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Enantioselective Formation of Substituted 3,4-Dihydrocoumarins by a Multicatalytic One-Pot Process

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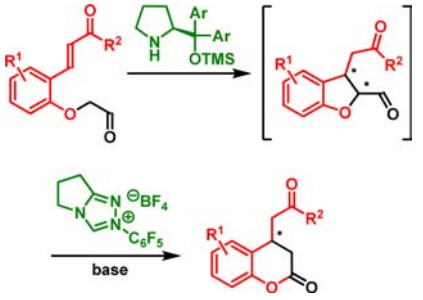
ABSTRACT



The formation of optically active 3,4-dihydrocoumarins is presented by merging aminocatalysis with an *N*-heterocyclic carbene-catalyzed internal redox reaction. The products are formed in good to excellent yields and in general with excellent enantioselectivities. Moreover, the developed procedure demonstrates the potential of enantioselective, multicatalytic sequences. By employing an enantiopure aminocatalyst in the enantiodifferentiating step, the challenges related to achieving high stereoinductions by deployment of optically active NHC-catalysts can be circumvented.

In recent years, the utilization of asymmetric, organocatalytic, multicatalytic, domino, and one-pot reactions has been widely explored in the development of complex reaction sequences.[1] In this regard, the reliability of aminocatalysts in inducing enantioselectivity in organocatalytic reactions has been combined with the intriguing reactivity of *N*-heterocyclic carbenes (NHC) for accessing molecular and stereochemical diversity.[2]

3,4-Dihydrocoumarins and related structures are of great interest for life science, as they are widely distributed in nature and are core structures in certain pharmaceuticals.[3]

(1) For recent reviews on organocatalytic domino and multicatalytic reaction sequences, see: (a) Wende, R. C.; Schreiner, P. R. *Green Chem.* **2012**, *14*, 1821. (b) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (c) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (d) Enders, D.; Grondahl, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(2) For a recent review, see: (a) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. For selected recent examples, see: (b) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 13628. (c) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Jørgensen, K. A. *Org. Lett.* **2010**, *12*, 5052. (d) Hong, B.; Dange, N. S.; Hsu, C.; Liao, J. *Org. Lett.* **2010**, *12*, 4812. (e) Hong, B.; Dange, N. S.; Hsu, C.; Liao, J.; Lee, G. *Org. Lett.* **2011**, *13*, 1338. (f) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835. (g) Jacobsen, C. B.; Jensen, K. L.; Udmark, J.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 4790. (h) Yankai, L.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310.

(3) For examples, see: (a) Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887. (b) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477. (c) Iinuma, M.; Tanaka, T.; Mizuno, M.; Katsuzaki, T.; Ogawa, H. *Chem. Pharm. Bull.* **1989**, *37*, 1813. (d) Hsu, F. L.; Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1985**, *33*, 3142.

(4) Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105.

(5) For other selected enantioslective formations of 4-substituted 3,4-dihydrocoumarins illustrating different synthetic approaches, see: (a) Chen, G.; Tokunaga, N.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2285. (b) Dong, C.; Alper, H. *J. Org. Chem.* **2004**, *69*, 5011. (c) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (d) Kim, H.; Yun, J. *Adv. Synth. Catal.* **2010**, *352*, 1881. (e) Gallagher, B. D.; Taft, B. R.; Lipshutz, B. H. *Org. Lett.* **2009**, *11*, 5374. (f) Kuang, Y.; Liu, X.; Chang, L.; Wang, M.; Lin, L.; Feng, X. *Org. Lett.* **2011**, *13*, 3814. (g) Teichert, J. F.; Feringa, B. L. *Chem. Commun.* **2011**, *47*, 2679. (h) Allen, J. C.; Kociok-Köhn, G.; Frost, C. G. *Org. Biomol. Chem.* **2012**, *10*, 32. (i) Lee, Y.; Seo, S. W.; Kim, S. *Adv. Synth. Catal.* **2011**, *353*, 2671.

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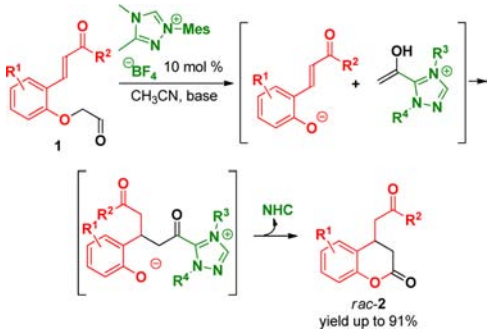
In 2009, Scheidt et al. reported the synthesis of racemic 3,4-dihydrocoumarins *rac*-**2** by an NHC-catalyzed internal redox process starting from the aryloxyacetaldehydes **1** (Scheme 1).[4] Whereas the products were isolated in good to excellent yields, the development of an enantioselective version of the protocol turned out to be challenging.[5] As such, an extensive screening of enantiopure NHCs never resulted in an enantioenrichment of more than 10% ee. This exemplifies the issue with the current lack of a successful general catalytic system for such enantioselective NHC-catalyzed transformations.[6]

Scheme 1. Scheidt et al.'s Procedure for the Formation of Racemic 3,4-Dihydrocoumarins *rac*-**2**[a]

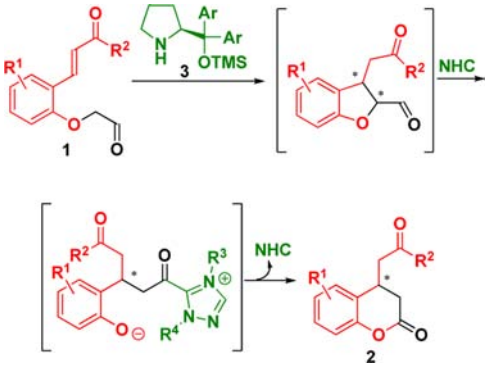


[a] Mes = mesityl.

Within the field of asymmetric organocatalysis, chiral secondary amines have been employed as catalysts in a range of diverse enantioselective functionalizations of enolizable aldehydes and enals.[7] In this regard, the diarylprolinol silyl ethers have proved to be general catalysts for activating substrates by enamine or iminium-ion intermediates.[8] We envisioned that the unsuccessful pursuit of a chiral carbene for catalyzing the enantioselective formation of 3,4-dihydrocoumarins (Scheme 1) might be circumvented by merging the reactivity of enamines derived from an enantiopure diarylprolinol silyl ether **3** with the synthetic potential of an achiral carbene (Scheme 2). As such, the enantioselectivity would be induced in the step preceding the NHC-catalyzed reaction.

However, as it appears from Scheme 2, such an approach entails three inherent issues: (*i*) The optical purity introduced in the initial addition must be maintained throughout the entire process. The necessity of a base to form the active carbene from its precursor in the second step might add to this challenge. (*ii*) The stereocenter generated in the α-position to the aldehyde upon attack of the enamine is destroyed in the subsequent NHC-catalyzed step. As such, an approach as illustrated in Scheme 2 is made difficult by the fact that, in order to attain a highly enantioenriched product **2**, it is a necessity that the initial addition step proceeds with good stereoselectivity in the formation of the stereocenter created on the Michael-acceptor part of **1**.[9] The catalyst, controlling the formation of the stereocenters via an enamine pathway, would be expected to primarily control the stereocenter adjacent to aldehyde functionality. Therefore, excellent control of the stereocenter the farthest away from the reactive enamine might be difficult to obtain. (*iii*) Even though the 3,4-dihydrocoumarins **2** have a simple molecular structure, the envisioned process for their enantioselective synthesis involves the formation and breaking of a number of bonds. As such, a high yielding route to these compounds can be challenging.

Scheme 2. Envisioned Approach for the Multicatalytic Formation of Enantioenriched 3,4-Dihydrocoumarins **2**



Despite these potential complications we decided to investigate if the development of a highly enantioselective formation of 3,4-dihydrocoumarins **2**, through a multicatalytic enamine/NHC sequence, was feasible. Our initial screening process was focused on determining the optimal conditions for the initial aminocatalyzed 1,4-addition (for optimization data, see Supporting Information). Through screening of solvents, acid additives, temperatures, and catalysts, we established that catalyst **3a** combined with catalytic amounts of *o*-nitrobenzoic acid in *o*-xylene was optimal for this initial step. Furthermore, the screening of carbene precursors and bases established that the carbene precursor **4** and DIPEA were superior for catalyzing the subsequent internal redox reaction leading to **2** (Figure 1).

(6) For selected examples on successful utilizations of enantioenriched NHCs in redox reactions employing α-functionalized aldehydes as substrates, see: (a) He, M.; Beahn, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (c) Vora, H. A.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860. (d) Reynolds, N. T.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 16406.

(7) For selected reviews on aminocatalysis, see: (a) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (b) *Chem. Rev.* **2007**, *107*, 12, special issue on organocatalysis. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (d) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (e) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (f) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(8) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(9) An apparent thought would be that this issue might be solved by employment of a chiral primary amine salt to activate the ketone moiety in **1** by formation of an iminium ion. However, we found that such a process was not feasible.

We then employed these conditions in the investigation of the scope of the developed one-pot process (Figure 1). It was found that the aryl ketone moiety in **1** can be neutral, electron-rich, and electron-poor in nature as demonstrated by the formation of products **2a**–**d**. The yields of 51–68% for these substrates are good especially considering that their formation relies on a multicatalytic process involving the breaking and formation of numerous bonds. The enantioselectivities for **2a**–**d** are in all cases very high reaching up to 92% ee. The formation of **2d**,**e** having a fluorine substituent in either the *para*- or *meta*-position is noteworthy, as fluorine holds a special place in medicinal chemistry.[10]

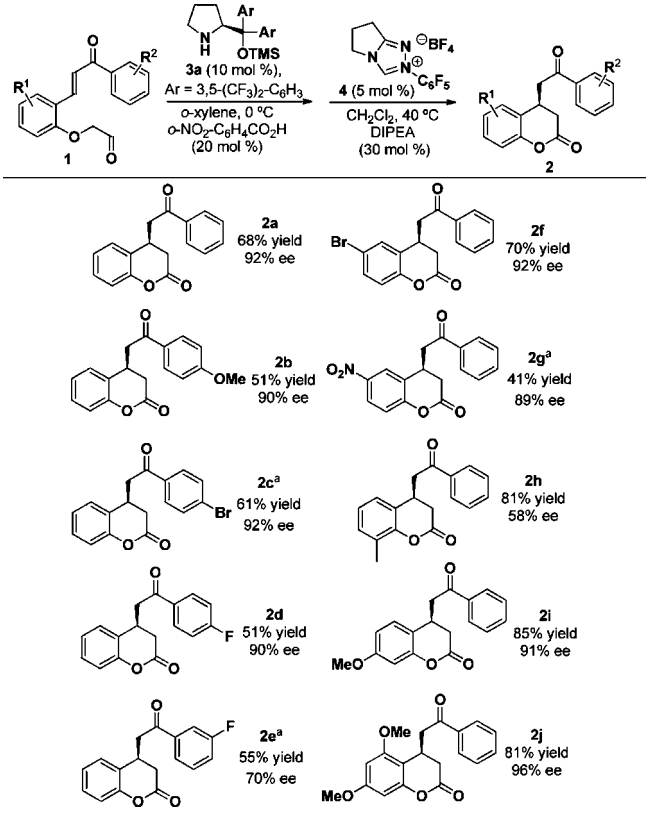


Figure 1. All reactions performed as follows: (Step 1) **1** (0.2 mmol), **3a** (10 mol %), *o*-NO_2–$C_6H_4CO_2H$ (20 mol %) in *o*-xylene (1.0 mL) at 0 °C; (Step 2) **4** (5.0 mol %), DIPEA (30 mol %), adding CH_2Cl_2 (0.2 mL) at 40 °C. Yields are isolated yields. Enantiomeric excesses were determined by UPC. See Supporting Information for further details. [a] **3a** (20 mol %) and *o*-NO_2–$C_6H_4CO_2H$ (40 mol %) used.

The products **2f**–**j** exemplify selected, possible substitution patterns on the aromatic tether. As depicted, substrates carrying both electron-donating and electron-withdrawing substituents can be employed. Moreover, these substituents can reside on the 5-, 6-, 7-, and 8-position on this ring illustrating the synthetic usefulness of this process. These products can all be isolated in moderate to high yields (41–85%), while maintaining high enantioselectivities up to 96% ee. However, substituents in the 8-position lower the enantioselectivity as exemplified by the formation of **2h** with 58% ee presumably due to steric reasons. Finally, the introduction of two substituents on the aromatic tether proved possible as demonstrated by the synthesis of **2j**.[11]

The absolute configuration of products **2** was determined to be *S* by single crystal X-ray analysis on the product **2f** (Figure 2, top). Figure 2 depicts the two possible transition states leading to the observed enantiomer of **2**. As we observed both the *cis*- and *trans*-diastereomer in the NMR spectra of the crude reaction mixtures, and as the enantiomeric excesses are in most cases excellent, it can be anticipated that both diastereoisomers are formed due to either low stereocontrol or epimerization on the aldehyde α-stereocenter. However, as this stereocenter is destroyed in the carbene catalyzed internal redox reaction, low diastereoselectivity does not transfer to the products.

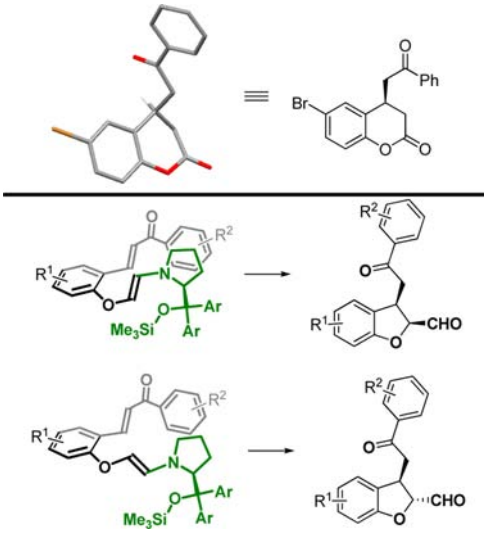


Figure 2. Assignment of absolute configuration and rationalization of the stereochemical outcome.

In conclusion, we have developed a multicatalytic one-pot reaction sequence relying on the well-established general enantioselective catalytic capabilities of a diarylprolinol silyl ether catalyst and an achiral NHC-catalyst for the formation of highly enantioenriched 3,4-dihydrocoumarins. The products were isolated in moderate to high yields, and the enantioselectivities

(10) (a) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (c) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (d) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: 2009.

(11) Attempts to extend the developed procedure to other Michael acceptors, such as nitroolefins and alkyl ketones, gave less satisfactory results.

were in most cases high. Moreover, the developed process illustrates the possibility of solving the issue with the lack of a general enantioselective carbene catalyst, by introducing an additional enantiodifferentiating aminocatalytic step. As such, this process might inspire further developments of such sequences.

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Supporting Information Available. Detailed experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.