Organocatalysis

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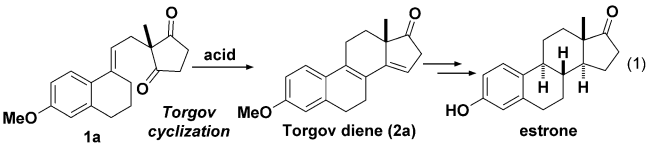
Catalytic Asymmetric Torgov Cyclization: A Concise Total Synthesis of (+)-Estrone**

*Sébastien Prévost, Nathalie Dupré, Markus Leutzsch, Qinggang Wang, Vijay Wakchaure, and Benjamin List**

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *An asymmetric Torgov cyclization, catalyzed by a novel, highly Brønsted acidic dinitro-substituted disulfonimide, is described. The reaction delivers the Torgov diene and various analogues with excellent yields and enantioselectivity. This method was applied in a very short synthesis of (+)-estrone.*



Steroids have versatile and often powerful biological activities, as well as an elegant tetracyclic molecular architecture.[1] Their synthesis has captured the imagination of chemists from the late 1930s until today, and has proven to be a treasure trove of new synthetic methods, including the Robinson annulation, proline-catalyzed intramolecular asymmetric aldolizations, C–H activations, cycloadditions, biomimetic polyene cyclizations, and transition metal catalyzed reactions.[2] The female sex hormone estrone is a prime synthetic target and several total syntheses have been described.[3] In 1963, Torgov et al. described a particularly efficient synthesis based on the acid-catalyzed conversion of diketone **1a** into diene **2a**, which is readily transformed into racemic estrone.[4] However, while researchers from Schering reported studies towards the development of a catalytic asymmetric version of this reaction, which bears some potential for the production of enantiopure steroid pharmaceuticals, high selectivity and turnover numbers have not been achieved.[5,6] Herein, we report a highly enantioselective Torgov cyclization, which is catalyzed by a novel chiral disulfonimide (DSI), and its application in the shortest total synthesis of (+)-estrone to date [Eq. (1)].

The Torgov reaction presumably involves four acid-catalyzed steps: 1) the isomerization of olefin **1a** to endocyclic compound **A**; 2) an intramolecular Prins reaction to give stabilized carbocation **B**; 3) its deprotonation to give alcohols **C** and **C′**; and 4) their isomerization and dehydration to give dienone **2a** (< Table 1). We hypothesized that the stereodetermining step, possibly the cyclization of intermediate **A** to cation **B**, could be catalyzed enantioselectively with recently developed enantiopure Brønsted acid catalysts through ketone activation.[7,8]

Indeed, when investigating the cyclization reaction of diketone **1a** in the presence of various enantiopure Brønsted acid catalysts, we found that commercially available TRIP (**3**) promoted the reaction to give diene **2a** at 50 °C efficiently but with a low enantiomeric ratio (e.r.; Table 1, entry 1).[9] Remarkably, the more acidic chiral DSIs (**4a**–**c**) catalyzed the transformation more rapidly and afforded diene **2a** at lower temperature and with higher enantioselectivity. Previously, our chiral DSI catalysts have mainly been applied as precatalysts in silicon-based Lewis acid catalysis,[10] but potential in asymmetric Brønsted acid catalysis has also been reported.[11] DSI **4a**, which bears electron-deficient aryl substituents, delivered the Torgov diene at 0 °C with a promising 84:16 e.r. (Table 1, entry 2). An improvement of the enantioselectivity was observed when novel DSI **4c**, which bears 3,5-$(SF_5)_2$-C_6H_3 substituents, was employed as the catalyst (Table 1, entry 4). The pentafluorothio moiety has previously been used as a bulkier and more electron-withdrawing alternative to the common trifluoromethyl group in medicinal chemistry and more recently also in organocatalysis.[12] After an extensive screening of the reaction conditions with this catalyst (see the Supporting Information), Torgov diene **2a** was obtained with 95:5 e.r. (Table 1, entries 5 and 6). However, the reaction time was still rather long. To address this issue, we designed the novel DSI catalyst **5**, which bears nitro groups in the 5 and 5′ positions to enhance its acidity without affecting the steric environment of its active site.[13] Indeed, DSI **5** proved to be a highly active catalyst although under the same reaction conditions, product **2a** was initially obtained with lower enantioselectivity (Table 1, entry 7). Nonetheless, the higher acidity of catalyst **5** enabled a smooth cyclization even at −40 °C to afford product **2a** with 97.2:2.8 e.r. (Table 1, entry 8). Under these conditions, a significant amount of intermediate **C** remained uncon-

[*] Dr. S. Prévost, Dr. N. Dupré, M. Leutzsch, Dr. Q. Wang, Dr. V. Wakchaure, Prof. Dr. B. List
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470, Mülheim an der Ruhr (Germany)
E-mail: list@mpi-muelheim.mpg.de

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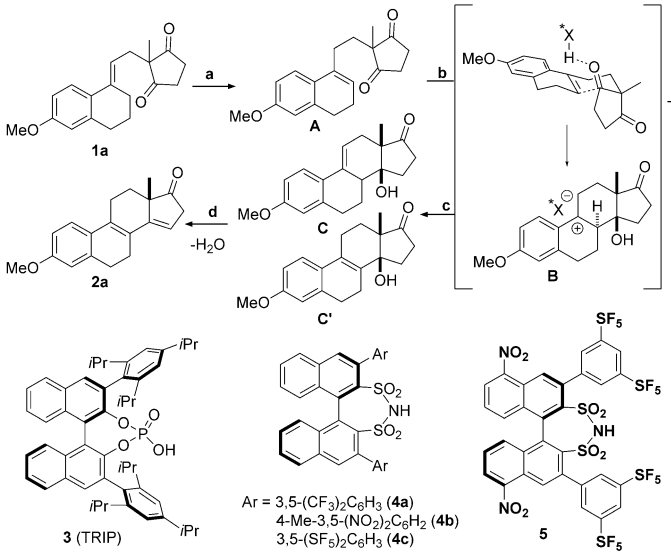
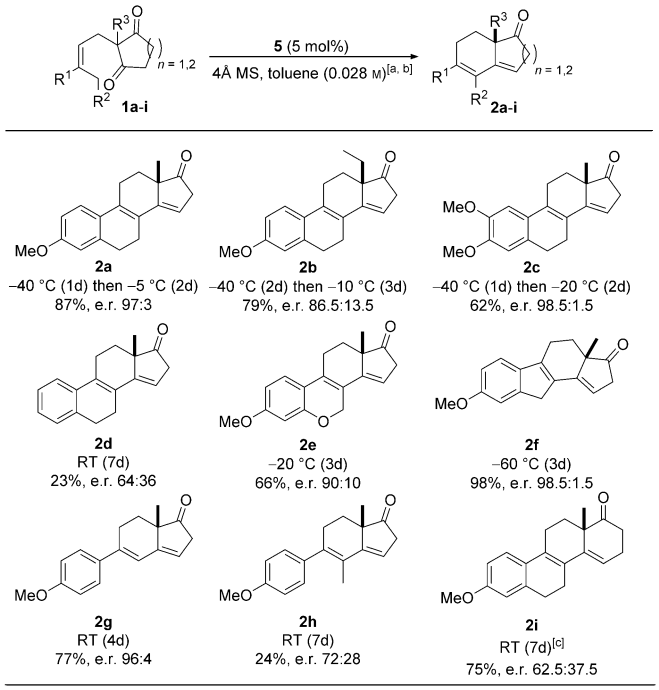
Table 1: Catalytic asymmetric Torgov cyclization.[a]



Entry	Cat. [mol%]	*T* [°C]	*t* [d]	**2a**:**C**[b]	e.r.[c]
1	**3** (20)	50	1	100:0	53.5:46.5
2	**4a** (20)	0	3	100:0	84:16
3	**4b** (20)	0	2	95:5	72.5:27.5
4	**4c** (20)	0	3	100:0	91:9
5[d]	**4c** (20)	0	3	100:0	95:5
6[d]	**4c** (10)	0	4	95:5	95.2:4.8
7[d]	**5** (10)	0	1	100:0	89:11
8[d]	**5** (5)	−40	5	80:20	97.2:2.8
9[d,e]	**5** (5)	−40, −5	1, 2	93:7	97:3

[a] Reactions were run on 0.02 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture after full conversion of **1a**. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reactions run with 4 Å MS at 0.028 M. [e] Reaction run at −40 °C for 1 day and then at −5 °C for 2 days.



Scheme 1. Other products of the asymmetric Torgov cyclization. [a] Reactions run on a 0.1 mmol scale. [b] Enantiomeric ratios were determined by HPLC analysis on a chiral stationary phase. [c] The reaction was performed at 0.1 M.

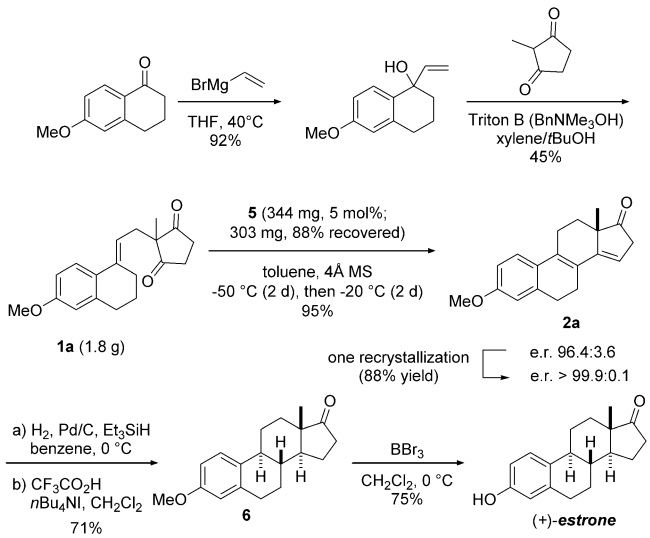
verted. Therefore, the optimal procedure involved raising the temperature to −5 °C after full conversion of the starting material (1 day at −40 °C).[14] This method furnished the Torgov diene with a good **2a**/**C** ratio (93:7) and an excellent 97:3 e.r. (Table 1, entry 9).

We also explored other substrates with our newly developed cyclization method (Scheme 1). Various diketones (**1a**–**g**) were subjected to the cyclization conditions and the products (**2a**–**g**) were isolated with moderate to excellent yield and enantioselectivity. Torgov diene **2a** was obtained in very good yield and with excellent enantioselectivity (87% yield, 97:3 e.r.). Interestingly, product **2b**, which has an ethyl instead of a methyl group at the C–D junction and is an intermediate in the synthesis of desogestrel,[3r] could also be obtained in good yield but with somewhat lower enantioselectivity (79% yield, 86.5:13.5 e.r.). An additional methoxy group in the A ring was well tolerated and product **2c** was obtained with excellent enantioselectivity even at lower temperature. However, the complete removal of the methoxy group at the A ring provided a much less reactive substrate, which was converted into the corresponding product **2d** only at room temperature and after 7 days. Modifications to the B ring are also very well tolerated. For example, the heterocyclic compound **2e** was obtained with good selectivity, as was the five-membered B ring product **2f**, which was synthesized with excellent yield and enantioselectivity. This approach was also suitable for the highly enantioselective synthesis of tricyclic diene **2g**, in which the B ring is absent, although a higher reaction temperature was required in this case. However, the more substituted diene **2h** gave only moderate results (24% yield, 72:28 e.r.). Interestingly, the six-membered D-ring analogue **1i** was also converted, albeit with lower enantioselectivity (75% yield, 62.5:37.5 e.r.).

To obtain a detailed insight into the mechanism of our Brønsted acid catalyzed asymmetric Torgov cyclization, we conducted an in situ NMR study. These experiments (including a racemization study and a kinetic analysis) suggest that the isomerization of intermediate **C** to **C'** by protonation and deprotonation is rate determining. We also found that at elevated temperatures, the intermediate steps prior to the final dehydration are reversible, thus rendering the second temperature utilized for the conversion of **C** to **C'** relevant for the stereochemical outcome.[15]

To illustrate the practical utility of our method, a gram-scale Torgov cyclization and the concise synthesis of (+)-estrone were realized (Scheme 2). Accordingly, diketone **1a** (1.8 g, obtained in two steps from commercially available 6-Methoxy-1-tetralone) was subjected to slightly modified asymmetric Torgov cyclization conditions (see the Supporting Information) to furnish 1.61 g (95% yield) of the Torgov diene **2a** with an e.r. value of 96.5:3.5.

A single recrystallization provided the product with essentially perfect enantiopurity (> 99.9:0.1 e.r.). Importantly,



Scheme 2. Gram-scale cyclization in a five-step synthesis of (+)-estrone.

DSI **5** could be conveniently recovered in 88% yield and reused after acidification without any loss of activity or selectivity. Torgov diene **2a** was then fully reduced by following a reported two-step procedure to give estrone methyl ether **6**.[6c] Subsequent methyl ether deprotection with BBr_3 yielded enantiopure (+)-estrone.

In summary, we have developed the first Brønsted acid catalyzed highly enantioselective Torgov cyclization. The reaction is catalyzed by a novel, highly acidic disulfonimide and provides facile access to several enantioenriched tri- and tetracyclic dienes. The methodology has been successfully applied to a gram-scale process and to the concise synthesis of (+)-estrone in what constitutes the shortest route reported to date.[15] Further explorations of disulfonimide-catalyzed reactions are currently in progress.

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