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Organocatalytic Asymmetric Reduction of δ-Nitro Dienes: a Viable Entry to Functionalized Amines and Highly Substituted Enantioenriched Cyclopentanes

Chiara Faverio,[a] Francesca Franco,*[a] Giulia Taini,[a] Laura Raimondi,[a] and Maurizio Benaglia*[a]

δ-nitro dienes were successfully synthesized and converted to δ-nitro alkenes with complete chemo and regioselectivity. The enantioselective organocatalytic reduction was also accomplished and afforded the product in up to 97% e.e. The chiral nitro alkene was further elaborated and employed as starting material in a stereoselective cyclization reaction that led to an almost enantiomerically pure highly functionalised cyclopentane featuring 5 contiguous stereocenters.

Introduction

The reductions of conjugated nitroolefins represents a powerful tool to access to nitroalkanes, useful precursors for the construction of new carbon–carbon bonds.[1] Moreover, nitro group can be conveniently transformed in a wide range of other functional group like amines,[2] carboxylic acids,[3] aldehydes,[4] and nitriles.[5] In the last decades, many efforts were devoted to the enantioselective reduction of nitroolefins. The organocatalytic stereoselective reduction of β,β-disubstituted nitroolefins with Hantzsch ester was firstly disclosed by List[6] and further explored by Bernardi and coworkers[7] and our group.[8] Nevertheless, no examples about the enantio, chemo and regioselective reduction of dienes trisubstituted at the double bond bearing the nitro group were found in the literature. Despite the paucity of methods to preparare δ-nitro alkenes **(2*E*)-1**, these compounds have found application in the synthesis of highly functionalized scaffolds such as poly-substituted pyrrolidines,[9] spiro-pyrazolones,[10] highly functionalized cyclopentanes,[11] and five and six-membered spirooxindoles,[12] that are employed in the APIs synthesis (Figure 1a). In addition, the (*Z*) isomer of δ-nitro alkene **(2*Z*)-1** could be exploited as a precursor of Piperlogomine (also called piplartine), an amide alkaloid derived from *Piper longum L.* (long piper). This natural compound exhibited cytotoxic and cytostatic activities against various cancer cell lines (colon, lung, breast, pancreatic, renal and prostate) in preclinical studies, and it is scheduled for Phase I human clinical trials (Figure 1b).[13]

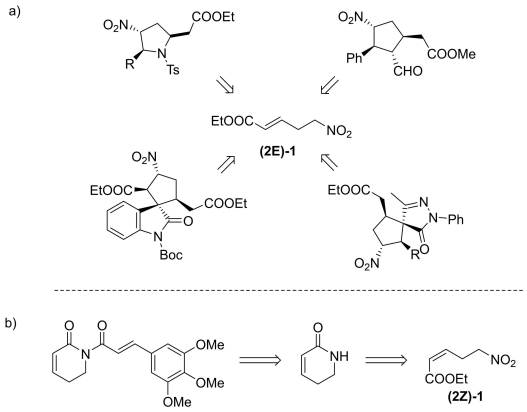

Figure 1. Application of **1** in the APIs synthesis.

Therefore, the development of novel strategies for the synthesis of δ-nitro alkenes is highly desirable; here we report a new reaction to afford enantioenriched δ-nitro alkene analogues and their synthetic manipulation.

Results and Discussion

Synthesis of dienes

At the beginning of our study, the synthesis of starting materials dienes was designed. After examining various retrosynthetic approaches, the option of choice involved a Horner-Wadsworth-Emmon reaction with an α,β-unsaturated aldehyde, followed by the chemoselective nitration of terminal double bond. Unfortunately, this approach was not successful in the synthesis of nitro diene **12**, as will be discussed later (Scheme 1).

Firstly, the 3-methyl-2-methylenebutanale **6** was prepared via Mannich reaction starting from isovaleraldehyde and aqueous formaldehyde in presence of diethylammonium

[a] *Dr. C. Faverio, Dr. F. Franco, Dr. G. Taini, Prof. L. Raimondi, Prof. M. Benaglia*
Dipartimento di Chimica
Università degli Studi di Milano
Via C. Golgi 19, 20133, Milano, Italy
E-mail: francesca.franco@unimi.it
maurizio.benaglia@unimi.it

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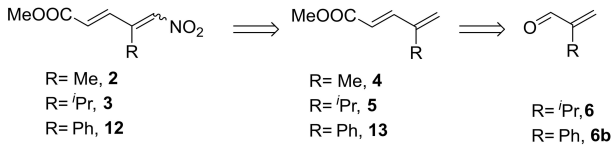


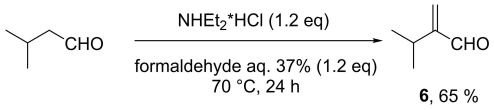
Scheme 1. Retrosynthetic approach to δ-nitro dienes.

chloride as reported by Burton.[14] The product was obtained in 65% yield and used in the next step without further purification (Scheme 2).

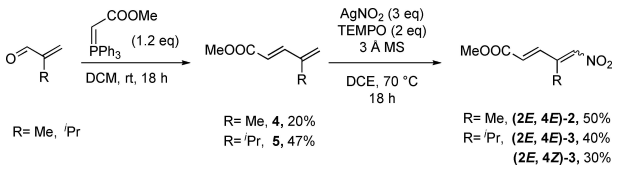
The α,β-unsatured aldehyde **6** and commercially available methacrolein were reacted with methyl (triphenyl–phosphoranylidene)acetate through a Wittig reaction, to afford the unsaturated esters **4** and **5**, respectively, that were obtained exclusively as *E* isomer in scarce to moderate yields (Scheme 3).

Then, the intermediates were subjected to nitration reaction performed in presence of silver nitrite and TEMPO, as reported by Maiti.[15] Under those reaction conditions the selective addition of nitro group on the terminal olefin was achieved. The compound **(2*E*,4*E*)-2** was isolated as single isomer, while the compound **3** was obtained as mixture of isomers which were separated by column chromatography. Each isomer of compound **3** was characterized and tested in the catalytic studies.

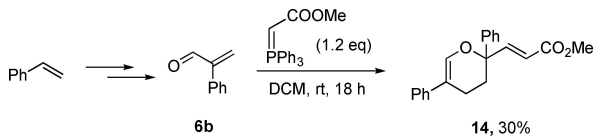
The synthesis of the methyl (*E*)-4-phenylpenta-2,4-dienoate **13** started from the styrene that was converted in the unsatured hemiacetal through a cyclopropanation/elimination reaction. 2-phenylacrylaldehyde was obtained by treatment with formic acid as previously reported[16] and, after crystallization, it was reacted with methyl (triphenyl–phosphoranylidene)acetate to give desired product. Unfortunately, the last step of this synthetic route did not afford target compound but the Methyl



Scheme 2. Mannich reaction using isovaleraldehyde to afford adduct **6**.



Scheme 3. Synthetic pathway to δ-nitro dienes **2** and **3**.



Scheme 4. Synthetic pathway to dihydropyrane **14**.

(*E*)-3-(2,5-diphenyl-3,4-dihydro-2H-pyran-2-yl)acrylate **14** in 30% yield probably due to a dimerization of aldehyde[17] before Wittig reaction (Scheme 4).

Catalytic diene reduction studies

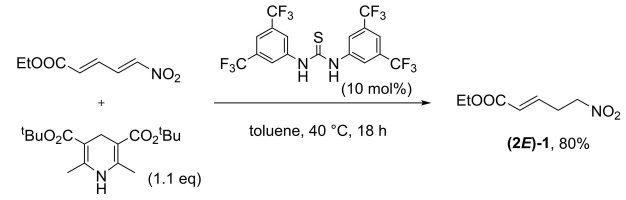
Our investigation on the catalytic reduction started with the assessment of the chemo- and the regioselectivity of the reduction performed in presence of Hantzsch ester (HE) as reductive agent and Schreiner's thiourea as organocatalyst (Scheme 5).

To our delight, the reaction worked with an excellent yield and complete regioselectivity, giving compound **(2*E*)-1** as unique product in 80% yield.

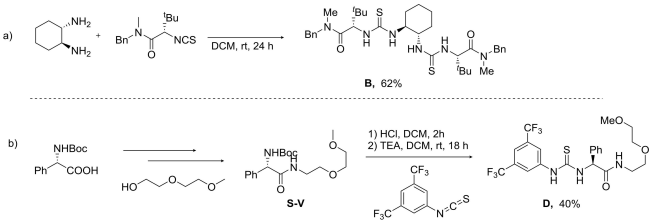
With this information in our hands, we decided to investigate the enantioselective reduction of dienes using the well-established system involving HE and chiral thiourea catalysts. In the preliminary screening, both known bifunctional thiourea-based Jacobsen[20] Takemoto[21] and List[22] catalysts (respectively **A, E** and **C**) and new bifunctional organocatalysts (**B** and **D**) were tested.

The synthesis of two new bifunctional catalysts with different activation mode were designed and completed. Catalyst **B** features two basic sites and an extended hydrogen bond network. As reported in Scheme 6a the catalyst **B** was obtained by addition of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane and enantiopure isothiocyanate previously prepared by literature procedure .[18] On the other hand the catalyst **D** is functionalized with a polyether chain resembling the chiral crown ethers studied by Williams[19] capable to form a pocket in which reagents may be activated by not covalent interaction.

The synthesis started from the manipulation of di(ethylene glycol) methyl ether to obtain the corresponding amine, that was reacted with Boc-L-α-phenylglycine to afford the coupling product **S-V**. After treatment with hydrochloric acid, 3,5-bis(trifluoromethyl)phenyl isothiocyanate was added to afford



Scheme 5. Regioselective reduction of olefin conjugated to nitro group.



Scheme 6. Synthetic route to catalyst **B** and **D**.

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the catalyst **D** with an overall yield of 40% on six synthetic steps (Scheme 6b).

Catalyst behavior was first studied in the reaction of methyl (2*E*,4*E*)-4-methyl-5-nitropenta-2,4-dienoate **(2*E*,4*E*)-2**.

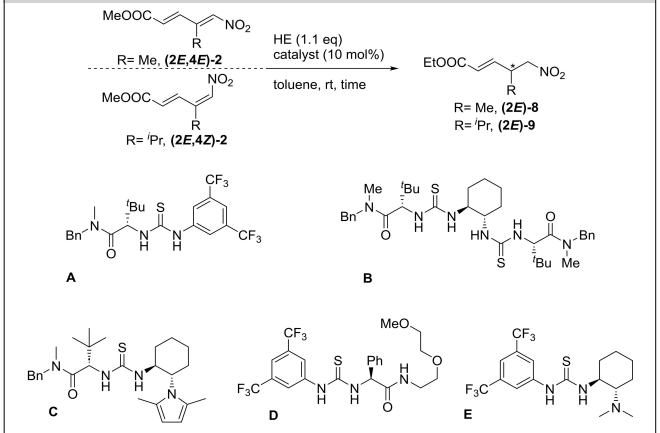
As reported in Table 1, the reduction of the compound **(2*E*,4*E*)-2** in the presence of catalyst **A** provided the desired product in good yield but poor enantiomeric excess (19% e.e., entry 1, Table 1). The reaction at lower temperature (−40 °C, 72 h, entry 2, Table 1) did not afford any product.

The application of the same catalytic system to the methyl (*Z*)-5-methyl-4-(nitromethyl)hex-2-enoate **(2*E*,4*Z*)-3** led to more promising results; indeed, using catalyst **E** the desired product was obtained in higher yield and enantioselectivity (entry 3, Table 1). With the idea to work in presence of an increased hydrogen bond network in the transition state, different organocatalysts were tested. The catalyst **B** and **D** were synthetized for the first time in this work and their preparation is reported in the supporting information. As reported in Table 1, with catalysts **A**, **B**, **C** and **D** enantiomeric excesses constantly higher than 83% were achieved, probably due to a rigid transition state. The best results were obtained both in presence of the catalyst **A** and **C** that were able to interact more efficiently with the reagents and led to the product in up to 97% e.e. The best performing catalyst was the chiral thiourea **A** that promoted the reaction in 87% yield and 97% e.e. (Table 1, entry 4, Scheme 7a), and that was selected for further studies. Under the optimized reaction conditions founded for the formation of compound **(2*E*,4*Z*)-3**, the reaction was attempted also starting from methyl (2*E*,4*E*)-5-methyl-4-(nitromethylene)hex-2-enoate **(2*E*,4*E*)-3** that provided the opposite enantiomer of **(2*E*)-9** in 67% yield and 63% e.e. (Table 1, entry 8, Scheme 7b). Unfortunately, the same conditions applied to the methyl (2*E*,4*Z*)-4-chloro-5-nitropenta-2,4-dienoate did not afford the desired product.

To probe the utility of the reaction further synthetic manipulations of the compound **(2*E*)-9** were performed. The metal free conversion of the nitro group to amine was achieved with trichlorosilane as reducing agent.[5] The methodology, reported in Scheme 8a, guaranteed the selective deoxygenation of nitro group in presence of sensitive functional group, affording the desired product **(2*E*)-10**, in 70% isolated yield, without erosion of enantiomeric excess.

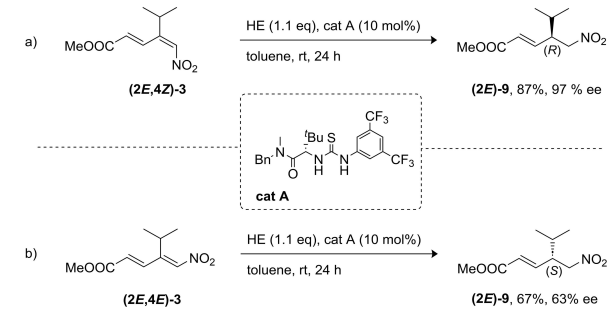
In addition, the nitro alkene **(2*E*)-9** was used as reactant in a cyclization reaction (Scheme 8b). The addition of enantioenriched δ-nitro olefin to trans-cinnamaldehyde, in the presence of a catalytic amount of Jorgensen-Hayashi prolinol derivative and 1,4-Diazabicyclo[2.2.2]octane (DABCO) as base, afforded the highly functionalized cyclopentane **11**. The target compound features five contiguous stereocenters and has never been reported in literature. It was obtained in very high yield, excellent diastereoisomeric ratio (*d.r.* 92:8) and 99% enantiomeric excess, evaluated on the major diastereoisomer. The absolute configuration, determined by X-ray analysis confirmed the (1*R*,2*S*,3*S*,4*S*,5*R*) configuration for compound **11** (Figure 2).

Table 1. Catalyst screening in the asymmetric reduction of δ-nitro dienes.[a]

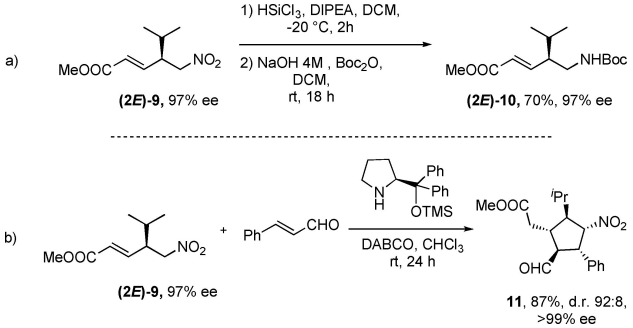


Entry	Compound	Catalyst	Time [h]	Yield [%][b]	Ee [%][c]
1	**(2*E*,4*E*)-2**	**A**	18	48	19
2[d]	**(2*E*,4*E*)-2**	**A**	72	n.d.	n.d.
3	**(2*E*,4*Z*)-3**	**E**	24	65	41
4	**(2*E*,4*Z*)-3**	**A**	24	87	97
5	**(2*E*,4*Z*)-3**	**B**	24	82	93
6	**(2*E*,4*Z*)-3**	**D**	24	99	83
7	**(2*E*,4*Z*)-3**	**C**	24	75	97
8	**(2*E*,4*E*)-3**	**A**	24	67	63

[a] Unless otherwise specified, reactions were performed on a 0.1 mmol scale of nitro diene **(2*E*,4*E*)-2** or **(2*E*,4*Z*)-3**, using 1.1 equiv. of Hantzsch ester, 10 mol% of organocatalyst at room temperature in 1.0 mL of solvent. [b] Isolated yield after chromatography. [c] Determined by HPLC analysis on chiral stationary phase. n.d. = not determined. [d] T = −40 °C.



Scheme 7. Application of enantioselective reduction to **(2*E*, 4*Z*)-3** and **(2*E*, 4*E*)-3** dienes.



Scheme 8. a) Product manipulation: nitro group reduction to amine; b) Synthesis of enantioenriched highly functionalized cyclopentane **11**.

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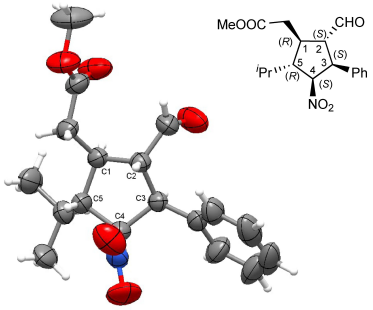

Figure 2. Representation of the crystal structure of compound **11** with anisotropic displacement parameters. Color code: O, red; C, grey; N, blue; H, white.

Based on crystallographic information, in order to account for the observed stereochemistry of the reaction the reported mechanism was proposed (Figure 3). The first step of the catalytic cascade reaction is the iminium activation of α,β-unsaturated aldehyde. The *Si face* of the iminium intermediate is shielded by the sterically hindered benzydryl–OTMS gorup of the catalyst, so the attack of the deprotonated nucleophile occurs on the *Re face*. It is interesting to underline that the presence of a stereogenic center on the starting material contributes to the control in the formation of the polysubstituted cyclopentane stereocenters. Indeed, the combination of the stereogenic center of the reactant and the prolinol catalyst guarantees the formation of product **11** as unique isomer, where the isopropyl residue on C-5 of cyclopentane has forced nitro group in *cis* position to the phenyl group (Figure 3).

From the established configuration of product **11** it was possible to assign the absolute configuration of substrate (**2*E*)-9** as (*R*) configuration. According to the reported mechanism, the integrity of the stereocenter on C-5 bearing the isopropyl group, generated in the enantioselective organocatalytic reduction, is not compromised in the cyclization reaction.

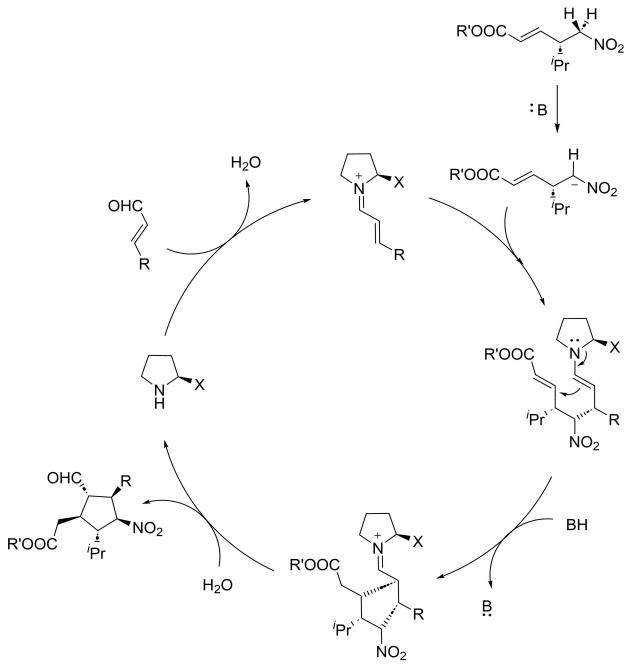

Figure 3. Proposed reaction mechanism.

Conclusions

In summary, a convenient approach for the synthesis of γ-alkyl δ-nitro dienes was disclosed. The adducts were employed in the chemo- and regioselective reduction to efficiently prepare δ-nitro alkenes. The enantioselective organocatalytic reduction performed in presence of a chiral thiourea and Hantzsch ester as reductive agent afforded the γ-alkyl δ-nitro alkene in up to 97 % e.e. The chiral nitro alkene was further elaborated and was successfully employed as starting material in a stereoselective cyclization reaction that affords an almost enantiomerically pure highly functionalised cyclopentane featuring five contiguous stereocenters.

Experimental section

General Procedure: In a 3 mL vial, 0.1 mmol of nitro diene ((**2*E*, 4*E*)-2** or **3**) was dissolved in anhydrous toluene. The catalyst (10 mol%) and Hantzsch ester (1.1 eq.) were added in this order under inert atmosphere. The mixture was stirred at room temperature for 24 hours. Then, the solvent was removed and the crude was purified by column chromatography.

Supporting Information

See the Supporting Information for synthetic procedures of starting materials and catalysts, experimental details on catalytic tests, characterization data for products, NMR spectra for all described compounds, HPLC chromatograms. Additional references cited within the Supporting Information.[23–32]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: nitro alkenes · organocatalysis · enantioselective reduction · dienes · chemoselectivity

[1] For preparation of nitroalkanes see: a) R. Ballini, A. Palmieri, *Adv. Synth. Catal.* **2018**, *360*, 2240; b) G. W. Kabalka, R. S. Varma, *Org. Prep. Proced. Int.* **1987**, *19*, 283; c) C. Faverio, M. F. Boselli, P. C. Gonzalez, A. Puglisi, M Benaglia, *Beilstein J. Org. Chem.* **2021**, *17*, 1041; For application of nitroalkanes in organic synthesis see: d) R. Ballini, A. Palmieri, P. Righi, *Tetrahedron* **2007**, *63*, 12099; e) L. S. Aitken, N. R. Arezki, A. Dell'Isola, A. J. A. Cobb, *Synthesis* **2013**, *45*, 2627; f) R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, *Tetrahedron* **2005**, *61*, 8971; See also: g) A. Palmieiri, *Eur. J. Org. Chem.* **2020**, 4247–4260; h) R. Ballini, A. Palmieri, M. Petrini *Org. Chem. Front.* **2022**,*9*, 6077–6113.

[2] a) M. Orlandi, D. Brenna, R. Harms, S. Jost, M. Benaglia, *Org. Process Res. Dev.* **2018**, *22*, 430; b) R. J. Rahaim, R. E. Maleczka, *Org. Lett.* **2005**, *7*, 5087; c) T. Ankner, G. Hilmersson, *Tetrahedron Lett.* **2007**, *48*, 5707.

[3] a) T. Ankner, G. Hilmersson, *Tetrahedron Lett.* **2007**, *48*, 5707; b) P. Marcé, J. Lynch, A. J. Blacker, J. M. J. Williams, *Chem. Commun.* **2016**, *52*, 1013; c) R. Ballini, M. Curini, F. Epifano, M. C. Marcotullio, O. Rosati, *Synlett* **1998**, *10*, 1049.

[4] a) K. Steliou, M.-A. Poupart, *J. Org. Chem.* **1985**, *50*, 4971; b) W. Adam, M. Makosza, C. R. Saha-Möller, C.-G. Zhao, *Synlett* **1998**, *12*, 1335.

[5] a) M. Pirola, C. Faverio, M. Orlandi, M. Benaglia, *Chem. Eur. J.* **2021**, *27*, 10247.

[6] N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**,*129*, 8976.

[7] a) E. Martinelli, A. C. Vicini, M. Mancinelli, A. Mazzanti, P. Zani, L. Bernardi, M. Fochi, *Chem. Commun.* **2015**, *51*, 658–660; b) L. Bernardi, M. Fochi, *Molecules* **2016**, *21*, 1000.

[8] E. Massolo, M. Benaglia, M. Orlandi, S. Rossi, G. Celentano, *Chem. Eur. J.* **2015**, *21*, 3589.

[9] T. Cheng, S. Meng, Y. Huang, *Org. Lett.* **2013**, *15*, 1958.

[10] N. K. Rana, K. Shukla, P. Mahto, R. K. Jha, V. K. Singh, *Tetrahedron* **2018**, *74*, 5270.

[11] G. L. Zhao, I. Ibrahem, P. Dziedzic, J. Sun, C. Bonneau, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 10007.

[12] M. Monari, E. Montroni, A. Nitti, M. Lombardo, C. Trombini, A. Quintavalla, *Chem. Eur. J.* **2015**, *21*, 11038.

[13] a) D. P. Bezerra, C. Pessoa, M. O. de Moraes, N. Saker-Neto, E. R. Silveira, L. v. Costa-Lotufo, *Eur. J. Pharm. Sci.* **2013**, *48*, 453–463; b) K. Piska, A. Gunia-Krzyżak, P. Koczurkiewicz, K. Wójcik-Pszczoła, E. Pękala, *Eur. J. Med. Chem.* **2018**, *156*, 13–20; c) S. K. Tripathi, B. K. Biswal, *Pharmacol. Res.* **2020**, *156*, 104772.

[14] A. W. J. Logan, J. S. Parker, M. S. Hallside, J. W. Burton, *Org. Lett.* **2012**, *14*, 2940.

[15] S. Maity, S. Manna, S. Rana, T. Naveen, A. Mallick, D. Maiti, *J. Am. Chem. Soc.* **2013**, *135*, 3355.

[16] I. Crossland, T. J. Blacklock, A. S. Kende, *Org. Synth.* **1981**, *60*, 6.

[17] I. L. Andujar-De Sanctis, D. A. Singleton, *Org. Lett.* **2012**, *14*, 5238.

[18] A. Puglisi, M. Benaglia, R. Annunziata, D. Rossi, *Tetrahedron: Asymmetry* **2008**, *19*, 2258.

[19] B. L. Allwood, H. Shahriari-Zavareh, J. F. Stoddart, D. J. Williams, *J. Chem. Soc. Chem. Commun.* **1984**, *22*, 1461.

[20] S. E. Reisman, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 7198.

[21] T Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672.

[22] N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976.

[23] J. R. Harjani, C. Liang, P. G. Jessop, *J. Org. Chem.* **2011**, *76*, 1683.

[24] I. T. Crouch, T. Dreier, D. E. Frantz, *Angew. Chem. Int. Ed.* **2011**, *50*, 6128.

[25] Agilent, CrysAlis PRO, Agilent Technologies Ltd, Yarnton, Oxfordshire, England, **2019**.

[26] G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2015**, *71*, 3.

[27] G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3.

[28] L. J. Farrugia, *J. Appl. Crystallogr.* **2012**, *45*, 849–854.

[29] Brandenburg, K. [or Brandenburg, K. & Putz, H., or Brandenburg, K. & Berndt, M.] *DIAMOND.* Crystal Impact GbR, Bonn, Germany, **1999**.

[30] I. T. Crouch, T. Dreier, D. E. Frantz, *Angew. Chem. Int. Ed.* **2011**, *50*, 6128.

[31] a) J. P. Djukic, A. Hijazi, H. D. Flack, G. Bernardinelli, *Chem. Soc. Rev.* **2008**, *37*, 406; b) T. E. Sloan, *Top. Stereochem.* **1981**, *12*, 1; c) K. Schlögl, *Top. Stereochem.* **1967**, *1*, 39; d) R. S. Cahn, C. Ingold, V. Prelog, *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385.

[32] S. Parsons, H. D. Flack, T. Wagner, *Acta Crystallogr. Sect. B* **2013**, *69*, 249.

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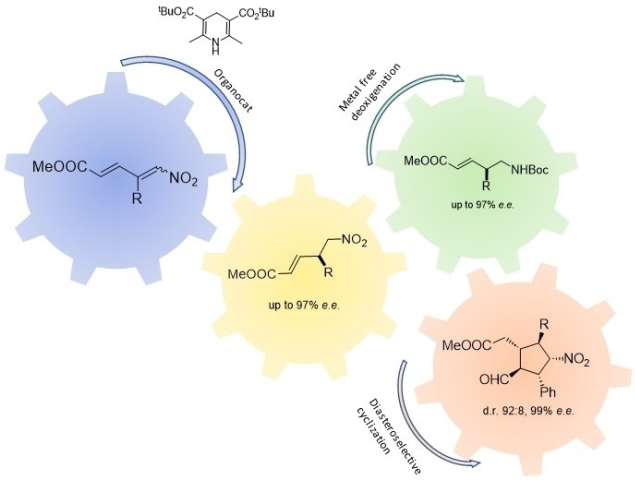

A new asymmetric organocatalytic reaction to afford enantioenriched δ-nitro alkene analogues and their synthetic manipulation are presented. The chiral nitro alkene was further used in a stereoselective cyclization reaction to afford an almost enantiomerically pure highly functionalised cyclopentane featuring five contiguous stereocenters.

Dr. C. Faverio, Dr. F. Franco, Dr. G. Taini, Prof. L. Raimondi, Prof. M. Benaglia**

1 – 6

Organocatalytic Asymmetric Reduction of δ-Nitro Dienes: a Viable Entry to Functionalized Amines and Highly Substituted Enantioenriched Cyclopentanes