# Exploiting the Distal Reactivity of Indolylmethylenemalononitriles: An Asymmetric Organocatalyzed [4+2] Cycloaddition with Enals Enables the Assembly of Elusive Dihydrocarbazoles

*Chem. Eur. J.* **2016**, *22*, 12637–12640

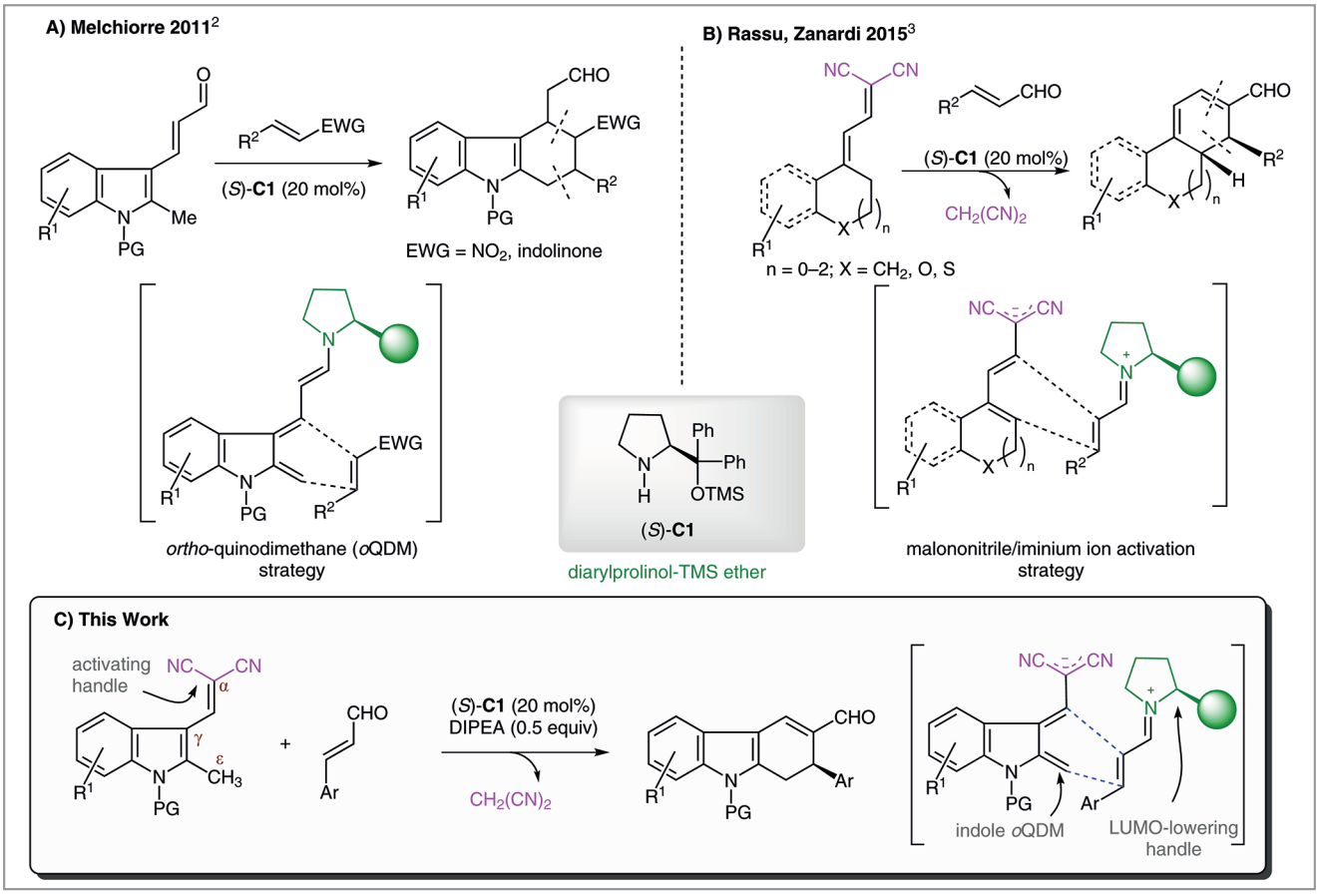
Since the advent of modern organocatalysis at the turn of the 21st century, asymmetric aminocatalysis, which uses chiral amines as catalysts, has been at the center of an explosive growth, culminating in the implementation of a myriad of high-impact stereoselective organic transformations, many of which are represented by efficient and creative organocatalytic formal [4+2] cycloadditions.[1] In particular, the use of aminocatalysts proved to be an extremely useful strategy to induce the transient generation of highly reactive *ortho*-quinodimethane (oQDM) intermediates from simple heteroaromatic compounds (e.g., methylindole-, methylpyrrole- or methylfuran-based heterocycles) while directing the pericyclic reactions with suitable dienophiles toward a highly stereoselective pathway. "Our approach provides straightforward access to complex, chiral polycyclic architectures, which would be difficult to synthesize by other catalytic methods, and should open new synthetic pathways to complex chiral molecules using nontraditional disconnections. The paper in *Chem. Eur. J.* is the result of a fruitful collaboration between two research groups: a group from the Università degli Studi di Parma (Italy), led by Professor Franca Zanardi, and their colleagues of the Consiglio Nazionale delle Ricerche (CNR) in Sassari (Italy), led by Dr. Gloria Rassu," said Professor Claudio Curti from the group in Parma, adding: "In this context, in 2011, we read with interest the work published by Melchiorre and co-workers[2] in which he reported a reliable synthetic strategy to access tetrahydrocarbazoles by adopting a [4+2] disconnection which relies on the in situ generation of active indole *ortho*-quinodimethane intermediates (*o*QDM) in reactions with suitable dienophiles (e.g., nitrostyrene or indolinone derivatives) under trienamine catalysis (Scheme 1A). During that period," continued Professor Curti, "we were focusing on the search for new, extended pro-nucleophilic structures, to be activated and exploited as polyenolate nucleophiles in organocatalytic, enantioselective vinylogous and hypervinylogous transformations. This search ended in 2015 with the discovery of a new, direct [4+2] eliminative cycloaddition modality to access chiral, polyfunctionalized carbocycles embedding fused cyclohexadiene frames by the use of remotely enolizable π-extended allylidenemalononitriles as electron-rich 1,3-diene precursors with both aromatic and aliphatic α,β-unsaturated aldehydes under iminium ion driven organocatalysis (Scheme 1B)."[3]

Inspired by these newly disclosed processes and mindful of Melchiorre's work, the groups involved in this collaboration wondered whether the use of the malononitrile activation strategy could also be applied to methylindole-based scaffolds. Professor Curti said: "It was while discussing these issues with Professor Giovanni Casiraghi, our inspiring mentor – actually, Professor Giovanni Casiraghi retired in 2010 but he continued to enthusiastically discuss chemistry with us until his recent death, on July 21, 2016 – that the idea came up: *Why don't we try to merge our malononitrile activation strategy with the indole ortho-quinodimethane modality by reacting 2-methylindole-based methylenemalononitriles and enals with the aid of a chiral secondary amine catalyst?*"

The authors reasoned that, if viable, this strategy would lead to interesting chiral, enantiopure, polyfunctionalized 2,9-dihydro-1*H*-carbazole-3-carboxaldehydes through a direct, domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade that could be envisaged as a formal [4+2] cycloaddition.

Initially, a set of experiments evaluating the feasibility of the transformation between *N*-Boc-protected 2-methylindolylmethylenemalononitrile and cinnamaldehyde promoted by a series of chiral, secondary amine catalysts were performed by Dr. Rassu in Sassari. "Pleasingly, Dr. Rassu found that promising results were obtained with the use of the popular Hayashi–Jørgensen α,α-diphenylprolinol trimethylsilyl ether catalyst (*S*)-**C1** that promoted the formation of the corresponding dihydrocarbazole adduct with exceptional enantioselectivity (99% ee), albeit in only moderate yields," explained Professor Curti. He continued: "We soon discovered that a competing retro-Knoevenagel reaction on the starting pro-nucleophilic methylenemalononitrile hampered the completion of the process, and variable amounts of related aldehyde precursors were detected in the crudes. Meticulous optimization of the reaction conditions (e.g., the use of DIPEA instead of $Et_3N$, and the fine-tuning of the nucleophile/electrophile molar ratio) allowed us to solve this problem, and a viable reaction with

  • Published online: November 17, 2016 • DOI: 10.1055/s-0036-1589372



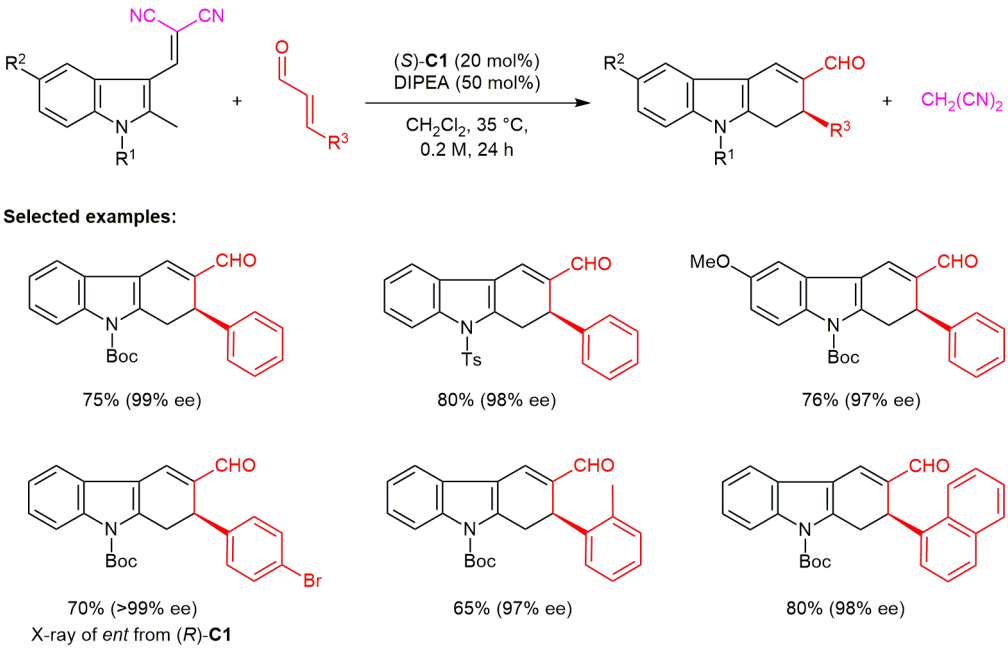

**Scheme 1** Merging the *o*QDM strategy with the malononitrile/iminium ion activation strategy toward the synthesis of chiral, enantiopure 2,9-dihydro-1*H*-carbazole 3-carboxaldehydes

improved isolated yield and very high enantioselectivity was finally at hand."

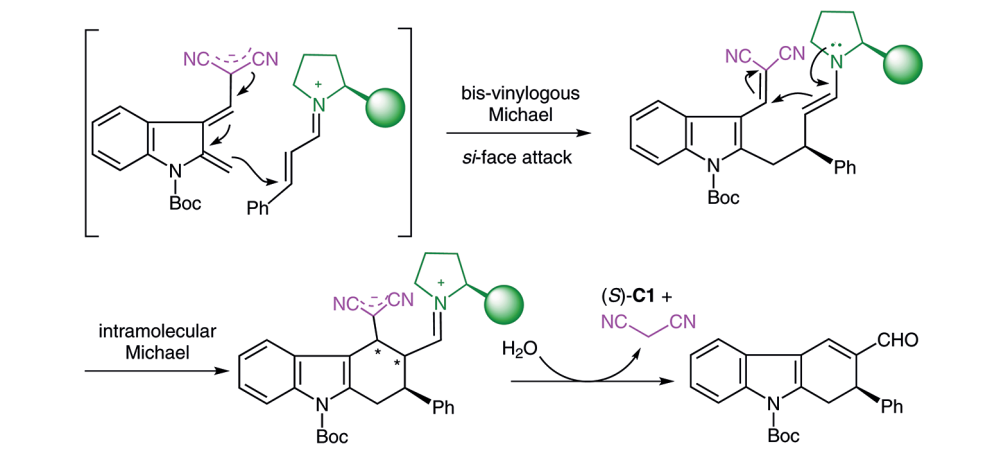
Professor Curti revealed that the reaction performed directly on the parent aldehyde precursor (in which the malononitrile group is missing) completely failed, highlighting the fundamental role exerted by the malononitrile moiety as activating handle of the nucleophilic indole counterpart.

"The scope and limitations of this [4+2] eliminative cycloaddition utilizing diversely substituted methylenemalononitriles and enals were then examined both in Parma and Sassari: it was found that the core structure of the formed formyl dihydrocarbazoles could be readily decorated at different positions without having a detrimental effect on either yield or enantioselectivity," said Professor Curti. Also, varied substituents at the aromatic moiety of the olefinic aldehyde derivatives were tolerated, regardless of their position and electronic properties. Professor Curti continued: "Interestingly, only electron-poor *N*-Boc-, *N*-Moc-, and *N*-Ts-protected indoles proved to be reliable substrates for this transformation, while the electron-rich *N*-Me derivative was completely inactive. This prompted us to invoke a direct correlation between the electronic nature of the N-protecting group and the p$K_a$ of the enolizable $CH_3$."

To achieve a better understanding of the reaction mechanism and transition states involved in this process, the absolute configuration of the dihydrocarbazole targets needed to be unveiled. Professor Curti explained: "Actually, since these scaffolds were quite unique and unprecedented, we couldn't find any structural correlation with known, stereodefined products, and X-ray crystallographic analysis of suitable crystals remained our only option." He continued: "Fortunately, after several attempts, we succeeded in obtaining good crystals of the p-bromocinnamaldehyde derivative obtained with catalyst (*R*)-**C1**; and in collaboration with Professor Giorgio Pelosi of the Department of Chemistry of the University of Parma we were able to unambiguously assign the (2*S*)-configuration




**Scheme 2** Enantioselective iminium ion mediated [4+2] eliminative cycloaddition: selected examples




**Scheme 3** Crucial reaction steps involved in the domino bis-vinylogous Michael/Michael/retro-Michael reaction cascade

of the sample by X-ray crystallographic analysis (consequently the 2*R*-configuration was assigned to all compounds derived from catalyst (*S*)-**C1**)." With these data at hand, Professor Curti and collaborators were able to propose a stepwise reaction mechanism for the key [4+2]: a domino bis-vinylogous Michael/Michael/*retro*-Michael reaction cascade in which the crucial enantioselective step resides in the attack of the nucleophilic methylene carbon of the indole *o*QDM intermediate to the *si*-face of the iminium ion derived from covalent association of the enal to the prolinol catalyst (*S*)-**C1**.

Professor Curti concluded: "This work represents our last advancement in the field of organocatalysis: further studies to apply the malononitrile/iminium ion activation strategy in the vinylogous realm is ongoing in our laboratories and will be disclosed in due course."

## About the authors

*Prof. C. Curti*

**Claudio Curti** is Assistant Professor of Organic Chemistry at the University of Parma (Italy), Department of Pharmacy. He earned his Laurea degree in Pharmaceutical Chemistry and Technology in 2002 at the University of Parma. In 2005, he graduated from the postgraduate School of Chemical Synthesis at the University of Milan (Italy). In 2001, he joined the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma) under the supervision of Professor Giovanni Casiraghi, where he would eventually take up his current position. His main research interests are in the field of asymmetric synthesis and organic chemistry methodology, focusing on the development of metal- and organocatalytic, enantioselective vinylogous and hypervinylogous processes and their exploitation in the synthesis of multifunctional natural and natural-like compounds, including densely functionalized heterocycles and polyphenol metabolites.

*Dr. G. Rossu*

**Gloria Rassu** is Research Executive at the Consiglio Nazionale delle Ricerche (CNR), Istituto di Chimica Biomolecolare (Sassari, Italy). She was born and raised in Sassari (Italy) and earned her Laurea degree in chemistry at the University of Sassari (Italy) in 1979. After five years postdoctoral work, she joined the research group of Professor Giovanni Casiraghi working on the development of a novel vinylogous aldol methodology and its exploitation in the total synthesis of densely functionalized chiral compounds. In 2001, she was promoted to First Researcher position and in 2002 she took up her present rank at the CNR. Her main scientific interests reside in the design and application of new catalytic, enantioselective, vinylogous processes toward the synthesis of biologically active molecules such as carbohydrate mimetics, nucleoside analogues, modified and conformationally constrained amino acids and glycopeptidomimetics for integrin receptor targeting.

*N. Brindani*

**Nicoletta Brindani** was born in Borgo Val di Taro, Parma (Italy) in 1988. She studied medicinal chemistry and technology at the University of Parma, where she received her Laurea degree in 2012. At present she is a PhD student of food science under the supervision of Professor Daniele Del Rio and Professor Claudio Curti working in the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma). Her research interests, centered in the field of organic synthesis, are focused toward the development of new asymmetric, vinylogous, and organocatalytic methodologies for the total synthesis of chiral bioactive molecules.

*Dr. V. Zambrano*

**Vincenzo Zambrano** was born in 1972 in Sassari (Italy). He obtained his degree in chemistry from the University of Sassari (Italy) in 1997 (supervisor: Professor Giovanni Minghetti). In 2003, he received his Ph.D. in chemistry from the University of Sassari (supervisors: Drs. Gloria Rassu and Luigi Pinna), working on the synthesis of a very large collection of carbasugars. In 2008, he became Technologist at the Istituto di Chimica Biomolecolare of CNR in Sassari. His research interests are focused on the stereoselective synthesis of bioactive molecules of natural and unnatural origin. He deals with the characterization and structural determination of organic compounds using one- and two-dimensional NMR techniques, in particular 1D (1H NMR, 13C NMR) and 2D (Cosy, Tocsy, HMQC and Noesy).

*Dr. L. Pinna*

**Luigi Pinna** was born in Sassari (Italy) in 1961. He graduated in chemistry from the University of Sassari (Italy) in 1987 and obtained his Ph.D. in chemical sciences from the same university in 1992. In 1990, he was the winner of an open selection for university researchers and since 1993 he has been a confirmed researcher at the Department of Chemistry and Pharmacy of the University of Sassa-

>>

ri. He is currently collaborating with the Bio-Organic Synthesis group of Department of Pharmacy of the University of Parma, and the Institute of Biomolecular Chemistry (ICB) of CNR (Sassari, Italy). His main scientific interests reside in the development of new, catalytic, enantioselective, vinylogous processes toward the synthesis of biologically active molecules.

*Prof. G. Pelosi*

**Giorgio Pelosi** graduated from the University of Parma (Italy) in 1987 and obtained his Ph.D. in 1991 from the same institution under the mentorship of Professor Mario Nardelli, at the time President of the International Union of Crystallography. During his Ph.D. he had the chance to develop skills in protein crystallography at the University of Pavia (Italy) under the supervision of Professor Martino Bolognesi. Then, he did postdoctoral research for one year at the Laboratory of Molecular Biophysics of the University of Oxford (UK) in the group of Professor Sir Jack Baldwin, supervised by Professor Janos Hajdu. He returned to the University of Parma where he was appointed Associate Professor in 1998. His research interests are in the chemistry of biologically active metal-containing compounds and structural chemistry based on X-ray crystallography.

*Prof. F. Zanardi*

**Franca Zanardi** is currently an Associate Professor of Organic Chemistry at the Department of Pharmacy, University of Parma (Italy). She received her Laurea degree in chemistry (1993) and her Ph.D. in bioorganic chemistry (1997) from the same university under the direction of Professor Giovanni Casiraghi. She became an Assistant Professor in 1998 and Associate Professor in 2002. Currently she leads the Bio-Organic Synthesis Group of the Department of Pharmacy (University of Parma). Her research interests concern the development of stereoselective, vinylogous, and hypervinylogous methodologies addressed at the synthesis of biologically relevant chiral nonracemic molecules in the bioorganic and pharmaceutical domains. She is also involved in several research programs aimed at the synthesis and applications of biologically relevant pseudopeptides to be exploited as therapeutic/diagnostic tools in various diseases.

## REFERENCES

(1) *Comprehensive Enantioselective Organocatalysis*, Vol. 1–3; P. I. Dalko, Ed.; Wiley-VCH: Weinheim, **2013**.
(2) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre *J. Am. Chem. Soc.* **2011**, *133*, 15212.
(3) N. Brindani, G. Rassu, L. Dell'Amico, V. Zambrano, L. Pinna, C. Curti, A. Sartori, L. Battistini, G. Casiraghi, G. Pelosi, D. Greco, F. Zanardi *Angew. Chem. Int. Ed.* **2015**, *54*, 7386.