Organocatalysis

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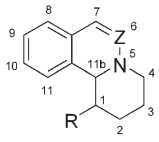
Organocatalytic Diastereo- and Enantioselective Annulation Reactions—Construction of Optically Active 1,2-Dihydroisoquinoline and 1,2-Dihydrophthalazine Derivatives**

*Kim Frisch, Aitor Landa, Steen Saaby, and Karl Anker Jørgensen**

The isoquinoline skeleton is found in a large number of naturally occurring and synthetic biologically active heterocyclic compounds.[1] In particular, interesting characteristics of 1,2-dihydroisoquinolines and the closely related 1,2,3,4-tetrahydroisoquinolines have been reported. Such characteristics include the ability to act as delivery systems that transport drugs through the otherwise highly impermeable blood-brain barrier.[2] These substances also exhibit sedative,[3] antidepressant,[4] antitumor, and antimicrobial activity.[1d,5] Many of these compounds, natural or synthetic in origin, are chiral and owe their chirality to a stereogenic carbon atom located adjacent to the nitrogen atom (carbon 11 b in Scheme 1).[1,6] Herin, we present the construction of optically active 1,2-dihydroisoquinoline and -phthalazine derivatives based on the general structure shown in Scheme 1.



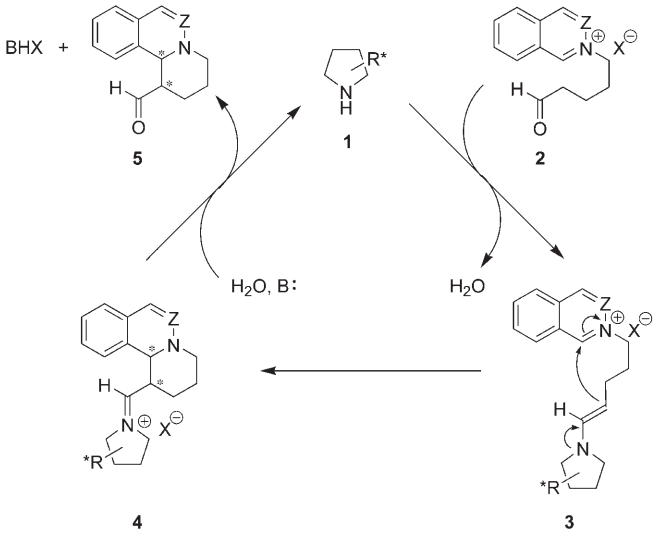
Scheme 1. Structural skeleton of the optically active synthesized compounds (R = CH_2OH, CHO; Z = CH, N).

Synthetic methodologies for the formation of chiral isoquinoline derivatives either involve the use of chiral building blocks or rely on diastereoselective reactions with a stoichiometric amount of chiral sources.[6,7a–d] To our knowledge, only few approaches are based on asymmetric catalysis.[7e–g,8] Herein we present a novel approach based on organocatalysis employing chiral C_2-symmetric secondary amines for the diastereo- and enantioselective annulation reaction of 2-(5-oxopentyl)isoquinolinium and -phthalazinium derivatives.

Asymmetric amine catalysis has received much attention in recent years, and a large number of reactions catalyzed by chiral secondary amines have been reported.[9,10] As 1,2-dihydroisoquinolines may be prepared by nucleophilic addition to isoquinolinium salts[7,11] we envisioned that aldehydes and/or ketones would be able to add to appropriate isoquinolinium salts under organocatalysis. Potentially, such a reaction would lead to the formation of optically active 1,2-dihydroisoquinoline derivatives that contain two adjacent stereocenters together with a carbonyl group suitable for further chemical transformations.

Initially, isoquinolines activated by ethyl chloroformate, were treated with, for example, 3-methylbutyraldehyde in the presence of different organocatalysts. However, all reactions studied proceeded with very low yield and stereoselectivity.

We next turned our attention to the intramolecular variant of the reaction.[12] Scheme 2 outlines our proposal for the catalytic intramolecular annulation reaction cycle. The



Scheme 2. Mechanistic proposal for the organocatalytic asymmetric annulation reaction.

first is the reaction of the chiral amine **1** with the aldehyde of the 2-(5-oxopentyl)isoquinolinium derivative **2** which results in the formation of the corresponding enamine **3** and H_2O. Attack of the nucleophilic enamine carbon atom at the electrophilic carbon atom of the isoquinolinium moiety then results in ring closure and formation of iminium ion **4**. Finally, **4** is hydrolyzed to give the 1,2-dihydroisoquinoline derivative **5** and HX, which is scavenged by an external base to regenerate the organocatalyst.

The synthetic route for model substrate 2-(5-oxopentyl)-isoquinolinium iodide (**2a**) (Scheme 2, Z = CH) used in the screening process is outlined in the Supporting Information. Table 1 presents the results for the screening of different chiral amines **1a–g** as catalysts for the annulation reaction of **2a**. It should be stressed that in all cases the reactions proceeded with good to high conversions without formation of by-products. However, the product **5a** was unstable and was protected to facilitate its isolation and full analysis.[13] Protection of the enamine moiety of **5a** in situ using $(CF_3CO)_2O$ gave the isolable compound **6a**, which was subsequently reduced with $NaBH_4$ to produce the fully analyzable alcohol **7a**.

(−)-(*S*)-Proline (**1a**) proved to be an effective catalyst for the annulation reaction of 2-(5-oxopentyl)isoquinolinium

[*] K. Frisch, Dr. A. Landa, Dr. S. Saaby, Prof. Dr. K. A. Jørgensen
The Danish National Research Foundation: Center for Catalysis
Department of Chemistry, Aarhus University
8000 Aarhus C (Denmark)
Fax: (+45) 8919-6199
E-mail: kaj@chem.au.dk

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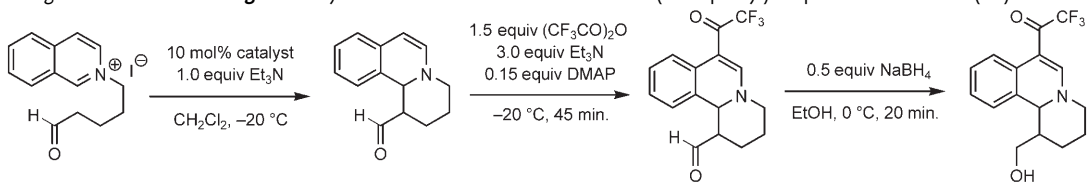
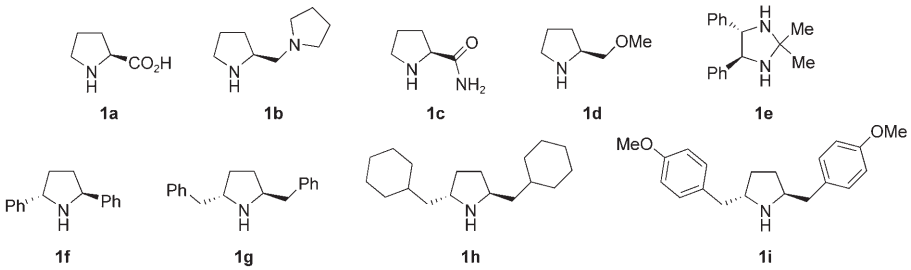
Supporting information for this article is available on the WWW unter http://www.angewandte.org or from the author.

Table 1: Screening of chiral amines **1a–g** as catalysts for the annulation reaction of 2-(5-oxopentyl)isoquinolinium iodide (**2a**)[a].



2a **5a** **6a** **7a**



1a **1b** **1c** **1d** **1e** **1f** **1g** **1h** **1i**

Entry	Catalyst	*t* [min]	Conversion [%][b]	d.r. (*trans*:*cis*)[c]	*ee* [%][d]
1[e]	**1a**	20	95	2:1	rac
2	**1b**	5	88	2:1	rac
3	**1c**	90	40	2:1	7
4	**1d**	10	92	2:1	11
5	**1e**	180	40	3:1	rac
6	**1f**	90	47	8:1	8
7	**1g**	190	94	8:1	84

[a] All reactions were performed on a 0.20-mmol scale. [b] The conversion of **2a** into **5a** was estimated by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy. The *trans*/*cis* ratio refers to the relationship between 1-H and 11b-H. [d] The *ee* value of the major diastereomer of compound **7a** was determined by chiral HPLC. [e] The reaction was performed at room temperature.

iodide **2a** with almost full conversion into the desired product **5a** after 20 min at room temperature (Table 1, entry 1). However, the diastereoselectivity of the reaction was low, and the two diastereomers were formed as racemates. For the catalysts **1b–e**, the annulation reaction also proceeded with low diastereo- and enantioselectivity (Table 1, entries 2–5). Improved diastereoselectivities were observed for the catalysts (2*S*,5*S*)-2,5-diphenylpyrrolidine (**1f**) and (2*S*,5*S*)-2,5-dibenzylpyrrolidine (**1g**). However, whereas **1f** gave very low enantioselectivity, catalyst **1g** produced the major diastereomer with 84% *ee* (Table 1, entries 6 and 7). A number of solvents were also screened for the annulation reaction of **2a** catalyzed by **1g**. In all cases high conversions (>75%) were observed; however, the stereoselectivity of the annulation reaction performed in CH_2Cl_2 was superior.[14]

Table 2 summarizes the results obtained from the screening of external bases in the annulation reaction of **2a**. In the absence of an external base, the reaction did not proceed (Table 2, entry 2). Furthermore, a 1:1 ratio of the amount of added base and the amount of formed product resulted (Table 2, entry 3 vs. 1). A possible explanation for these observations is protonation of the catalyst which renders it unreactive. Also, compound **5a** could revert back to **2a** owing to the presence of HI. The essential external base also promotes a racemic background reaction in the absence of the chiral amine catalyst (Table 2, entry 4), and dropwise addition of Et_3N over the course of 4 h resulted in a significant improvement only in the diastereoselectivity (Table 2, entry 5 vs. 1). Application of a stronger base, such as DBU, resulted in a conversion and diastereomeric ratio similar to those obtained with Et_3N. However, the reaction was almost racemic, therefore indicating that the background reaction caused by the achiral base superseded the chiral-amine-catalyzed reaction (Table 2, entry 6). The use of bases of similar strength to that of Et_3N, such as diisopropylethylamine (DIPEA) and quinuclidine, resulted in a higher diastereo-

Table 2: Screening of external bases for the organocatalytic annulation reaction of **2a** catalyzed by **1g**.[a]

Entry	External base (equiv)	*t* [h]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	Et_3N (1.0)	3	94	8:1	84
2	none	5	0	–	–
3	Et_3N (0.15)	5	15	n.d.	n.d.
4[e]	Et_3N (1.0)	3	25	>98:2	rac
5[f]	Et_3N (1.0)	4	94	12:1	86
6	DBU (1.0)	0.5	94	10:1	7
7	DIPEA (1.0)	o.n.[g]	92	10:1	84
8	quinuclidine (1.0)	1	94	12:1	78
9	*N*-methylmorpholine (1.0)	96	37	8:1	44
10	2,6-di-*tert*-butylpyridine (1.0)	96	0	–	–

[a] All reactions were performed at −20°C in the presence of **1g** (10 mol%) in CH_2Cl_2 on a 0.20 mmol scale. [b] The conversion of **2a** into **5a** was estimated by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy of **7a** (the *trans*/*cis* ratio refers to the relationship between 1-H and 11b-H). [d] The *ee* value of the major diastereomer of compound **7a** was determined by chiral HPLC. [e] Reaction performed without a catalyst. [f] Slow addition of the external base. [g] Overnight reaction.

meric ratio, whereas the conversion and enantioselectivity were either unaltered or lower (Table 2, entries 7, 8 vs. 1). A decrease in the strength of the added base had a significant effect on the conversion of the reaction. The use of *N*-methylmorpholine resulted in a slow reaction and the production of compound **5a** with low conversion and low enantiomeric excess, whereas 2,6-di-*tert*-butylpyridine gave no conversion at all (Table 2, entries 9 and 10, respectively). In conclusion, 1 equivalent of Et_3N as an external base proved to be optimal for the annulation reaction.

Table 3 summarizes the results of the annulation reaction of **2a** catalyzed by C_2-symmetric disubtituted pyrrolidines **1g**–**i** under various reaction conditions. The conversion and diastereoselectivity of the annulation reaction were found to be independent of the catalyst loading (Table 3, entries 1–4). However, a significant drop in the enantiomeric excess (indicating considerable involvement of the racemic background reaction caused by the external base) was observed with low catalyst loadings. An increase in the catalyst loading from 10 to 20 mol% did not significantly improve the stereoselectivity (Table 3, entries 1–4). A decrease in the reaction temperature from −20 to −40°C maintained a high conversion of the reaction, but resulted in a significant increase in both the diastereo- and enantioselectivity to 15:1 and 92% *ee*, respectively (Table 3, entry 5 vs. 3).

Table 3: Catalyst modifications and screening of catalyst loading and reaction temperature for the annulation reaction of 2-(5-oxopentyl)-isoquinolinium iodide **2a**[a].

Entry	Cat.	*t* [h]	*T* [°C]	Loading [mol%]	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**1g**	4.5	−20	2	95	9:1	41
2	**1g**	3	−20	5	94	9:1	71
3	**1g**	3	−20	10	94	8:1	84
4	**1g**	3	−20	20	94	8:1	87
5	**1g**	o.n.[e]	−40	10	94	15:1	92
6	**1h**	6	−20	10	90	7:1	36
7	**1i**	o.n.[e]	−40	10	96	15:1	88

[a] All reactions were performed in the presence of Et_3N (1 equiv) in CH_2Cl_2. Entry 1 was performed on a 0.40-mmol scale, entries 2–7 on a 0.20-mmol scale. [b] The conversion of **2a** into **5a** was estimated by ^{1}H NMR spectroscopy. [c] Determined by ^{1}H NMR spectroscopy of **7a** (the *trans*/*cis* ratio refers to the relationship between 1-H and 11b-H). [d] The *ee* value of the major diastereomer of compound **7a** was determined by chiral HPLC. [e] Overnight reaction.

The dependence of the structural and electronic properties of **1g** on the stereoselectivity of the reaction was also investigated. Replacement of the phenyl groups of **1g** by bulky non-aromatic groups, such as cyclohexyl groups (catalyst **1h**), did not change the diastereoselectivity of the reaction. However,catalyst **1h** was slightly less active than catalyst **1g**, and the enantioselectivity decreased significantly (Table 3, entry 6 vs. 3). The effect of the electron density of the aromatic substituents was tested by applying a catalyst with electron-donating substituents such as (2*S*,5*S*)-2,5-bis(4-methoxybenzyl)pyrrolidine (**1i**). The results in Table 3, entry 7 show that no significant changes in the outcome of the reaction were observed when **1i** was applied as catalyst.

With the optimized conditions for the catalytic diastereo- and enantioselective annulation reaction at hand, the scope and limitation of the system was investigated (Table 4). In general, the annulation reactions proceeded with good to high conversions (70–100%), high diastereoselectivity (d.r. ≥ 15:1) and excellent enantioselectivity (85–96% *ee*). Products with functional groups suitable for further manipulations were obtained (Table 4, entries 2 and 4), and the scope of the annulation reaction could be extended beyond isoquinolinium salts to substrates based on the phenanthridine and phthalazine skeleton (Table 4, entries 5 and 6). Limitations of the reaction were observed for substrates based on the electron-rich isoquinolines 5,7-dimethoxyisoquinoline (Table 4, entry 7) and 6,7-dimethoxyisoquinoline (the latter gave < 10% conversion after several days).

The reported yields are for two (Table 4, entries 3, 5, and 6) or three (Table 4, entries 1, 2, 4, and 7) reaction steps that were performed to obtain compounds that could be isolated and fully analyzed.[15] Additionally, although the final products **7a–g** were obtained in low yields, the conversions of **2a–g** into **5a–g** in the catalytic enantioselective annulation step were high. With the exception of substrate **2g** (Table 4, entry 7), the catalytic annulation reaction proceeded without the formation of by-products.

Compound **7b** was obtained as a white solid, which after a single recrystallization from CH_2Cl_2 and hexane gave crystals suitable for X-ray crystallographic analysis.[16] The analysis revealed that the absolute configurations of the newly formed stereocenters at C1 and C11b could both be described as *S* (Figure 1).

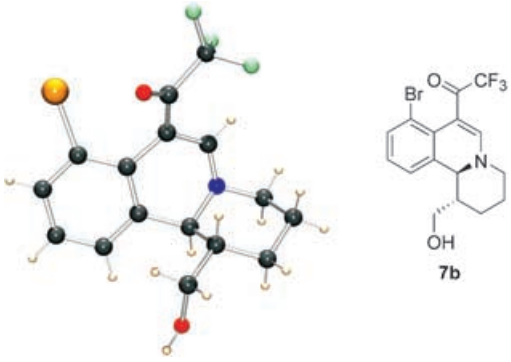
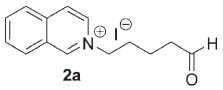
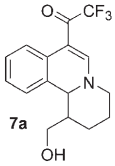
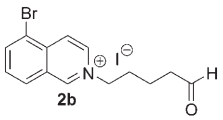
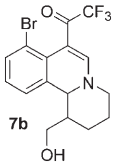
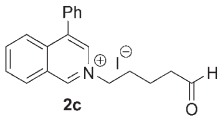
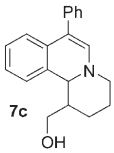
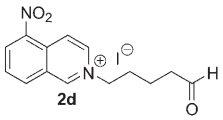
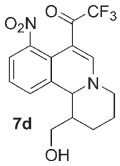
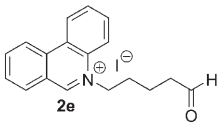
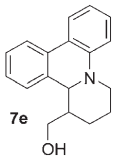
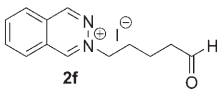
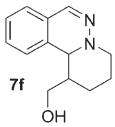
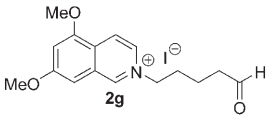
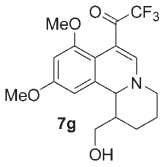


Figure 1. X-ray crystal structure of compound **7b**.

A proposal for the transition state involved in the stereoselective step of the annulation reaction is presented in Figure 2. In this transition state a favorable interaction between the isoquinolinium moiety and a phenyl ring of the catalyst—a cation–π interaction[17]—was anticipated. The phenyl ring, positioned parallel to and above the cationic isoquinolinium moiety with a face-to-face interaction,[17a–c] allows the *Re* face of the enamine double bond to approach the *Si* face of the iminium double bond without significant steric hindrance. With this approach, the annulation reaction results in the product with 1*S* and 11b*S* configurations at the formed stereocenters in accordance with the experimental observation.

Table 4: Scope and limitation of the organocatalytic annulation reaction catalyzed by **1g**.[a]

Entry	Substrate	Product	Conv. [%][b]	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	 **2a**	 **7a**	94	41	15:1	92
2	 **2b**	 **7b**	70	40	24:1	92
3	 **2c**	 **7c**	70	18	16:1	85
4	 **2d**	 **7d**	100	38	36:1	93
5	 **2e**	 **7e**	100	73	>98:2	96
6	 **2f**	 **7f**	100	59	>98:2	93
7	 **2g**	 **7g**	50	18	10:1	49

[a] All reactions were performed at −40 °C in the presence of **1g** (10 mol %) and Et_3N (1.0 equiv) in CH_2Cl_2 on a 0.40 mmol scale. Reaction were carried out overnight (15–21 h) for entries 1–6. For entry 7 the reaction time was 10 days. [b] The conversion of **2a**–**g** into **5a**–**g** was estimated by ^{1}H NMR spectroscopy. [c] Yields of isolated compounds **7a**–**g** based on **2a**–**g**, respectively. [d] Determined by ^{1}H NMR spectroscopy of compounds **5a**–**g** or **6a**–**g** (the *trans*/*cis* ratio refers to the relationship between 1-H and 11b-H). [e] The *ee* values of the major diastereomer of compounds **7a**–**g** were determined by chiral HPLC.

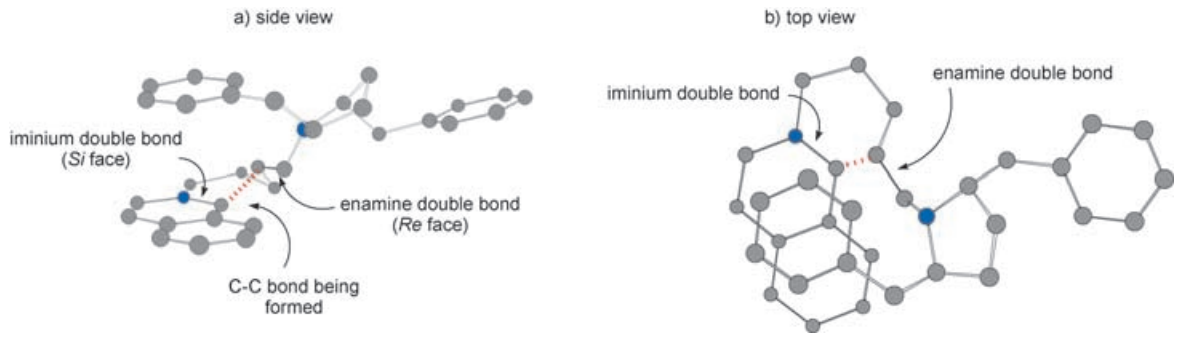


Figure 2. Proposed transition state in the annulation reaction catalyzed by **1g**.

In conclusion, we have developed the first organocatalytic diastereo- and enantioselective annulation reaction of 2-(5-oxopentyl)isoquinolinium derivatives. The reactions generally proceed with good to high conversions (70–100%), high diastereoselectivities (d.r. $\geq$ 15:1), and good to excellent enantioselectivities (85–96% *ee*). The scope of the annulation reaction is demonstrated in the synthesis of a series of optically active 1,2-dihydroisoquinoline and -phthalazine derivatives. The stereochemical outcome of the organocatalytic asymmetric annulation reaction is explained on the basis of a favourable cation–π interaction between the isoquinolinium moiety and one of the phenyl rings of the catalyst.

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[15] Compounds **7c** and **7g** were slightly unstable, which can account for the lower yield of isolation of these compounds.

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