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PROFESSIONNAL EXPERIENCES

2007-	CNRS senior research scientist; COBRA, Rouen Normandy University, France.
2002-2007	CNRS research scientist; LCMT, Caen Normandy University, France.
2002	R&D researcher; research center of RHODIA Company at Lyon, France.
2001-2002	Postdoctoral Associate; Advisor: Prof. Istvan E. Markó, UCLouvain, Belgium. *Pt-NHC complexes in hydosilylation.*
1999-2001	Postdoctoral Associate; Advisor: Prof. H. Hiemstra, Amsterdam University, Nethelands. *Total synthesis of Solanoeclepin A.*

EDUCATION

1994-1998	Ph.D. Organic Chemistry, IRCOF, Rouen Normandy University, France. *Heterocyclic and supramolecular chemistry*
1993-1994	M.S. Organic Chemistry, Rouen Normandy University, France.

ADMINISTRATIVE & INSTITUTIONAL RESPONSIBILITIES

2015-2020	Member of 2 scientific councils of joint laboratories with industrial partners (Holodiag-2015-18 and Oril industrie-2020)
2016-	Representative of the organic synthesis domain in Carnot I2C
2019-	Coordinator of the Heterocycles axis of Labex SynOrg
2018-	Member of the Advisor Commission of faculty specialists (CCSE, section 32) – University of Rouen, France.
2016-2011	Member of unit council of COBRA Laboratory.

RESEARCH INTERESTS

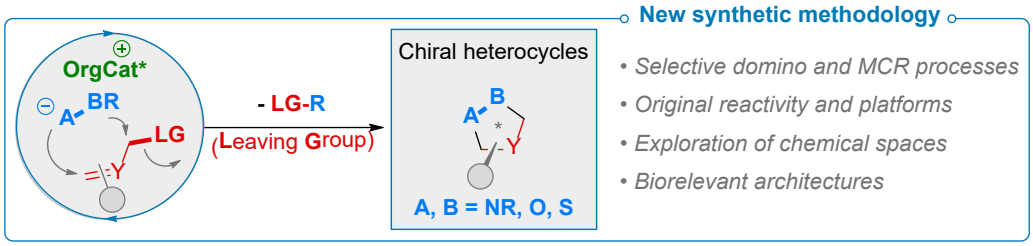
• Chiral bio-relevant heterocycles • Exploration of reactivity and building blocks (Meldrum's acid, triazine, isoxazolidin-5-one…) • Brønsted base or Phase Transfer Catalyst in organocatalysis • Asymmetric synthesis • Domino and MCR processes • Chemical diversity

SCIENTIFIC ACHIEVEMENTS

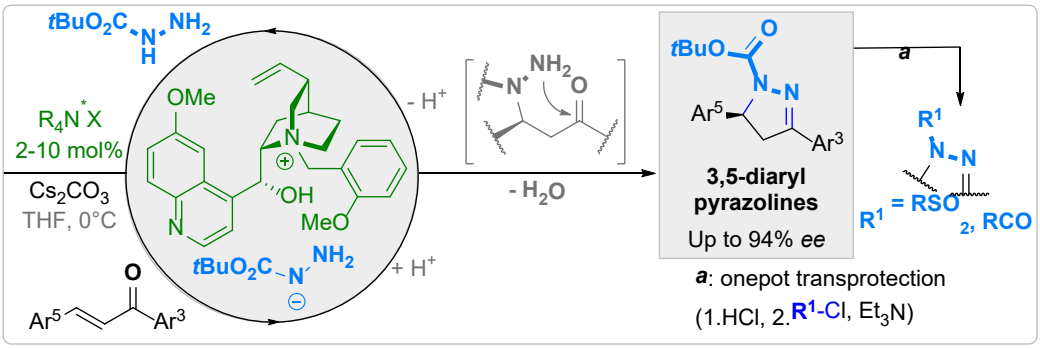
Academic record (h-index: 21), 61 publications, 6 book chapters, 5 patents, 26 invited lectures (academia & industry)

Organocatalytic synthesis of chiral bio-relevant heterocycles

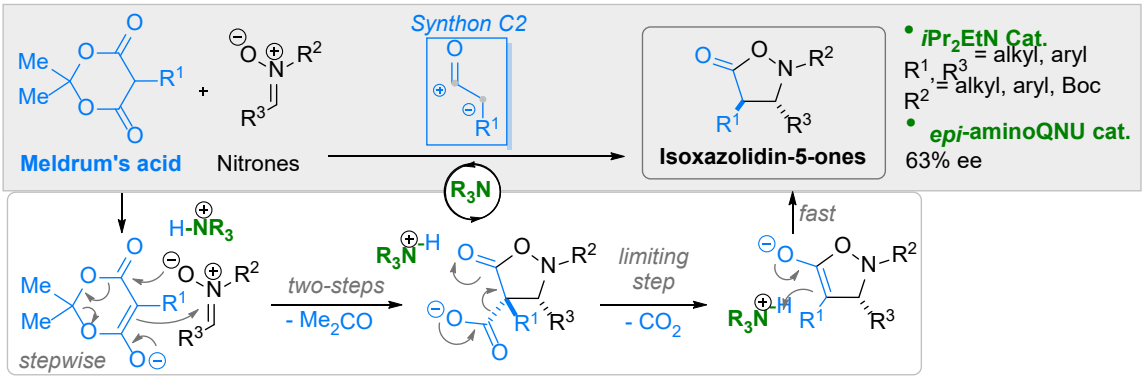
The development of *catalysts or catalytic systems*, able to accelerate the construction of molecular architectures, is at the heart of modern research in *sustainable* organic synthesis: seeking atom, time and energy economy in order to minimize the economic and environment imprint. In quest of efficiency, our research endeavors deal with the achievement of catalytic domino and multicomponent synthetic methodologies capable to furnish original chiral products, with a focus on *chiral heterocycles*, or precursors derived thereof, known as valuable building blocks for the elaboration of medicinally relevant compounds while exploring the 3D chemical space. *OUR KEY WORDS* • Chiral bio-relevant heterocycles • Domino and MCR processes • Asymmetric synthesis • Ion-paired organocatalytic strategies by means of Brønsted bases or phase transfer catalysts • Useful reactivity and platforms in synthesis (Meldrum's acid, triazine, isoxazolidin-5-one…). ***Our reviews:*** (a) Brière, J.-F., Oudeyer, S.; Dalla, V., Levacher, V. *Chem. Soc. Rev.* **2012**, 2003 (ion-pairs organocatalysis). (b) Oudeyer, S.; Brière, J.-F.; Levacher, V. *Eur. J. Org. Chem.* **2014**, 6103 (organocatalytic protonation). (c) Mahé, O.; Brière, J.-F.; Dez, I. *Eur. J. Org. Chem.* **2015**, 2559 (Chitosan in organocatalysis). (d) *Chiral Quaternary Ammonium Salts in Organocatalysis* Oudeyer, S.; Levacher, V.; Brière, J.-F.; In ISTE Press – Elsevier, **2017**, p 87. (e) Segovia, C.; Lebrêne, A.; Levacher, V.; Oudeyer, S.; Brière, J.-F. *Catalysts* **2019**, 131. (Barbituric acid and catalysis). (f) Macchia, A.; Eitzinger, A.; Brière, J.-F.*; Waser*, M.; Massa, A.* *Synthesis* **2021**, 107 (isoxazol-5-ones and isoxazolidin-5-ones).



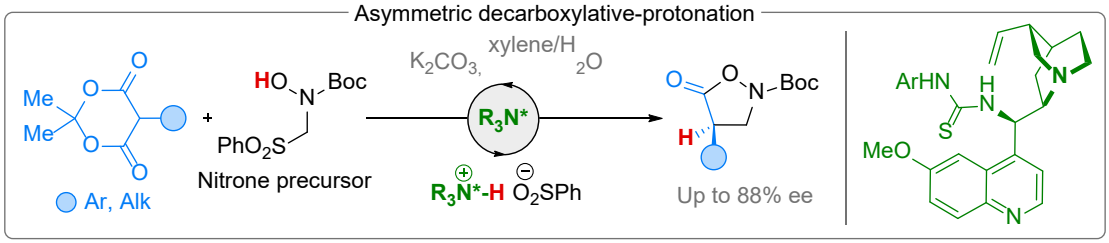
I. Bisnucleophiles. Under catalytic phase-transfer conditions the formation of an original chiral ion pair between quininium cation and hydrazine anion led to an enantioselective **domino aza-Michael-cyclocondensation reaction** to furnish enantioenriched **3,5-diaryl pyrazolines**. A convenient one-pot protocol was set to allow the introduction of various functional groups (R^1) on the nitrogen atom through a *N*-Boc transprotection process. (a) Mahé, O.; Dez, I.; Levacher, V.; Brière, J.-F. *Ang. Chem., Int. Ed.* **2010**, 7072. (b) *Org. Biomol. Chem.* **2012**, 3943. (c) Mahé, O.; Frath, D.; Dez, I.; Marsais, F.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2009**, 3648 (catalyse racémique à l'aide de TBD). (d) Gembus, V.; Bonnet, J.-J.; Janin, F.; Bohn, P.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2010**, 3287. ; Gembus, V.; Furman, C.; Millet, R.; Mansouri, R.; Chavatte, P.; Levacher, V.; Brière, J.-F. *Eur. J. Med. Chem.* **2012**, 396. (towards CB-ligands). (e) Noël, R.; Gembus, V.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2014**, 1245 (Oxa-Michael version).



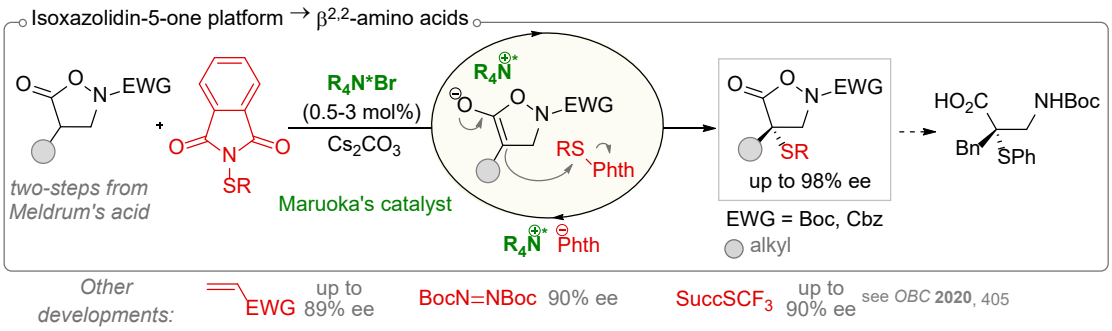
II. The Meldrum's acid platform in organocatalysis. In search for new reactivities in organocatalysis, we have recently highlighted a unique behavior of **Meldrum's acid derivatives** with various nitrones leading to an unprecedented access to **isoxazolidin-5-ones**; useful precursors of β-amino acids or nucleoside mimics. In the presence of a catalytic quantity of Brønsted base, Meldrum's acid derivatives, thanks to their high acidity (pK_a = 4.8 in water), react as a C2 synthon, likely *via* a **domino (3+2) annelation-fragmentation-decarboxylation-protonation reaction**. The overall-mechanism was probed by the combined ESI-IMS-MS and DFT technics. (a) Postikova, S.; Tite, T.; Levacher, V.; Brière, J.-F. *Adv. Synth. Catal.* **2013**, *355*, 2513. (b) Lespes, N.; Pair, E.; Maganga, C.; Bretier, M.; Tognetti, V.; Joubert, L.; Levacher, V.; Hubert-Roux, M.; Afonso, C.; Loutelier-Bourhis, C.; Brière, J.-F. *Chem. Eur. J.* **2018**, *24*, 4086.



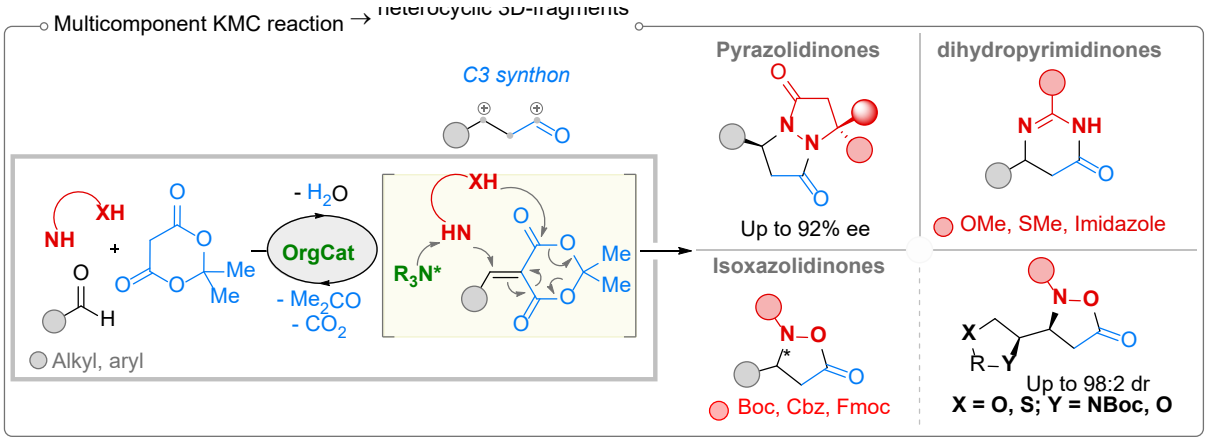
Subsequently, an organocatalytic enantioselective decarboxylative protonation reaction was achieved en route to α-substituted isoxazolidin-5-one derives as β^2-amino acids precursors. Tite, T.; Sabbah, M.; Levacher, V.; Brière, J.-F. *Chem. Commun.* **2013**, *49*, 11569.



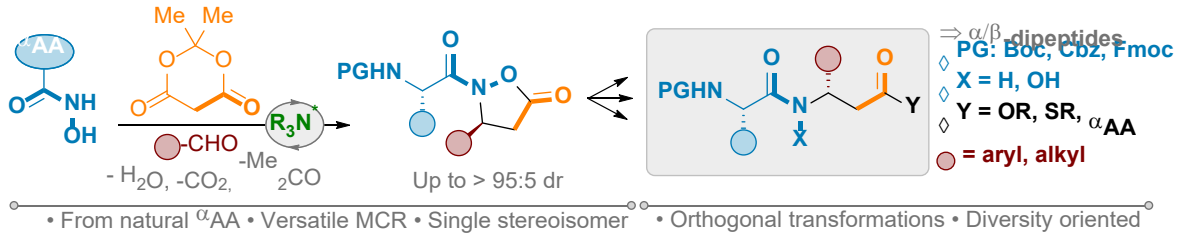
The readily availability of α-substituted *N*-alkoxycarbonyl isoxazolidin-5-ones allowed us to investigate the unprecedented catalytic α-functionalization reaction (C-S, C-N and C-C bonds) under PTC conditions. This isoxazolidinone proved to be a useful platform for the construction of valuable $\beta^{2,2}$-amino acids derivatives. (a) Cadart, T.; Berthonneau, C.; Perrio, S. ; Levacher, V.; Brière, J.-F. *Chem. Eur. J.* **2016**, 15261. (b) Cadart, T.; Levacher, V.; Perrio, S.; Brière, J.-F. Adv. Synth. Catal. **2018**, 1499. (c) *C-SCF_3 bond construction, thanks to the contribution of Mario Waser (Univ. Linz, Austria) and Dominique Cahard (Univ. Rouen Normandie):* Eitzinger, A.; Brière, J. F.; Cahard, D.*; Waser, M.* *Org. Biomol. Chem.* **2020**, 405. *For other uses of this platform, see*: Macchia, A.; Eitzinger, A.; Brière, J.-F.*; Waser*, M.; Massa, A.* *Synthesis* **2021**, 107 (review).



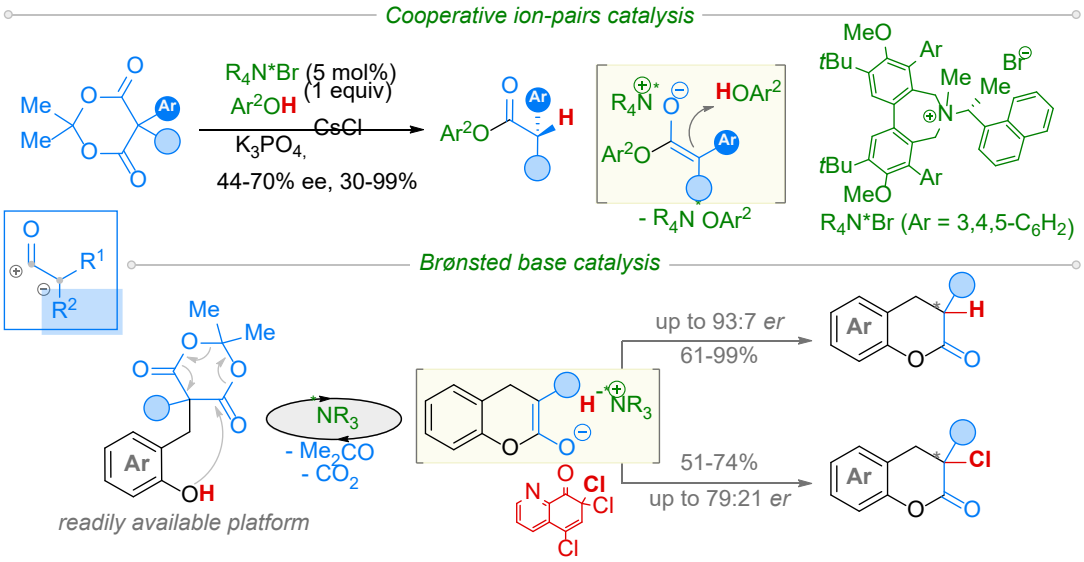
We discovered a novel regio- and stereoselective organocatalysed **multicomponent Knoevenagel-aza-Michael-Cyclocondensation (KMC) reaction** allowing straightforward syntheses of 1,5-diazabicyclo[3.3.0]octane-2,6-diones, isoxazolidinones and 5,6-dihydropyrimidin-4-ones (modified Biginelli-Atwal condensation) as 3D-heterocyclic fragments. This sequence exploit the high electrophilicity of alkylidene Meldrum's acid intermediates as 3C synthon. (a) Pair, E.; Berini, C.; Noël, R.; Sanselme, M.; Levacher, V.; Brière, J.-F. *Chem. Commun.* **2014**, 10218. (b) Berini, C.; Sebban, M.; Oulyadi, H.; Sanselme, M.; Levacher, V.; Brière, J.-F. *Org. Lett.* **2015**, 5408. (c) Pair, E.; Levacher, V.; Brière, J.-F. RSC *Adv.* **2015**, 46267. (d) A. Le Foll Devaux, E. Deau, E. Corrot, L. Bischoff, V. Levacher, J.-F. Brière, *Eur. J. Org. Chem.* **2017**, 3265.



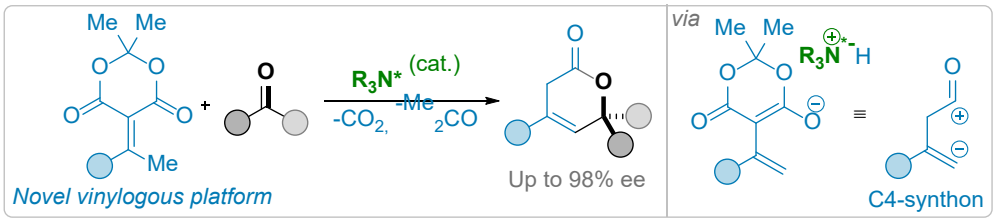
Thanks to the multicomponent KMC reaction, a diversity oriented synthesis of original α,β-dipeptides was allowed. Martzel, T.; Annibaletto, J.; Millet, P.; Pair, E.; Sanselme, M.; Oudeyer, S.; Levacher, V.; Brière, J.-F. *Chem. Eur. J.* **2020**, 8541.



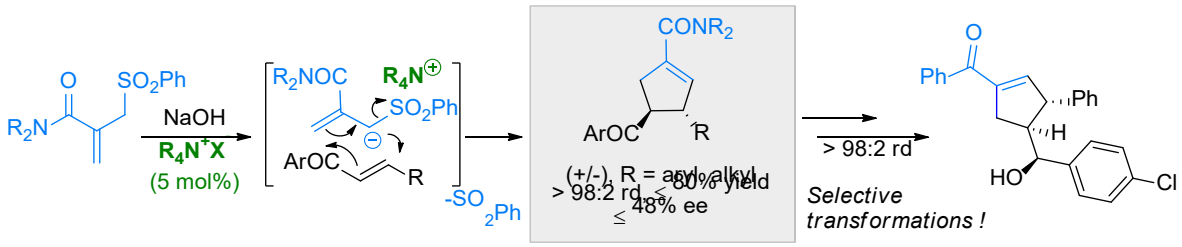
In collaboration with Dr. Sylvain Oudeyer (Univ. Rouen Normandie). Thanks to its electrophilic properties, the disubstituted Meldrum's acid platform reacts as a disubstituted C2-synthon under the organocatalytic addition of phenol derivatives. This strategy was successfully applied to the enantioselective decarboxylative-protonation and -chlorination reactions (*vide infra*). (a) Legros, F.; Martzel, T.; Brière, J.-F.; Oudeyer, S.;* Levacher, V. *Eur. J. Org. Chem*. **2018**, 1975. (b) Martzel, T.; Annibaletto, J.; Levacher, V.; Brière, J.-F.*; Oudeyer, S.* *Adv. Synth. Catal.* **2019**, 995.



In collaboration with Prof. Giang Vo-Thanh (ICMMO, Univ. Paris-Saclay). Alkylidene Meldrum's acid derived from ketones as a Novel Platform for the vinylogous series for the organocatalytic synthesis of dihydropyranones. Wittmann, S.; Martzel, T.; Pham truong, C.-T.; Toffano, M.; Oudeyer, S.; Guillot, R.; Bournaud, C.; Gandon, V.; Brière, J.-F.*; Vo-Thanh, G.* *Angew. Chem., Int. Ed.* **2021**, 11110.

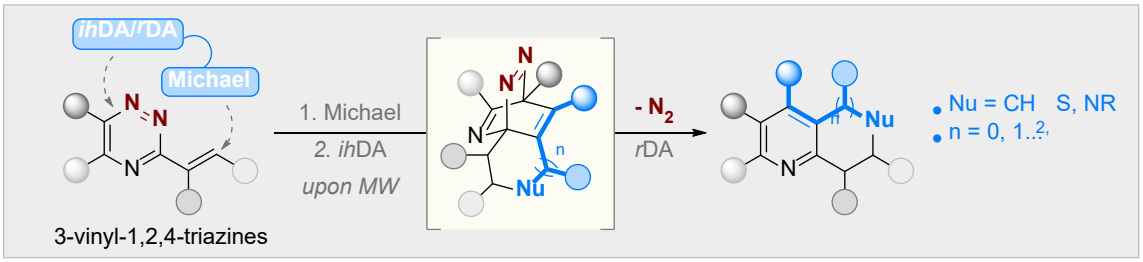


III. Formal organocatalysed cycloaddition. A *trans* and regioselective **anionic domino formal (3+2) cycloaddition-S_N2' reaction** was achieved with allylic sulfones having an MBH acrylamide backbone under phase transfer organocatalytic conditions giving rise to the formation of unprecedented densely substituted cyclopentene derivatives amenable to selective transformations. Gembus, V.; Postikova, S.; Levacher, V.; Brière, J.-F. *J. Org. Chem.* **2011**, 4194.



In collaboration with Stéphane Perrio (Univ. Caen Normandie), the catalytic formation of allylic sulfone anions is currently under investigation upon innovative sulfinate organocatalysis. (a) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Adv. Synth. Catal.* **2016**, 96. (b) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Eur. J. Org. Chem.* **2018**, 5069. (c) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Adv. Synth. Catal.* **2018**, 2696.

IV. 3-vinyl-1,2,4-triazine platforms (in collaboration with Prof. Franck Suzenet and Dr. Marie-Aude Hiebel – Univ. Orléans, France). The dual-functionality of the 3-vinyl-1,2,4-triazine platforms was highlighted through Michael type reactions followed by domino *inverse-electron-demand-hetero*-Diels–Alder (*ih*DA)/*retro*-Diels–Alder (*r*DA) reactions thanks to suited mode of activation; en route to new chemical space with non-aromatic/heteroaromatic fused bicycle architectures. (a) Lorion, M.; Guillaumet, G.; Brière, J.-F.*; Suzenet, F.* *Org. Lett.* **2015,** 3154. (b) Berthonneau, C.; Buttard, F.; Hiebel, M.-A.; Suzenet, F.*; Brière, J.-F.* *Adv. Synth. Catal.* **2017**, 4106. (c) Jouha, J.; Buttard, F.; Lorion, M.; Berthonneau, C.; Khouili, M.; Hiebel, M.-A.; Guillaumet, G.; Brière, J.-F.*; Suzenet, F.* *Org. Lett.* **2017**, 4770.



Based on the use of alkoxyamine nucleophiles, an organocatalytic aza-Michael reaction to substituted 3-vinyl-1,2,4-triazines was achieved and extended the scope towards the elaboration of an array of biorelevant tetrahydro-[1,6]-naphthyridines variously substituted on the aliphatic moiety. Buttard, F.; Berthonneau, C.; Hiebel, M.-A.; Brière, J.-F.*; Suzenet, F.* *J. Org. Chem.* **2019**, 3702.