A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Catalytic Asymmetric [4+2]-Cycloadditions Using Tropolones: Developments, Scope, Transformations and Bioactivity

Authors: Karl Anker Jørgensen, Niels Hammer, Jeremy David Erickson, Vibeke Henriette Lauridsen, Joakim Bøgelund Jacobseb, Bente Kring Hansen, Kristian Mark Jacobsen, and Thomas Bjørnskov Poulsen

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201808221
Angew. Chem. 10.1002/ange.201808221

Link to VoR: http://dx.doi.org/10.1002/anie.201808221
http://dx.doi.org/10.1002/ange.201808221

WILEY-VCH

10.1002/anie.201808221

WILEY-VCH

COMMUNICATION

Catalytic Asymmetric [4+2]-Cycloadditions Using Tropolones: Developments, Scope, Transformations and Bioactivity

Niels Hammer, Jeremy D. Erickson, Vibeke H. Lauridsen, Joakim B. Jakobsen, Bente K. Hansen, Kristian M. Jacobsen, Thomas B. Poulsen, and Karl Anker Jørgensen*

Abstract: An organocatalyzed asymmetric [4+2]-cycloaddition between tropolones and electron-deficient dienophiles is presented. Complex and biologically interesting dihydrohomobarrelenone scaffolds are formed through a Diels-Alder reaction utilizing bifunctional Brønsted-base catalysis, affording the corresponding bridged bicyclic cycloadducts in up to quantitative yields with good enantio- (up to 92% *ee*) and diastereoselectivity (up to >20:1 d.r.). The synthetic value of the obtained products are explored by downstream transformations, including photoisomerizations, and biological relevancy by *in-vivo* testing in MCF-7 cancer cells.

Tropolones are a class of aromatic compounds exhibiting diverse and well-documented bioactivity such as antibacterial, antifungal, and anticancer activity, often attributed to its bi-chelating ability (Figure 1a).[1] Owing to their natural abundance and unique properties, both synthetic and natural tropolones have received significant attention in order to identify possible lead compounds. However, given the multitude of reported biological targets, simple tropolones are criticized as unspecific, rendering them as suboptimal drug candidates. Despite this, complex chemical modifications of tropolones are scarcely reported in literature and most existing derivatizations concern only the addition of simple substituents such as alkyl or aromatic groups to the tropolone scaffold.[2]

Attention to the biological activity of more complex tropolonic derivatives, such as cycloadducts, has been sparse,[2d,3] regardless of the potential to combine the chelating acyloin functionality with increased steric effects and new moieties, such as covalently modifying groups. The introduction of stereochemistry is known to influence selectivity and potency towards biological targets; two such tropolonic examples are the natural alkaloid colchicine, used in the treatment of gout, and the potent genotoxin goupiolone B (Figure 1b).[4] Thus, there is an unmet need for research regarding the further chiral functionalisation of tropolones.

Cycloadditions are useful synthetic tools in contemporary organic chemistry with regards to obtaining molecular complexity in a selective manner. Yet, the inherent aromatic character and electron-deficient nature of tropolones renders them less reactive in these methodologies, as demonstrated by previous reports wherein harsh conditions such as high temperature or pressure is needed.[5] This has been somewhat addressed by applying triethylamine as base catalyst, however this still leaves stereoselectivity unaddressed (Figure 1c).[6] Asymmetric Diels-Alder reactions involving unactivated compounds with dienols such as 3-hydroxy-2-pyrones and pyridones have successfully been promoted by HOMO-activation *via* bifunctional Brønsted-base catalysis.[7] By simultaneous deprotonation and hydrogen-bond activation of an electron-deficient dienophile, asymmetric cycloadditions can be carried out under mild conditions. Hence, we set out to develop a synthetic strategy that would include enantioselective modification of simple tropolones without altering the α-hydroxy-ketone chelating motif. Based on these previous examples of base-mediated Diels-Alder reactions, we envisioned that a bifunctional Brønsted base could facilitate HOMO-activation of tropolone, enhancing the reactivity towards a large variety of hydrogen-bond activated electron-deficient dienophiles (Figure 1d). In addition to containing the acyloin moiety, the resulting products would include an α,β-unsaturated ketone, which is a common motif in bioactive small-molecules that acts through targeted covalent inhibition.[8]

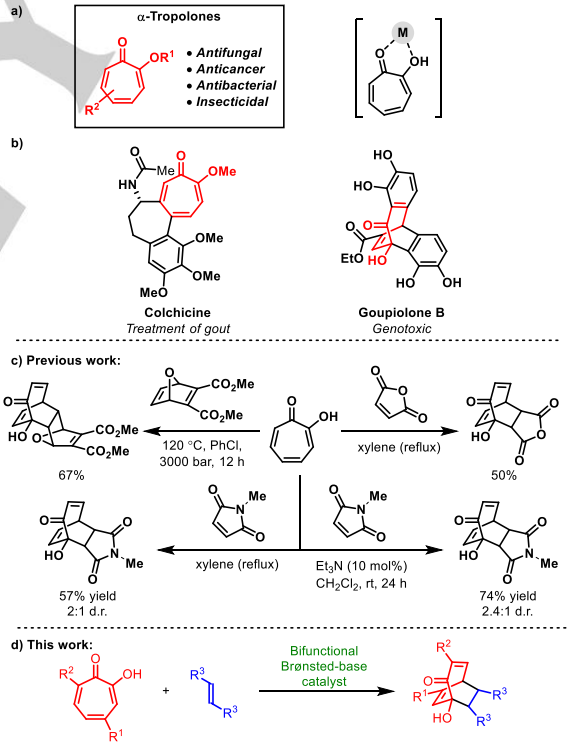


Figure 1. Tropolones and cycloadditions using tropolones.

We herein present the first organocatalytic strategy involving HOMO-activation of tropolones (seven-membered cyclic trienes) *via* bifunctional Brønsted-base catalysis. The synthetic value of the obtained products is demonstrated by a selection of transformations, including photoisomerizations into complex chiral norcaranes. Furthermore, a selection of products underwent preliminary experiments to probe their performance in cellular systems.

[a] *N. Hammer, Dr. J. D. Erickson, Dr. V. H. Lauridsen, J. B. Jakobsen, B. K. Hansen, K. M. Jacobsen, Prof. Dr. T. B. Poulsen and Prof. Dr. K. A. Jørgensen*
Department of Chemistry, Aarhus University, 8000 Aarhus C (Denmark)
E-mail:kaj@chem.au.dk

Supporting information for this article is given via a link at the end of the document.

Accepted Manuscript

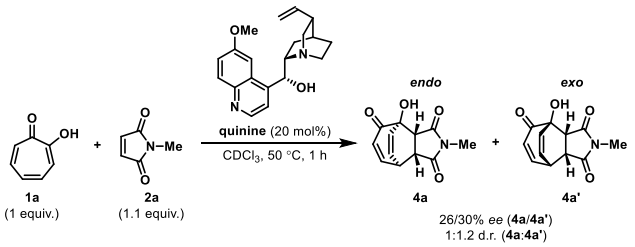
This article is protected by copyright. All rights reserved.

10.1002/anie.201808221

WILEY-VCH

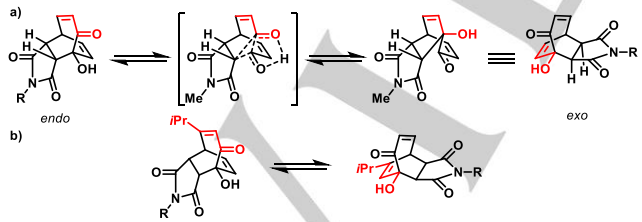
COMMUNICATION

Investigations were initiated by exploring the reactivity between tropolone **1a** and *N*-methylmaleimide **2a**, using the bifunctional Brønsted-base quinine (Scheme 1). The cycloaddition went to full conversion within 1 h to afford cycloadducts **4a**/**4a'** (*endo*/*exo*) with a promising enantioselectivity, but low diastereomeric ratio. Intrigued by these results, we commenced a screening of reaction conditions and organocatalysts. We discovered that the reaction is very sensitive to the structure of the catalyst, with relatively small changes resulting in large differences in the enantiomeric excess of the product (see SI). Furthermore, the reaction of 2-methoxytropone under similar reaction conditions proceeds much slower and were therefore not investigated further.



Scheme 1. Preliminary reaction between tropolone **1a** and *N*-methylmaleimide **2a**, using the bifunctional Brønsted-base quinine.

In the course of the screening, we observed that the diastereomeric ratio was highly unpredictable and variable. Despite indications of complete initial *endo*-selectivity, we propose that the observed deterioration of the diastereomeric ratio can be attributed to a subsequent step-wise acyloin rearrangement resulting from the α-hydroxyketone motif at the bridgehead (Scheme 2a).[6,9] Essentially, the rearrangement forms the *exo*-isomer of the opposite enantiomer. It should be noted, that for the adducts resulting from the Diels-Alder reaction with substituted tropolones, such as β-thujaplicin, the isomerized products are distinctly different, and essentially generates a constitutional isomeric ratio (i.r.) (see SI and Scheme 2b). It was observed, that the rearrangement was accelerated by the presence of base, as well as elevated temperatures and exposure to silica gel. As a result, small variances in work-up and purification procedures strongly impact the observed isomeric ratios of the isolated products. A solution to this problem is presented later.

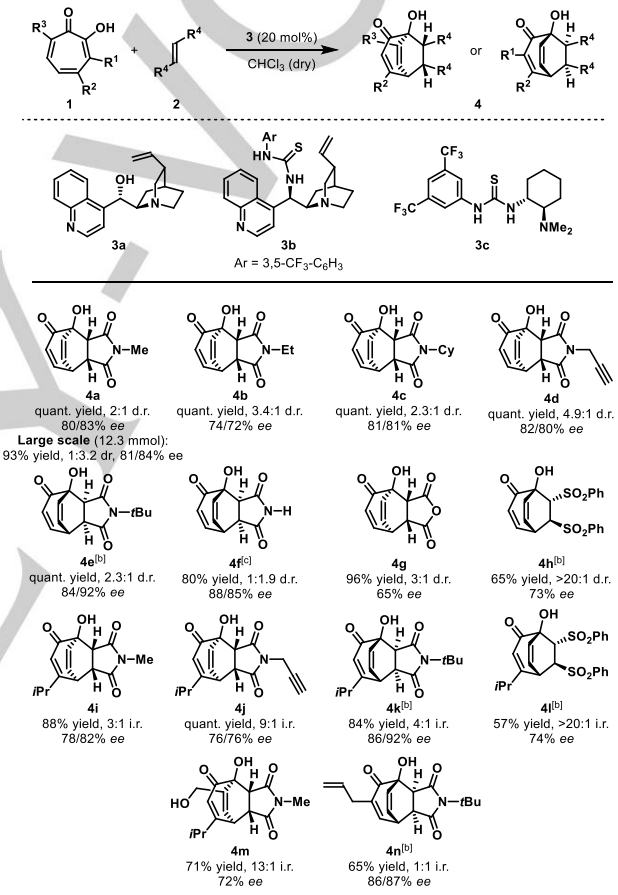


Scheme 2. The intramolecular acyloin rearrangement.

We proceeded by investigating the reaction scope, starting with a selection of *N*-substituted maleimides **2a**-**e** and tropolone **1a** (Table 1). Using *N*-methylmaleimide **2a** and 20 mol% of cinchonine **3a**, the reaction went to full conversion in 44 h at -35 °C, affording dihydrohomobarrelenone **4a** with a 10:1 crude d.r. Following flash column chromatography, **4a** was isolated in quantitative yield as a mixture with **4a'** in 2:1 d.r. and 80/83% *ee*.

Under identical conditions, maleimides substituted with ethyl-, cyclohexyl-, or propargyl groups (**2b**-**d**) easily underwent the cycloaddition affording **4b**-**d** in quantitative yields with good to moderate enantio- and diastereoselectivity. Interestingly, *N*-tertbutylmaleimide **2e** was not stereochemically compatible with organocatalyst **3a**, providing a racemic product. However, switching to the cinchonine-derived thiourea catalyst **3b** allowed us to isolate cycloadduct **4e** in a quantitative yield with a 2.3:1 d.r. and 84/92% *ee*. Subsequently, we found that altering the characteristics of the bifunctional catalyst further allowed a scope of electron-deficient dienophiles to form cycloadducts in decent to good enantiomeric excess.

Table 1. Scope of the organocatalyzed [4+2]-cycloaddition.[a]



[a] All reactions were performed using **1** (0.1 mmol), **2** (0.3 mmol), and **3a** (0.02 mmol) in 0.6 mL dry $CHCl_3$. The reported yields are for both isomers. The *ee*, d.r. and i.r. values (major/minor) were determined by ^{1}H NMR and chiral-phase UPC^2 after FC. The absolute configuration was determined by X-ray crystallographic analysis, see SI. [b] Organocatalyst **3b** (0.02 mmol) was used. [c] Organocatalyst **3c** (0.02 mmol) was used.

Using Takemoto's bifunctional catalyst **3c**, maleimide **2f** was employed, providing dihydrohomobarrelenone **4f** in 80% yield with moderate diastereoselectivity and good enantioselectivity. The increased reactivity of maleic anhydride **2g** was managed by lowering the temperature to -60 °C using catalyst **3a**. This allowed the desired product (**4g**) to be isolated in excellent yield albeit with 65% *ee*. Gratifyingly, the linear dienophile *trans*-1,2-bis(phenylsulfonyl)ethylene **2h** tolerated the reaction conditions well, affording **4h** as a single diastereomer with moderate yield

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201808221
WILEY-VCH

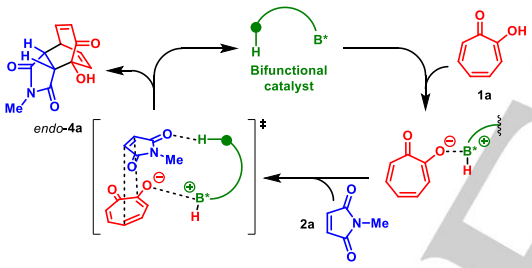
COMMUNICATION

and enantioselectivity. Alterations to the tropolone scaffold were also tolerated, as shown in **4i**-**n**.

To study the scalability of the catalytic strategy, the cycloaddition between tropolone **1a** and *N*-methylmaleimide **2a** was performed on a 12.3 mmol scale. After 62 h, cycloadduct **4a** was isolated in 93% yield, maintaining the enantioselectivity. Notably, the crude diastereoselectivity was observed to be 16:1 (**4a**:**4a'**) however following flash chromatography, this was inverted to 1:3.2 d.r. Finally, it should be noted that maleimides substituted with aromatic moieties, such as phenyl and benzyl groups reacted readily in the cycloaddition, although with unsatisfactory enantioselectivities.

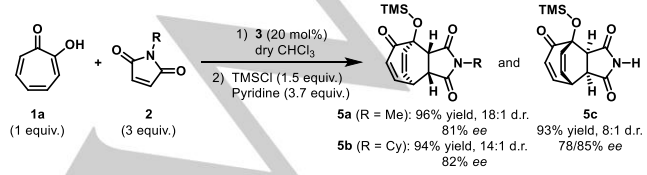
During the scope investigations, it was found that crystallization of the cycloadducts occurred in a conglomerate fashion, allowing for chiral resolution. To demonstrate, 2.14 mmol of **4a**/**4a'** was recrystallised in ethyl acetate, and re-isolated in 73% yield with an improved 88/89% *ee*. This proved helpful with regards to producing optically pure crystals for X-ray crystallographic analysis.

We propose the reaction mechanism follows the trends of asymmetric bifunctional-base catalysis. As such, the diene undergoes HOMO-activation through deprotonation of the α-hydroxy group while the dienophile is simultaneously directed and activated by hydrogen bonds (Scheme 3).[7b,c,10] The Brønsted-base activation is supported by the experiments performed with 2-methoxytropone.



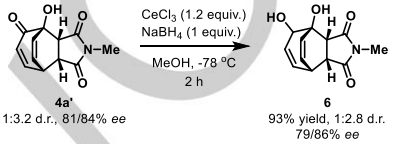
Scheme 3. Proposed reaction mechanism.

To address the acyloin rearrangement (Scheme 2), which deteriorated the diastereomeric ratio of the isolated cycloadducts, we envisioned modifying the hydroxyl-group in a one-pot procedure to block the intramolecular proton shift and carbonyl re-formation. Following the standard reaction conditions of the cycloaddition, the crude mixture containing **4a** was treated with trimethylsilyl chloride and pyridine to cap the hydroxyl-group. Full conversion into the corresponding TMS-protected cycloadduct **5a** was observed within 40 min and isolated in 96% yield, 18:1 d.r. and 81% *ee* (Scheme 4). Similarly, the one-pot silylation strategy was successfully employed on cycloadducts with good pre-isolation diastereomeric ratios (**4c**,**e** to **5b**,**c**), demonstrating the practicability of the strategy.



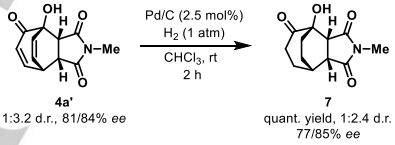
Scheme 4. One-pot silylation strategy.

To further investigate the synthetic application of the unprotected adducts, the attention turned towards the challenge of performing selective reductive transformations. The dihydrohomobarrelenone scaffold features several reducible moieties, such as two olefins and a maleimide, which complicates selective hydride-based reductions. However, we decided to focus on the α,β-unsaturated ketone, as the Luche reduction is well-known for its 1,2-selectivity. Gratifyingly, a diastereomeric mixture of **4a**/**4a'**, procured from the large-scale synthesis, underwent the reaction in a regioselective manner, obtaining the desired 1,2-diol **6** in 93% yield with conserved diastereo- and enantiopurity (Scheme 5).



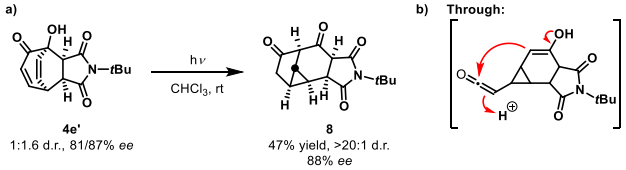
Scheme 5. Regioselective Luche reduction.

Next, we investigated the possibility of performing a hydrogenation of the two olefins, which would afford a fully saturated core structure. Using Pd/C hydrogenation at atmospheric pressure gave **7** in a quantitative yield.



Scheme 6. Pd/C hydrogenation of the two olefins in cycloaddition product **4a'**.

Based on preceding photochemical transformations, we believed that the dihydrohomobarrelenones **4** would be eligible for photoisomerizations forming complex polycyclic compounds.[5d,11] The formed norcarane derivates would include fully substituted chiral cyclopropanes, which are often considered challenging synthetic targets.[12] To our delight, the photoisomerization proceeded smoothly when subjecting a mixture of cycloadduct **4e**:**4e'** to light in $CHCl_3$, yielding the tetracyclic norcarane **8** in 47% yield, >20:1 d.r. and maintaining the enantiomeric excess (Scheme 7a).



Scheme 7. Photoisomerization of **4a** into tetracyclic norcarane **8**.

Following the formation of the cyclopropane through a diradical pathway, the intermediate features an electrophilic ketene that undergoes nucleophilic attack by intramolecular enolate addition, forming the tetracyclic norcarane **8** (Scheme 7b). To explore this reaction further, we envisaged using the silylated cycloadducts **5** in a complementary photochemical reaction. As TMS-enolates are bulkier and have reduced nucleophilic character compared to enolates, intramolecular cyclization is less likely. If combined with a nucleophilic solvent like methanol, the ketene should form a methyl ester, ultimately yielding a simpler norcarane scaffold. Gratifyingly, irradiating a methanolic solution of silylated adducts **5a**,**b**, procured the desired products in

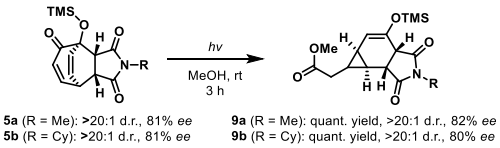
Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201808221
WILEY-VCH

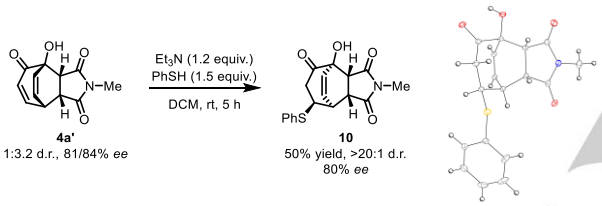
COMMUNICATION

quantitative yields, with complete preservation of the diastereo- and enantioselectivity (Scheme 8).



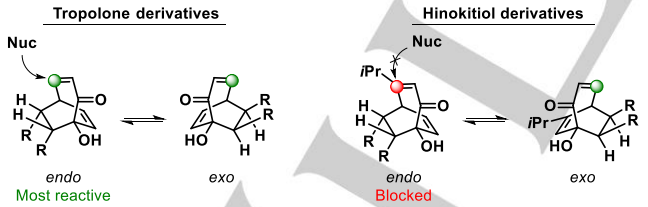
Scheme 8. Photoisomerization of **5a**,**b** into norcaranes **9a**,**b**.

Small-molecules bearing Michael acceptors may be both potent and selective modulators of biological macromolecules as well as non-discriminant alkylators of mainly proteinogenic thiol groups.[8] The aforementioned acyloin-rearrangement has unique consequences for this type of reactivity within the cycloadducts **4** as the rearrangement interconverts two different α,β-unsaturated ketones. To investigate the thiol-reactivity of **4a/4a'**, we first attempted a hetero-Michael addition using thiophenol. Following 5 h of reaction time, the Michael adduct **10** was isolated in 50% yield, >20:1 d.r. and with conservation of the enantiomeric excess (Scheme 9). Gratifyingly, the absolute configuration of **10** was obtained following X-ray crystallographic analysis, establishing the preceding stereochemistry of the cycloadducts formed using catalyst **3a**.



Scheme 9. Thiophenol Michael addition.

Interestingly, the outcome of the thiophenol-addition suggests that the *endo*-product (**4a**) is markedly more reactive towards thiols which explains formation of **10** in accordance with the Curtin-Hammett principle. By comparison, cycloadducts derived from hinokitiol (e.g. **4i/4i'** and **4j/4j'**) also contain two Michael-acceptor motifs formed reversibly *via* the acyloin rearrangement, however the presumed reactive *endo* α,β-unsaturated ketone present in **4i**/**4j** is blocked at the β-carbon atom (Scheme 10).



Scheme 10. Michael acceptor properties of tropolone and hinokitiol derivatives.

To study how these fundamental stereochemical properties of the cycloadducts impact their performance in a complex biological system, we subjected live MCF-7 cancer cells to increasing quantities of the optically active propargyl-derivatives **4d** and **4j** to investigate their proteomic reactivity. Following cell lysis, click-conjugation with FAM-azide was performed and covalent binding targets was detected *via* in-gel fluorescence measurementsThese experiments demonstrated that **4d** is promiscuous and labels a large number of cellular proteins, but – remarkably – **4j** was almost devoid of reactivity at the concentrations tested (Figure 2a), which suggest that the α,β-unsaturated ketone **4j'** (and **4d'**) indeed is not a biologically competent electrophile. In accordance with these observations, **4d** was cytotoxic whereas **4j** was not (Figure 2b).[13]

In conclusion, we have developed an asymmetric Brønsted-base catalyzed [4+2]-cycloaddition between tropolones and electron-deficient dienophiles to produce a broad selection of chiral dihydrohomobarrelenones. The obtained products are successfully subjected to a large variety of synthetic transformations, such as selective reductions and photoisomerizations. The preliminary biological investigations show that despite of their complex natural-product-looking scaffold, tropolone-cycloadducts should be critically assessed for potential non-specific interactions, however by judicious scaffold-selection these liabilities can be strongly reduced or even eliminated. Such compounds could be advantageously applied in future biochemical or cell-based screens.

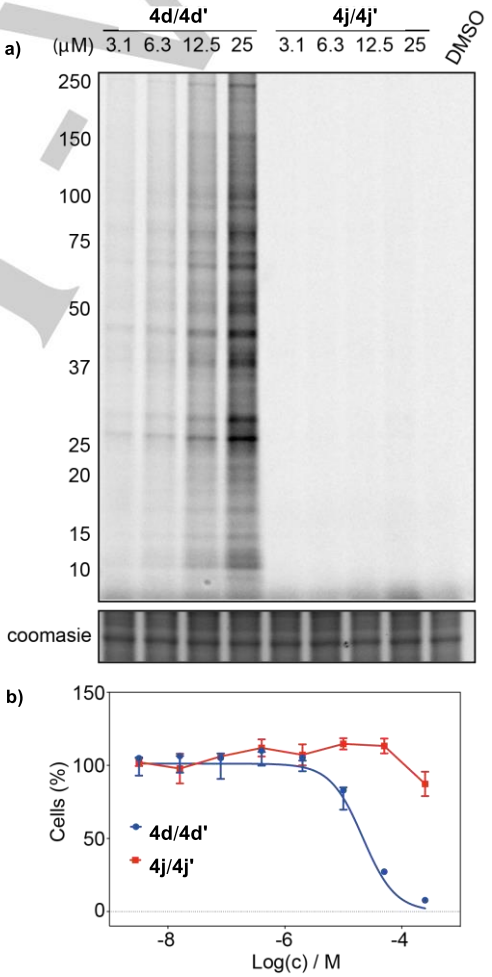


Figure 2. a) In-gel fluorescence assay. b) Viability of MCF-7 cancer cells.

Acknowledgements

This work was made possible by financial support from Carlsberg Foundation Semper Ardens, Aarhus University and DNRF.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/anie.201808221

Keywords: Tropolone • Organocatalysis • Cycloaddition • Bioactivity • Photoisomerization

[1] For general reviews regarding the physiochemical properties and biological activity of tropolones: a) R. Bentley, *Nat. Prod. Rep.* **2008**, *25*, 118-138; b) J. Zhao, *Curr. Med. Chem.* **2007**, *14*, 2597-2621. c) P. L. Pauson, *Chem. Rev.* **1955**, *55*, 9-136; d) Y. Dutt, R. P. Singh, M. Katyal, *Talanta* **1969**, *16*, 1369-1382; for selected examples, see: e) Y. Morita, E. Matsumura, T. Okabe, M. Shibata, M. Sugiura, T. Ohe, H. Tsujibo, N. Ishida, Y. Inamori, *Biol. Pharm. Bull.* **2003**, *26*, 1487-1490; f) K. Nakano, T. Chigira, T. Miyafusa, S. Nagatoishi, J. M. Caaveiro, K. Tsumoto, *Sci. Rep.* **2015**, *5*, 15337; g) Y. Morita, E. Matsumura, H. Tsujibo, M. Yasuda, Y. Sakagami, T. Okabe, N. Ishida, Y. Inamori, *Biol. Pharm. Bull.* **2001**, *24*, 607-611.

[2] a) E. Zachary Oblak, E. S. D. Bolstad, S. N. Ononye, N. D. Priestley, M. Kyle Hadden, D. L. Wright, *Org. Biomol. Chem.* **2012**, *10*, 8597-8604; b) M. Koufaki, E. Theodorou, X. Alexi, F. Nikoloudaki, M. N. Alexis, *Eur. J. Med. Chem.* **2010**, *45*, 1107-1112; c) J. Potenziano, R. Spitale, M. E. Janik, *Synth. Commun.* **2005**, *35*, 2005-2016; d) K. Cheng, X. Wang, S. Zhang, H. Yin, *Angew. Chem. Int. Ed.* **2012**, *51*, 12246-12249.

[3] S. Chakrabarty, M. S. Croft, M. G. Marko, G. Moyna, *Bioorg. Med. Chem.* **2013**, *21*, 1143-1149.

[4] a) A. A. Ghawanmeh, K. F. Chong, S. M. Sarkar, M. A. Bakar, R. Othaman, R. M. Khalid, *Eur. J. Med. Chem.* **2018**, *144*, 229-242. b) Y. Matsuo, A. Yoshida, Y. Saito, T. Tanaka, *Angew. Chem. Int. Ed.* **2017**, *56*, 11855-11859; c) D. Mesa-Siverio, A. Estévez-Braun, Ángel G. Ravelo, Jose R. Murguia, A. Rodríguez-Afonso, *Eur. J. Org. Chem.* **2003**, 4243-4247.

[5] a) G. R. Tian, S. Sugiyama, A. Mori, H. Takeshita, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2393-2399; b) G. R. Tian, S. Sugiyama, A. Mori, H. Takeshita, *Chem. Lett.* **1987**, *16*, 1557-1560; c) T. Nozoe, S. Seto, T. Ikemi, *Proc. Jpn. Acad.* **1952**, *27*, 655-657; d) C. Tabarez, A. L. Radcenco, G. Moyna, *Tetrahedron Lett*. **2016**, *57*, 1515-1517.

[6] a) H. Okamura, H. Iiji, T. Hamada, T. Iwagawa, H. Furuno, *Tetrahedron* **2009**, *65*, 10709-10714; b) M. Eugui, K. Rasquin, A. L. Radcenco, L. Suescun, G. Moyna, *Tetrahedron Lett.* **2018**, *59*, 1560-1563.

[7] For reviews on asymmetric bifunctional Brønsted-base catalysis: a) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703-4832; b) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632-653; for selected examples of cycloadditions with pyrones and pyridones: c) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365. d) K. J. Bartelson, R. P. Singh, B. M. Foxman, L. Deng, *Chem. Sci.* **2011**, *2*, 1940-1944; e) J. Y.-T. Soh, C.-H. Tan, *J. Am. Chem. Soc.* **2009**, *131*, 6904-6905; for selected examples of cycloadditions catalysed by bifunctional Brønsted-base catalysis: f) W. Wanqing, M. Long, Z. Lizhi, L. Chi-Sing, *Adv. Synth. Catal.* **2011**, *353*, 1135-1145; g) A. Zea, G. Valero, A.-N. R. Alba, A. Moyano, R. Rios, *Adv. Synth. Catal.* **2010**, *352*, 1102-1106.

[8] P. A. Jackson, J. C. Widen, D. A. Harki, K. M. Brummond, *J. Med. Chem.* **2017**, *60*, 839-885.

[9] a) S. Itô, H. Takeshita, Y. Shoji, Y. Toyooka, T. Nozoe, *Tetrahedron Lett.* **1968**, *9*, 3215-3218; b) S. Itô, A. Mori, Y. Shoji, H. Takeshita, *Tetrahedron Lett.* **1972**, *13*, 2685-2688.

[10] a) G. Tanriver, B. Dedeoglu, S. Catak, V. Aviyente, *Acc. Chem. Res.* **2016**, *49*, 1250-1262; b) W.-Y. Siau, J. Wang, *Catal. Sci. Technol.* **2011**, *1*, 1298-1310.

[11] a) C. Tabarez, A. Khrizman, P. Moyna, G. Moyna, *Tetrahedron* **2012**, *68*, 8622–8629; b) C. Tabarez, C. Waterman, A. L. Rapp, P. Moyna, G. Moyna, *Tetrahedron Lett.* **2009**, *50*, 7128-7131.

[12] M. Eugui, F. Parpal, A. López Radcenco, G. Moyna, *Org. Prep. Proced. Int.* **2018**, *50*, 260-287.

[13] It should be noted that similar results were obtained with the racemic analogues.

Accepted Manuscript

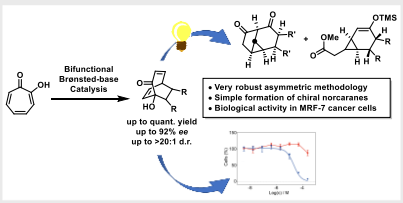
This article is protected by copyright. All rights reserved.

10.1002/anie.201808221

WILEY-VCH

COMMUNICATION

Text for Table of Contents



*Niels Hammer, Jeremy D. Erickson, Vibeke H. Lauridsen, Joakim B. Jakobsen, Bente K. Hansen, Kristian M. Jacobsen, Thomas B. Poulsen and K. A. Jørgensen**

Page No. – Page No.

Catalytic Asymmetric [4+2]-Cycloadditions Using Tropolones: Developments, Scope, Transformations and Bioactivity

Accepted Manuscript

WILEY-VCH

This article is protected by copyright. All rights reserved.