.5 Hz, 1H), 6.99–7.46 (m, 10 H), 8.81 (s, CHO, 1H). ^{13}C NMR (100 Hz, DMSO-d_6) δ: 8.9, 27.9, 32.6, 40.7, 72.9, 85.5, 125.4, 126.3, 127.2, 128.1, 129.2, 130.5, 139.6, 141.7, 163.2 ppm. EIMS m/z 340 (M^+). Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 66.73; H, 6.17; N, 8.57. Compound **5c**: Yellow liquid, yield 88%. IR (KBr) ν_{max} 3447, 2961, 1652, 1548, 1453, 1329, 1156, 1021, 921, 817, 707, 672, 541 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) δ: 1.12 (d, J = 6.6 Hz, 3H), 1.87 (bs, exch. D_2O, 1H), 2.48–2.59 (m, 1H), 2.89 (dd, J = 11.6, 8.9 Hz, 1H), 3.42 (t, J = 11.6 Hz, 1H), 5.12 (d, J = 10.7 Hz, 1H), 5.44 (dd, J = 10.9, 2.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.40–7.68 (m, 5 H), 7.74 (d, J = 8.2 Hz, 2H), 8.79 (s, CHO, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 8.8, 27.7, 32.8, 40.4, 72.3, 85.5, 120.2, 125.4, 127.5, 128.8, 130.6, 131.5, 138.2, 140.7, 162.0 ppm. EIMS m/z 418, 420 (M^+, M^++2). Anal. Calcd for $C_{19}H_{19}BrN_2O_4$: C, 54.43; H, 4.57; N, 6.68. Found: C, 54.78; H, 4.90; N, 6.37. Compound **5f**: Yellow liquid, yield 80%. IR (KBr) ν_{max} 3441, 2968, 1657, 1551, 1454, 1332, 1152, 1020, 925, 810, 709, 679 cm^{-1}. ^1H NMR (400 MHz; DMSO-d_6) δ: 0.98 (d, J = 7.1 Hz, 3H), 1.72 (bs, exch. D_2O, 1H), 2.36–2.43 (m, 1H), 2.45 (s, 3H), 2.91 (dd, J = 11.9, 8.3 Hz, 1H), 3.37 (t, J = 11.9 Hz, 1H), 5.03 (d, J = 10.5 Hz, 1H), 5.40 (dd, J = 10.7, 2.6 Hz, 1H), 7.10–7.42 (m, 5 H), 8.01–8.04 (m, 2H), 8.10–8.15 (m, 2H), 8.72 (s, CHO, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 7.6, 25.1, 28.8, 30.6, 41.1, 71.9, 85.7, 126.0, 127.2, 128.1, 129.2, 130.3, 134.7, 137.8, 141.1, 162.5 ppm. EIMS m/z 354 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 68.03; H, 5.96; N, 8.17.