CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

# Accepted Article

**Title:** N-Heterocyclic Carbene Catalyzed [3+2] Cycloaddition of Enals with Masked Cinnamates for the Asymmetric One-Pot Synthesis of Adipic Acid Derivatives

**Authors:** Dieter Enders, Xiang-Yu Chen, Sun Li, He Sheng, Qiang Liu, Ehsan Jafari, Carolina von Essen, and Kari Rissanen



**To be cited as:** *Chem. Eur. J.* 10.1002/chem.201703579

**Link to VoR:** http://dx.doi.org/10.1002/chem.201703579

Supported by
ACES

WILEY-VCH

10.1002/chem.201703579

COMMUNICATION

WILEY-VCH

# N-Heterocyclic Carbene Catalyzed [3+2] Cycloaddition of Enals with Masked Cinnamates for the Asymmetric One-Pot Synthesis of Adipic Acid Derivatives

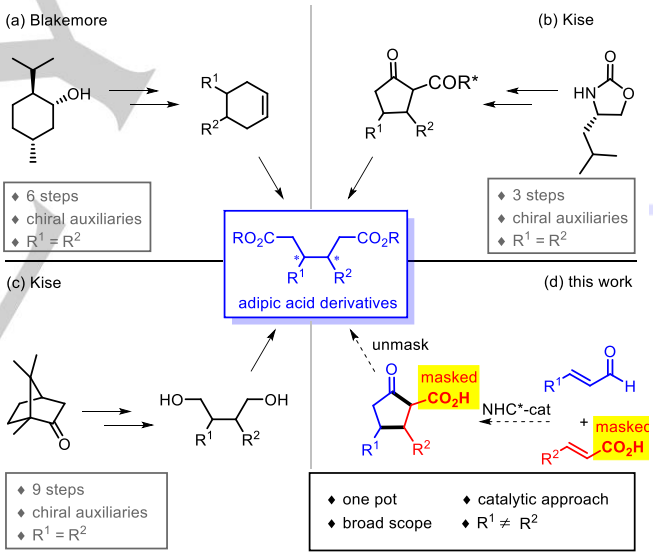
Xiang-Yu Chen+, Sun Li+, He Sheng, Qiang Liu, Ehsan Jafari, Carolina von Essen, Kari Rissanen and Dieter Enders*

Dedication ((optional))

**Abstract:** A novel short entry to 3,4-disubstituted adipic acids has been developed by employing an asymmetric NHC-catalyzed [3+2] cycloaddition of enals with masked cinnammates in moderate to good yields and high stereoselectivities. The synthetic utility of the protocol was demonstrated by the basic conversion of the masked cyclopentanone intermediates to *3S,4S*-disubstituted adipic acid precursors of pharmaceutically important gababutins.

Adipic acids and their derivatives, as important chemical building blocks, have received a great deal of attention due to their wide applications in the chemical and pharmaceutical field.[1] Thus, considerable efforts have been devoted to the synthesis of structurally diverse adipic acid derivatives.[2] However, to date there are only very few approaches to enantiopure adipic acid derivatives. One typical entry is the oxidation of chiral cyclohexenes, which could be obtained via (—)-menthol (Scheme 1, strategy a).[3] Another approach involving the electroreductive hydrocoupling of cinnamoyloxazolidinones was successfully realized by Kise and co-workers (Scheme 1, strategy b).[4] Later, they developed another protocol to chiral adipic esters via the electroreductive hydrocoupling of cinnamates derived from (+)-camphor (Scheme 1, strategy c).[5] Despite this progress, all these approaches employ chiral auxiliaries and few syntheses exist starting from achiral substrates.[6] To the best of our knowledge, catalytic diastereo- and enantioselective strategies to chiral adipic acid derivatives starting form achiral, simple substrates has so far not been realized, and therefore will be highly desirable.

In the last few decades N-heterocyclic carbenes (NHCs) emerged as efficient organocatalysts for various synthetically important asymmetric bond formations,[7] for instance the conjugate umpolung of α,β-unsaturated aldehydes.[8] In 2007, Nair and co-workers first reported the NHC-catalyzed formal [3+2] cycloaddition of enals with cyclic Michael acceptors for the synthesis of spirocyclopentanes.[9] Only until recently have enantioselective variants been developed by Glorius[10] et al. and our group[11] by using heterocyclic Michael acceptors. However, the asymmetric formal [3+2] cycloaddition of enals with simple linear Michael acceptors is still a challenge, [12] presumably due to the competitive homoenolate/enolate domino process[13] or the difficulty of releasing the NHC catalyst via nucleophilic attack of a carbon atom.[14] Thus, a highly enantioselective variant of this kind of transformation remains elusive so far. Herein, we describe the first example of a one pot strategy to enantioenriched adipic acid derivatives via NHC-catalyzed formal [3+2] cycloaddition of enals with masked cinnnamates (Scheme 1, strategy d).




**Scheme 1.** Typical approaches to chiral 3,4-disubstituted adipic acid derivatives.

4-Nitro-5-styrylisoxazoles, known as valuable masked cinnamate equivalents and developed by Adamo et al., have been exploited and utilized for the synthesis of complex molecules.[15] Several chiral catalysts have been developed for the transformations of 4-nitro-5-styrylisoxazoles, such as aminothioureas,[16] trienamines,[17] and phase transfer catalysts.[18] In 2012 Adamo et al. reported an interesting NHC-catalyzed cycloaddition of 4-nitro-5-styrylisoxazoles with enals to generate racemic cyclopentanones.[19] Our group has been interested in the development of NHC-catalyzed asymmetric variants of important organic transformations.[20] Very recently, we successfully developed stereoselective cycloadditions of 4-

[*] Dr. X.-Y. Chen, S. Li, H. Sheng, Q. Liu, Dr. E. Jafari
Prof. Dr. D. Enders
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: enders@rwth-aachen.de

Dr. C. von Essen, Prof. Dr. K. Rissanen
Department of Chemistry, Nanoscience Center, University of Jyvaskyla, 40014 JYU (Finland)

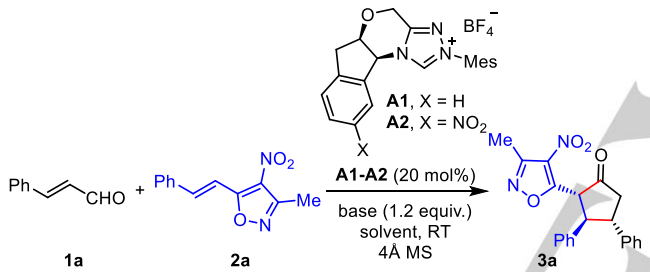
+ X.-Y. Chen and S. Li contributed equally

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

nitro-5-styrylisoxazoles by using NHC catalysis.[21] We envisaged that diverse chiral adipic acid derivatives could be easily synthesized via a chiral-NHC-catalyzed [3+2] cycloaddition of enals with 4-nitro-5-styrylisoxazoles.

Initially, the model reaction of the enal **1a** and 3-methyl-4-nitro-5-alkenyl-isoxazole **2a** was investigated under NHC catalysis (Table 1). In the presence of the tetracyclic NHC **A1** derived from aminoindanol,[22] and DBU as the base, the desired cycloadduct **3a** could be obtained in encouraging 22% yield, with 13:1 dr and 78% ee (entry 1). A solvent screening showed that the reaction in DCM, DCE, toluene or MTBE provided poorer results than in THF (entries 2–5). The yield and enantioselectivity was improved when NHC **A2** with a strongly electron-withdrawing nitro group[23] was employed (entry 6). Other bases, such as DIPEA, CsOAc and $Cs_2CO_3$ were evaluated, but gave inferior results (entries 7–9). Further improvement was realized by degassing the reaction mixture (entry 10). When the reaction was carried out in DME with degassing, the desired product **3a** was obtained in 57% yield with unchanged diastereo- and enantioselectivity (entry 11).

**Table 1:** Optimization of the reaction conditions.

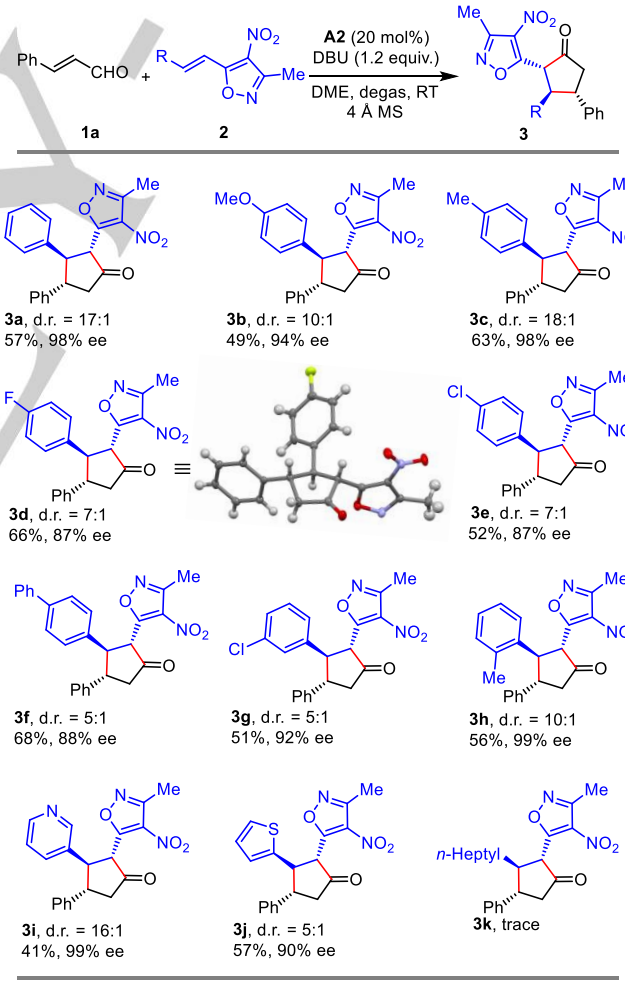



| Entry | NHC | Solvent | Base | Yield [%][a] | d.r.[b] | ee [%][c] |
|---|---|---|---|---|---|---|
| 1 | **A1** | THF | DBU | 22 | 13:1 | 78 |
| 2 | **A1** | DCM | DBU | 22 | 16:1 | 56 |
| 3 | **A1** | DCE | DBU | 42 | 20:1 | 66 |
| 4 | **A1** | Toluene | DBU | trace | — | — |
| 5 | **A1** | MTBE | DBU | trace | — | — |
| 6 | **A2** | THF | DBU | 30 | 15:1 | 97 |
| 7 | **A2** | THF | DIPEA | trace | — | — |
| 8 | **A2** | THF | CsOAc | trace | — | — |
| 9 | **A2** | THF | $Cs_2CO_3$ | trace | — | — |
| 10[d] | **A2** | THF | DBU | 43 | 15:1 | 99 |
| 11[d] | **A2** | DME | DBU | 57 | 17:1 | 98 |

[a] Yield of isolated product **3a** after chromatography. [b] The d.r. values were determined by $^1$H NMR analysis. [c] The ee was determined by chiral HPLC analysis of the purified product on a chiral stationary phase. [d] The reaction mixture was degassed.

With the optimized reaction conditions in hand, the scope of the reaction was then briefly investigated (Table 2). It was found that both 3-methyl-4-nitro-5-alkenyl-isoxazoles with electron-donating (4-$MeOC_6H_4$ and 4-$MeC_6H_4$) and electron-withdrawing (4-$FC_6H_4$ and 4-$ClC_6H_4$) groups worked well for the reaction, giving the desired cycloadducts **3b–e** in moderate to good yields with good diastereo- (7:1-18:1 d.r.) and high enantioselectivities (87-98% ee). The *para*-phenyl substituted isoxazole substrate also led to the efficient formation of the corresponding product **3f**. Both substrates with a *meta*-substituent (3-$ClC_6H_4$) and *ortho*-substituent (2-$MeC_6H_4$) worked well (**3g** and **3h**). Notably, the reaction of a substrate with a 3-pyridyl group was also successful and provided the desired product **3i** in 41% yield with 16:1 d.r. and 99% ee. The 2-thienyl substituted substrate was also tolerable providing the corresponding cycloaddition **3j** in moderate to good yield with high stereoselectivities. Unfortunately, an alkyl substituted substrate gave only a trace amount of the product under the current reaction conditions (**3k**).

**Table 2:** Stereoselective [3+2] cycloaddition with various masked cinnamates.




All reactions were carried out on 0.4 mmol scale. Yields of isolated products **3** after chromatography. The d.r. was determined by $^1$H NMR analysis and the ee by HPLC analysis of the purified product on a chiral stationary phase.

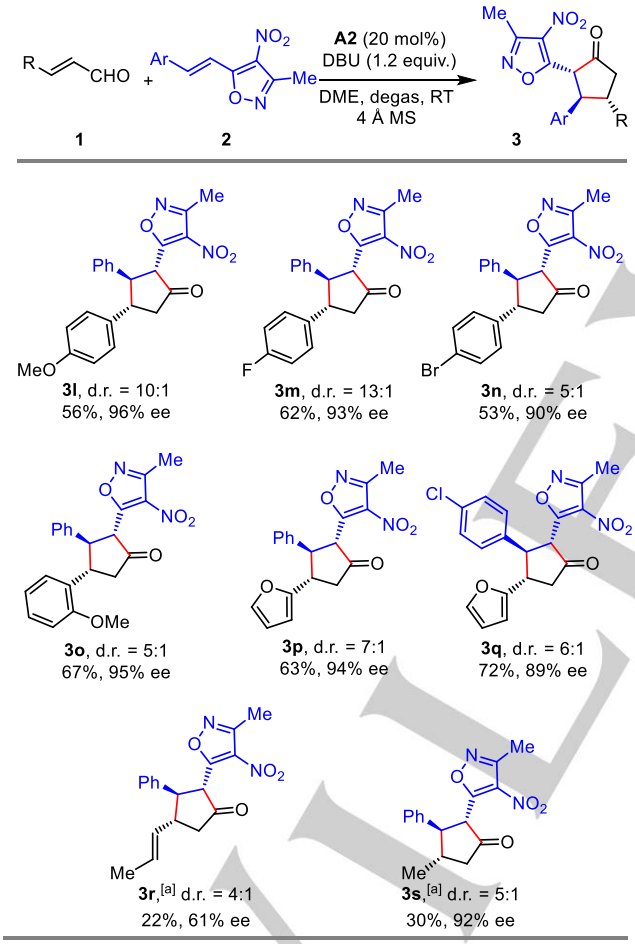
10.1002/chem.201703579



The absolute configuration of the cycloadduct **3d** was determined by the X-ray structure analysis[24] and the configurations of all other products were assigned accordingly.

The scope of the reaction with respect to the enals was also examined (Table 3). The enals with electron-donating or electron-withdrawing substituents (4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, and 4-BrC$_6$H$_4$) proceeded smoothly and gave the desired products **3l–n** in moderate to good yields and diastereomeric ratios with excellent enantioselectivities. Both a bulky aryl group (2-MeOC$_6$H$_4$) and a heteroaryl group (2-furyl) were also tolerated, affording cycloadducts **3o–q** in good yields with high stereoselectivities. The reaction of β-alkenyl and β-alkyl enals also worked, but in very low yield (22%) with 61% ee (**3r**), 30% yield with 92% ee (**3s**), respectively.

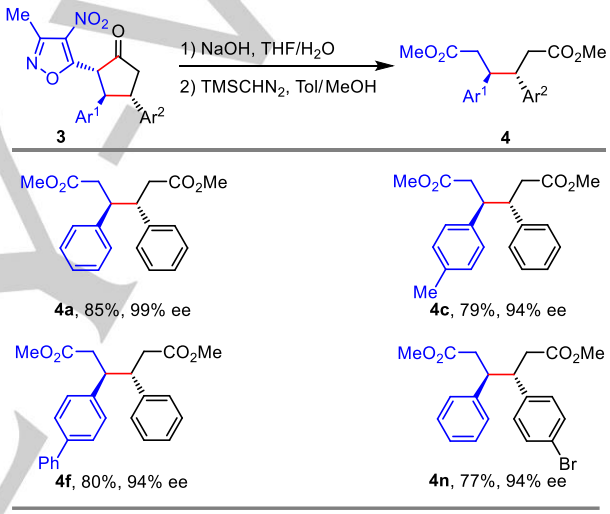
**Table 3:** Stereoselective [3+2] cycloaddition with various enals.



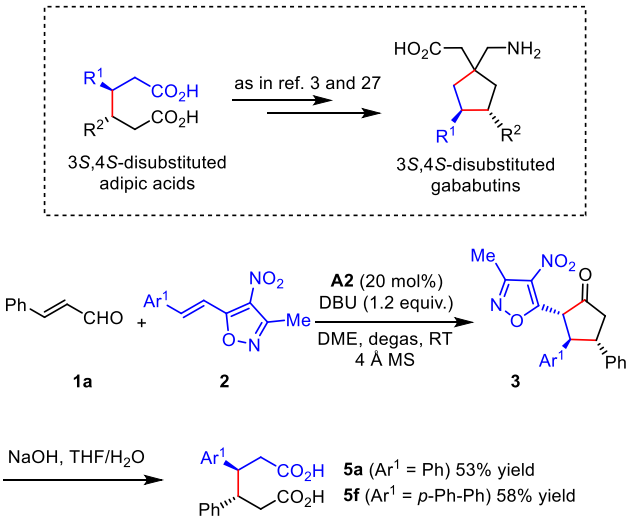

All reactions were carried out on 0.4 mmol scale. Yields of isolated products **3** after chromatography. The d.r. was determined by $^1$H NMR analysis and the ee by HPLC analysis of the purified product on a chiral stationary phase. [a] The products **3r**, **s** are slightly contaminated by impurities.

To demonstrate the synthetic utility of the present catalytic strategy, a convenient protocol for the asymmetric synthesis of 3,4-disubstituted adipic acid esters was developed. The resulting cyclopentanones could be easily transformed to 3,4-disubstituted adipic esters by treatment with aqueous NaOH followed by esterification (Scheme 2). The corresponding adipic esters **4a**, **4c**, **4f** and **4n**, with electron donating, *para*-phenyl and electron withdrawing substituents, respectively, were obtained in good yields without erosion of the stereoselectivity.

The synthetic utility of this catalytic protocol was further demonstrated by aiming at the 3*S*,4*S*-disubstituted gababutins, which bind to the $\alpha_2\delta$ calcium channels,[25] and have been developed as treatments for various diseases, such as insomia, depression, hypokinesia and epilepsy.[26] As shown in Scheme 3, the [3+2] cycloaddition of **2** with cinnamaldehyde **1a** followed by unmasking of the resulting cycloadducts **3** led to the one-pot formation of the 3*S*,4*S*-disubstituted adipic acids **5**, precursors in the previous syntheses of 3*S*,4*S*-disubstituted gababutins.[3, 27] This application showcases the utility of NHC-organocatalysis and opens a novel short stereoselective entry to 3,4-disubstituted gababutins.




**Scheme 2.** Synthesis of 3*S*,4*S*-disubstituted adipic esters.




**Scheme 3.** One pot asymmetric synthesis of 3*S*,4*S*-disubstituted adipic acids, as intermediates for the synthesis of 3*S*,4*S*-disubstituted gababutins.

In summary, we have developed an organocatalytic asymmetric synthesis of 3,4-disubstituted adipic acid derivatives employing a NHC-catalyzed [3+2] cycloaddition of enals and masked cinnamates to afford the corresponding cyclopentanones bearing a masked carboxylic acid group in moderate to good yields with high stereoselectivities. The new protocol was successfully applied for the one-pot asymmetric synthesis of 3,4-disubstituted adipic acids as precursors of pharmaceutically important gabapentins.

## Acknowledgements ((optional))

Support from the European Research Council (ERC Advanced Grant 320493 "DOMINOCAT") is gratefully acknowledged. We thank BASF SE for the donation of chemicals.

**Keywords:** N-heterocyclic carbene • adipic acid • cycloaddition• gabapentins • organocatalysis

[1] a) A. Castellan, J. C. J. Bart, S. Cavallaro, *Catal. Today.* **1991**, *9*, 237; b) K. M. Draths, J. W. Frost, *J. Am. Chem. Soc.* **1994**, *116*, 399; c) Y. Deng, Z. Ma, K. Wang, J. Chen, *Green Chem* **1999**, *1*, 275; d) M. Dugal, G. Sankar, R. Raja, J. M. Thomas, *Angew. Chem. Int. Ed.* **2000**, *39*, 2310; e) R. Raja, G. Sankar, J. M. Thomas, *Angew. Chem. Int. Ed.* **2000**, *39*, 2313; f) S. Van de Vyver, Y. Roman-Leshkov, *Catal. Sci. Technol.* **2013**, *3*, 1465; g) J. Mormul, J. Breitenfeld, O. Trapp, R. Paciello, T. Schaub, P. Hofmann, *ACS Catal.* **2016**, *6*, 2802.

[2] a) J. Inanaga, Y. Handa, T. Tabuchi, K. Otsubo, M. Yamaguchi, T. Hanamoto, *Tetrahedron Lett.* **1991**, *32*, 6557; b) S. Kanemasa, H. Yamamoto, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 8505; c) L.-H. Zhou, D.-q. Shi, Y. Gao, W.-b. Shen, G.-y. Dai, W.-x. Chen, *Tetrahedron Lett.* **1997**, *38*, 2729; d) P. K. Kundu, S. K. Ghosh, *Org. Biomol. Chem.* **2009**, *7*, 4611.

[3] D. C. Blakemore, J. S. Bryans, P. Carnell, M. J. Field, N. Kinsella, J. K. Kinsora, L. T. Meltzer, S. A. Osborne, L. R. Thompson, S. C. Williams, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 248.

[4] N. Kise, S.-i. Mashiba, N. Ueda, *J. Org. Chem.* **1998**, *63*, 7931.

[5] N. Kise, K. Iwasaki, N. Tokieda, N. Ueda, *Org. Lett.* **2001**, *3*, 3241.

[6] T T. Kikukawa, T. Hanamoto, J. Inanaga, *Tetrahedron Lett.* **1999**, *40*, 7497.

[7] For recent selected reviews, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; c) J. W. Bode, *Nat. Chem* **2013**, *5*, 813; d) X.-Y. Chen, S. Ye, *Synlett* **2013**, *24*, 1614; e) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664; f) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; g) M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* **2014**, *510*, 485; h) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696; i) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, *115*, 9307; j) R. S. Menon, A. T. Biju, V. Nair, *Chem. Soc. Rev.* **2015**, *44*, 5040; k) M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; l) C. Zhang, J. F. Hooper, D. W. Lupton, *ACS Catal.* **2017**, *7*, 2583; m) E. Reyes, U. Uria, L. Carrillo, J. L. Vicario, *Synthesis* **2017**, *49*, 451.

[8] a) C. Burstein, F. Glorius, *Angew. Chem. Int. Ed.* **2004**, *43*, 6205; b) S. S. Sohn, E. L. Rosen, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 14370.

[9] a) V. Nair, B. P. Babu, S. Vellalath, E. Suresh, *Chem. Commun.* **2008**, 747; b) J. R. Struble, J. Kaeobamrung, J. W. Bode, *Org. Lett.* **2008**, *10*, 957.

[10] C. Guo, M. Schedler, C. G. Daniliuc, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 10232.

[11] a) L. Wang, S. Li, P. Chauhan, D. Hack, A. R. Philipps, R. Puttreddy, K. Rissanen, G. Raabe, D. Enders, *Chem. Eur. J.* **2016**, *22*, 5123; b) S. Li, L. Wang, P. Chauhan, A. Peuronen, K. Rissanen, D. Enders, *Synthesis* **2017**, *49*, 1808.

[12] The enantioselective synthesis of cyclopentanone enol tautomer was realized via formal cycloaddition of α,β-unsaturated imines with *cis*-enals and isatin-derived enals, respectively, followed by tautomerization, see: a) X. Chen, X. Fang, Y. R. Chi, *Chem. Sci.* **2013**, *4*, 2613; b) L. Wang, S. Li, M. Blümel, R. Putreddy, A. Peuronen, K. Rissanen, D. Enders, *Angew. Chem. Int. Ed.* **2017**, DOI: 10.1002/anie.201704210.

[13] a) V. Nair, S. Vellalath, M. Poonoth, E. Suresh, *J. Am. Chem. Soc.* **2006**, *128*, 8736; b) P.-C. Chiang, J. Kaeobamrung, J. W. Bode, *J. Am. Chem. Soc.* **2007**, *129*, 3520; c) B. Cardinal-David, D. E. A. Raup, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 5345; d) P. Verma, P. A. Patni, R. B. Sunoj, *J. Org. Chem.* **2011**, *76*, 5606.

[14] a) V. Nair, B. P. Babu, S. Vellalath, V. Varghese, A. E. Raveendran, E. Suresh, *Org. Lett.* **2009**, *11*, 2507; b) D. T. Cohen, B. Cardinal-David, K A. Scheidt, *Angew. Chem. Int. Ed.* **2011**, *50*, 1678; c) B. Maji, L. Ji, S. Wang, S. Vedachalam, R. Ganguly, X.-W. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8276; d) N. A. White, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 8504.

[15] a) M. F. A. Adamo, S. Chimichi, F. De Sio, D. Donati, P. Sarti-Fantoni, *Tetrahedron Lett.* **2002**, *43*, 4157; b) M. F. A. Adamo, D. Donati, E. F. Duffy, P. Sarti-Fantoni, *J. Org. Chem.* **2005**, *70*, 8395; c) M. F. Adamo, E. F. Duffy, *Org. Lett.* **2006**, *8*, 5157; d) M. F. Adamo, E. F. Duffy, V. R. Konda, *Heterocycles* **2007**, *71*, 1173.

[16] a) Q.-L. Pei, H.-W. Sun, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem.* **2011**, *76*, 7849; b) J. Zhang, X. Liu, X. Ma, R. Wang, *Chem Commun.* **2013**, *49*, 9329; c) P. Chauhan, S. Mahajan, G. Raabe, D. Enders, *Chem. Commun.* **2015**, *51*, 2270.

[17] Y. Li, F. J. Lopez-Delgado, D. K. B. Jørgensen, R. P. Nielsen, H. Jiang, K. A. Jørgensen, *Chem. Commun.* **2014**, *50*, 15689.

[18] a) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh, M. F. Adamo, *Angew. Chem. Int. Ed.* **2009**, *48*, 9342; b) C. D. Fiandra, L. Piras, F. Fini, P. Disetti, M. Moccia, M. F. A. Adamo, *Chem. Commun.* **2012**, *48*, 3863; 18c) L. Piras, M. Moccia, M. Cortigiani, M. F. Adamo, *Catalysts* **2015**, *5*, 595.

[19] D. S. Illera, S. Suresh, M. Moccia, G. Bellini, M. Saviano, M. F. A. Adamo, *Tetrahedron Lett.* **2012**, *53*, 1808.

[20] a) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem. Int. Ed.* **1995**, *34*, 1021; b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534.

[21] X.-Y. Chen, Q. Liu, P. Chauhan, S. Li, A. Peuronen, K. Rissanen, E. Jafari, D. Enders, *Angew. Chem. Int. Ed.* **2017**, *56*, 6241.

[22] a) M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* **2005**, *70*, 5725; b) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128* 8418.

[23] a) C. Zhao, F. Li, J. Wang, *Angew. Chem. Int. Ed.* **2016**, *55*, 1820; b) X. Wu, Y. Zhang, Y. Wang, J. Ke, M. Jeret, R. N. Reddi, S. Yang, B. A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.* **2017**, *56*, 2942.

[24] CCDC 1561240 (**3d**) contains 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.

[25] D. C. Blakemore, J. S. Bryans, P. Carnell, C. L. Carr, N. E. Chessum, M. J. Field, N. Kinsella, S. A. Osborne, A. N. Warren, S. C. Williams, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 461.

[26] a) B. Corrigan, D. E. Feltner, D. Ouellet, J. L. Werth, A. E. Moton, G. Gibson, *Br. J. Clin. Pharmacol.* **2009**, *68*, 174; b) M. C. Kjellsson, D. Ouellet, B. Corrigan, M. O. Karlsson, *Pharm. Res.* **2011**, *28*, 2610; c) J. E. Quintero, F. Pomerleau, P. Huettl, K. W. Johnson, J. Offord, G. A. Gerhardt, *Brain Res.* **2011**, *1401*, 1.

[27] a) J. S. Bryans, D. C. Horwell, A. J. Thorpe, D. J. Wustrow, P.-W. Yuen, (Warner-Lambert Company), US 6635673 B1, **2003**; b) H. J. Betche, E. A. Irdam, A. G. Padilla, B. Pearlman, W. R. Perrault, J. Vanalsten, T. S. Franczyk, (Pharmacia & Upjohn Company LLC), WO2007 010387 (A2), **2007**.

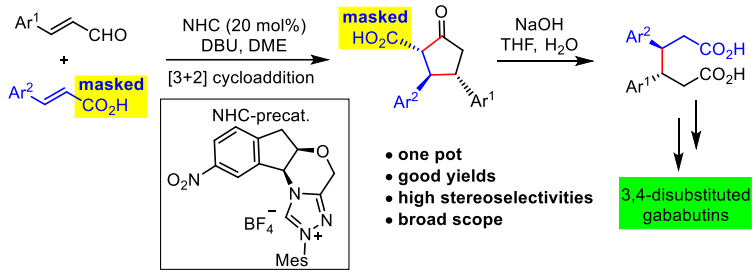
10.1002/chem.201703579


WILEY-VCH

**Entry for the Table of Contents** (Please choose one layout)

Layout 2:

# COMMUNICATION




**One-pot to adipic acids:** The NHC-catalyzed asymmetric [3+2] cycloaddition of enals with masked cinnamates opens a new short entry to adipic acid derivatives in moderate to good yields and high stereoselectivities. The utility of the protocol is showcased by the one-pot asymmetric synthesis of 3*S*,4*S*-disubstituted adipic acids, precursors for the synthesis of 3,4-disubstituted gababutins, which are used for the treatment of various diseases.

*Xiang-Yu Chen, Sun Li, He Sheng, Qiang Liu, Ehsan Jafari, Carolina von Essen, Kari Rissanen and Dieter Enders*

***Page No. – Page No.***

**N-Heterocyclic Carbene Catalyzed [3+2] Cycloaddition of Enals with Masked Cinnamates for the Asymmetric One-Pot Synthesis of Adipic Acid Derivatives**