Asymmetric Synthesis

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An Asymmetric Organocatalytic One-Pot Strategy to Octahydroacridines**

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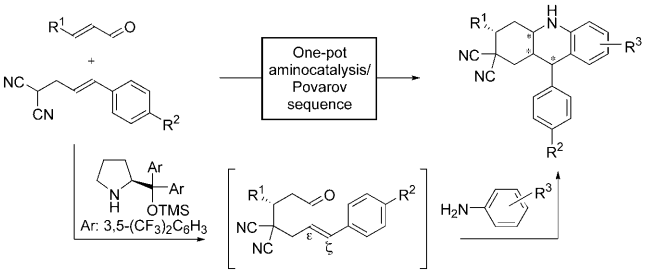
A major focus of organocatalysis[1] has been the development of domino, cascade, and one-pot reactions.[2] These classes of reactions enable the construction of molecules with great structural complexity with a minimum of manual operations, thereby saving time, effort, and production cost. Moreover, given the current focus on the development of more environmental-friendly procedures, these reactions, with their fewer purification steps, are useful alternatives to the classical stepwise approaches.

Recently, the aza-Diels–Alder reaction between an *N*-aryl imine and an olefin moiety (the Povarov reaction)[3] has attracted considerable attention,[4,5] as this reaction provides a simple route to a variety of nitrogen-containing polycyclic structures. In general, N heterocycles are of broad interest due to their vast abundance in natural and pharmaceutical compounds, and for instance tetrahydroquinolines have shown biological activity in numerous examples.[6] However, though they possess a tetrahydroquinoline core structure, suggesting potentially interesting biological properties, the class of octahydroacridines remains virtually unexplored due to their limited availability. This type of compounds may be accessed through an intramolecular Povarov reaction, in which an ε,ζ-unsaturated aldehyde upon condensation with an aryl amine, subsequently undergoes a formal cycloaddition and re-aromatization, affording the final product. However, access to optically active octahydroacridines has so far exclusively been based on a chiral pool approach and, furthermore, limited diastereomeric control is often observed.[7] To the best of our knowledge, no catalytic asymmetric approaches to these interesting N-heterocyclic structures have been described to date.

We imagined a route (Scheme 1), in which the addition of malononitrile derivatives to an α,β-unsaturated aldehyde employing aminocatalysis would furnish a suitable intermediate, which could be trapped in a following condensation/cyclization cascade by an aniline derivative. Optimally, the stereocenter of the initial addition step would direct the subsequent cycloaddition, hereby controlling the formation of the optically active octahydroacridines with high diastereoselectivity.



Scheme 1. Synthetic outline for the formation of octahydroacridines. TMS = trimethylsilyl.

Herein, we describe a protocol for the preparation of a series of octahydroacridines having four stereocenters with excellent enantio- and diastereomeric control. A rationale for the stereochemical outcome of the reaction is proposed, and further derivatizations of the products are demonstrated, such as the selective hydrolysis of one of the nitrile functionalities, leading to octahydroacridines with five stereocenters.

In order to reach an efficient one-pot protocol, the initial organocatalytic addition step was first investigated. At the outset, slightly modified conditions to those previously reported[2e] were applied. Accordingly, with malononitrile **2a**, 2 equiv of hex-2-enal (**1a**), and 10 mol% of (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine (**3**) as the catalyst in CH_2Cl_2, full and clean conversion to the desired Michael addition intermediate was observed. Consequently, the anticipated condensation/Povarov cascade was attempted, and, gratifyingly, the addition of 1.5 equiv of 4-nitroaniline (**4a**) and 2 equiv of trifluoroacetic acid (TFA) to the diluted reaction mixture at −30 °C gave clean conversion to the proposed product with excellent diastereomeric control. With these conditions in hand, the scope of the reaction was examined by varying the α,β-unsaturated aldehyde **1**, malononitrile **2**, and aniline **4** (Table 1).

The developed reaction concept showed great tolerance towards a variety of aliphatic α,β-unsaturated aldehydes **1**. Saturated and unsaturated side chains of different length were successfully applied (Table 1, entries 1–5, 18) and, furthermore, benzyl ether and homobenzyl functionalities were tolerated (entries 6 and 7). Generally, high yields (59 to 93%), taking into account the multiple reaction steps being involved, were observed with excellent stereocontrol (89 to 99% *ee* and >20:1 d.r. in all examples). Interestingly, no

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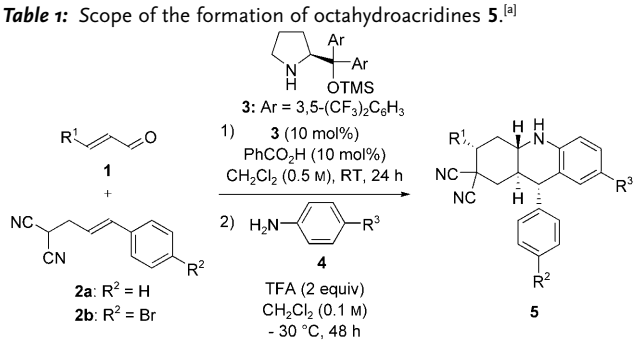
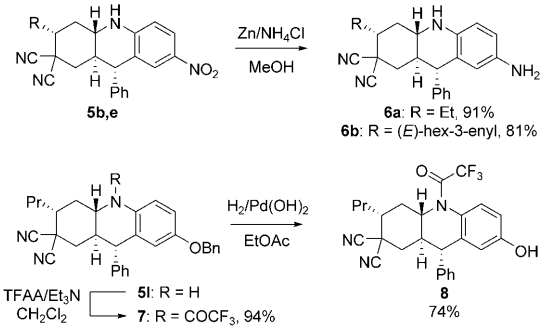
Table 1: Scope of the formation of octahydroacridines **5**.[a]



Entry	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]	d.r.[d]
1	Pr	H	NO_2	**5a**, 93	92[e]	>20:1
2	Et	H	NO_2	**5b**, 91	93	>20:1
3	hexyl	H	NO_2	**5c**, 75	93	>20:1
4	(*Z*)-hex-3-enyl	H	NO_2	**5d**, 59	92	>20:1
5	(*E*)-hex-3-enyl	H	NO_2	**5e**, 83	92	>20:1
6	CH_2OBn	H	NO_2	**5f**, 63	92	>20:1
7	CH_2CH_2Ph	H	NO_2	**5g**, 85	99	>20:1
8	Pr	Br	NO_2	**5h**, 77	92	>20:1
9	Pr	H	H	**5i**, 68	94	>20:1
10	Pr	H	Me	**5j**, 70	89	>20:1
11	Pr	H	OMe	**5k**, 73	93	>20:1
12	Pr	H	OBn	**5l**, 71	94	12:1
13	Pr	H	CF_3	**5m**, 71	92	>20:1
14	Pr	H	Br	**5n**, 84	92	>20:1
15	Pr	H	F	**5o**, 75	89	>20:1
16	Pr	H	CO_2Et	**5p**, 78	92	>20:1
17	Pr	Br	Br	**5q**, 73	89	>20:1
18	(*Z*)-hept-4-enyl	H	Br	**5r**, 71	89	>20:1

[a] For reaction conditions, see the Supporting Information. [b] Yield after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [e] Determined after *N*-Boc protection.



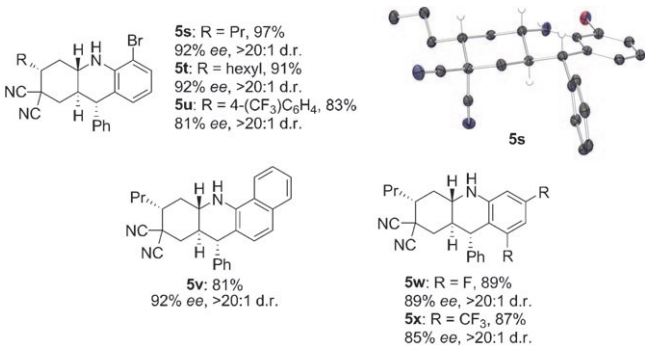
Scheme 2. Formation of hydroxy- and amino-functionalized octahydroacridines. TFAA = trifluoroacetic anhydride.

competing cyclization with the double bond of the α,β-unsaturated aldehyde side chain took place in the synthesis of **5d**, **5e**, and **5r**.

The scope of the 4-substituted aniline moiety was then examined, and significant variation of the aniline substituent could be performed. Both electron-rich (Table 1, entries 10–12), neutral (entry 9), and electron-poor anilines (entries 1–8, 13–18) were applied, resulting in high yields (59 to 93%) and excellent enantioselectivities (89 to 99% *ee*). In all cases except for product **5l**, only one diastereoisomer was observed. Finally, variation of the nucleophile was possible, applying (*E*)-2-(3-(4-bromophenyl)allyl)malononitrile (**2b**) in the initial addition step (Table 1, entries 8 and 17). The resulting products **5h** and **5q** were isolated in comparable yields (77 and 73%) and enantiomeric excesses (92 and 89% *ee*).

Of the investigated anilines, only those containing 4-amino and 4-hydroxy substituents posed a problem. However, these functionalities could easily be introduced by subsequent reduction of the installed nitro- or benzyloxy groups in good yields as demonstrated for **5b**,**e**,**l** (Scheme 2). For **5l** preliminary protection of the aniline nitrogen atom was necessary. Notably, no competing reduction of the double bond in **5e** or the nitriles was observed.

To further test the methodology, different substitution patterns of the anilines were explored. Initially, *ortho*-substituted bromoaniline was applied with a variety of α,β-unsaturated aldehydes with excellent results for the aliphatic α,β-unsaturated aldehydes (**5s**,**t**, Scheme 3). X-Ray crystal-

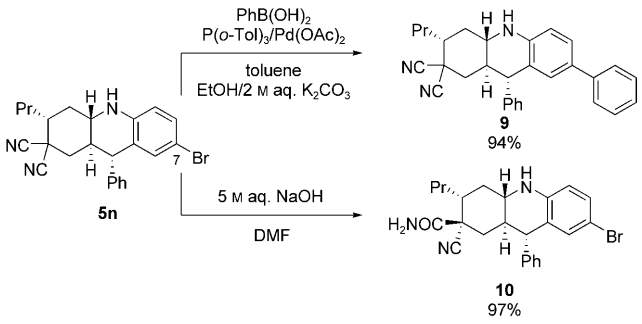


Scheme 3. Examples of *ortho*- and *meta*-substituted anilines and X-ray structure of product **5s** (most hydrogen atoms are omitted for clarity).

lography[8] of **5s** provided the absolute configuration of the formed compounds. Furthermore, an electron-poor aromatic aldehyde, (*E*)-3-(4-(trifluoromethyl)phenyl)acrylaldehyde, could successfully be implemented giving compound **5u**, although slightly lower enantioselectivity was observed.[9] Finally, 1-aminonaphthalene and two disubstituted anilines were utilized, accessing the optically active octahydroacridines **5v**,**w**,**x** with tetrasubstituted aromatic moieties.

In order to demonstrate the synthetic value of the formed octahydroacridines, a series of transformations was performed. The aryl bromide **5n** was applied in a palladium-catalyzed Suzuki coupling to introduce a phenyl group in the 7-position affording **9** in near quantitative yield (94%, Scheme 4).

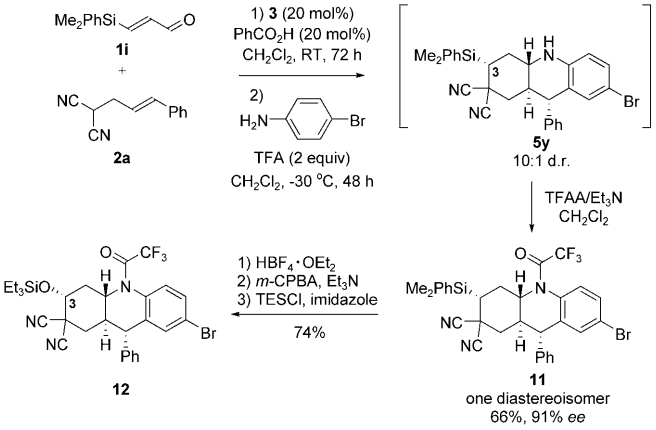
A potential drawback of the developed methodology is that the products have a geminal dinitrile functionality. Accordingly, a procedure to differentiate the two groups would be highly useful. To our delight, when subjecting **5n** to basic, aqueous conditions, we were able to selectively hydrolyze the equatorial nitrile to the corresponding primary amide **10** (Scheme 4), hereby creating an all-carbon quaternary, fifth



Scheme 4. Suzuki coupling and hydrolysis of **5n**.

stereocenter. The configuration of **10** was unambiguously assigned by X-ray crystallography.[8]

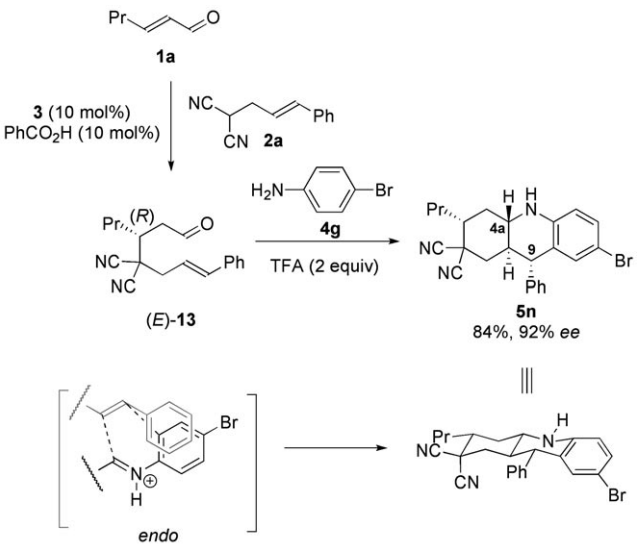
Next, it was possible to introduce a silicon group in the 3-position (Scheme 5) by employing a dimethylphenylsilyl (DMPS)-substituted enal. Due to the sterically demanding aldehyde, longer reaction time and higher catalyst loading



Scheme 5. Tamao–Fleming oxidation of DMPS group in **11**. *m*-CPBA = *meta*-chloroperbenzoic acid, TES = triethylsilyl.

were necessary in the addition step. However, the ensuing Povarov reaction proceeded smoothly to yield **5y** with a diastereomeric ratio of 10:1. The crude product was then directly protected with trifluoroacetic anhydride (TFAA) enabling the isolation of the major diastereoisomer **11** in 66% yield and 91% *ee*. The DMPS group constitutes a masked hydroxy group, as it can be oxidized employing the Tamao–Fleming reaction.[10] Accordingly, we were able to perform the oxidation with retention of configuration at C3 by a two-step procedure, affording the hydroxylated product, which was isolated after conversion into its corresponding triethylsilyloxy ether **12**. The hydroxy group may serve as a chemical handle for further functionalization of the molecule.

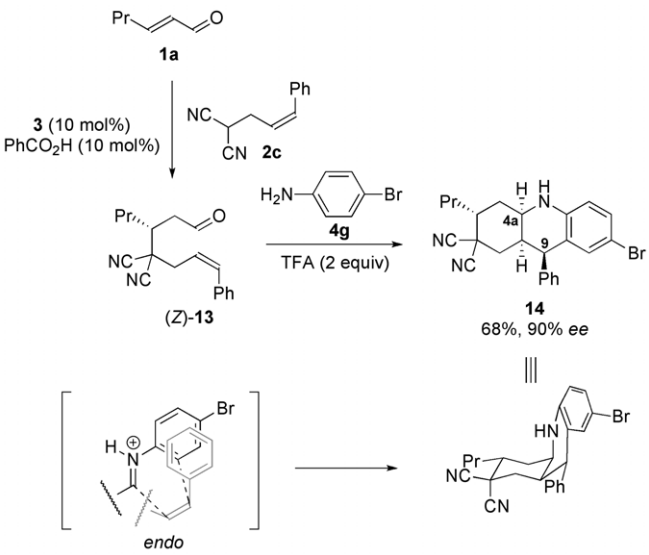
By the developed protocol, four stereocenters are formed selectively. The initial Michael addition affords the first stereocenter (*R*), corresponding to the usually observed selectivity, when applying **3** as catalyst.[11] The stereochemical outcome of the following Povarov reaction can be rationalized by an *endo* transition state as depicted in Scheme 6. The



Scheme 6. *Endo* transition state and resulting selectivity applying **2a**.

intermediate iminium ion product adopts a chairlike conformation with the substituent of the original aldehyde, the protonated imine and the olefin moiety in pseudo-equatorial positions. Simultaneously, π–π overlap of the aromatic moieties aligns the molecule for the ensuing formal cycloaddition in an *endo* transition state affording the product with the observed diastereoselectivity.

The importance of the *endo* approach was confirmed by an additional experiment, in which a nucleophile with *Z* geometry at the double bond, **2c**, was applied (Scheme 7). In order to achieve the secondary π–π overlap, the iminium ion would have to rotate 180° into a pseudo-axial position in the transition state compared to when **2a** was employed (compare Scheme 6 and 7). This should lead to a product with inverted configuration at C4a and C9 compared to the



Scheme 7. *Endo* transition state and resulting selectivity applying **2c**. The *ee* of **14** was determined after *N*-trifluoroacetylation.

originally formed products **5**. Satisfyingly, inversion at these two centers was indeed observed, affording the product **14** in 68% yield. The absolute configuration of **14** was unambiguously verified by X-ray crystallography.[8]

Furthermore, when conducting the experiment with nucleophiles without the aromatic substituent on the double bond and thereby lacking the ability to be involved in π–π interactions, no cyclization was observed (see Supporting Information). However, this may also simply indicate the necessity of a cation-stabilizing substituent on the double bond due to build up of positive charge at the C9 center in the transition state.

In conclusion, we have designed a method for the formation of octahydroacridines with high levels of yield and stereogenic control. The system displays great tolerance towards different aldehydes, anilines, and nucleophiles. The synthetic usefulness of the products was demonstrated through a number of transformations, and finally, the use of different nucleophiles verifies an *endo* transition state in which π–π overlap of the aromatic moieties plays an important role in the reactivity and selectivity of the system.

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[8] See supporting information for crystal structures. CCDC 795017 (**5s**), 797340 (**10**), and 795018 (**14**) contain 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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