# Dr Jean-François Brière

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## PROFESSIONNAL EXPERIENCES

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| 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

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| 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

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| 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 |
| 2016-2011 | Member of unit council of COBRA Laboratory. |
| 2021- | Member of the management team of COBRA laboratory. |

## RESEARCH INTERESTS

• Chiral heterocycles • (Organo)Catalysis and asymmetric synthesis • Photocatalysis and electrosynthesis • Domino and MCR processes in sustainable chemistry • Molecular platforms in synthesis: ▪ Meldrum's acid ▪ Triazines ▪ Isoxazolidin-5-one as precursors of β-amino acids

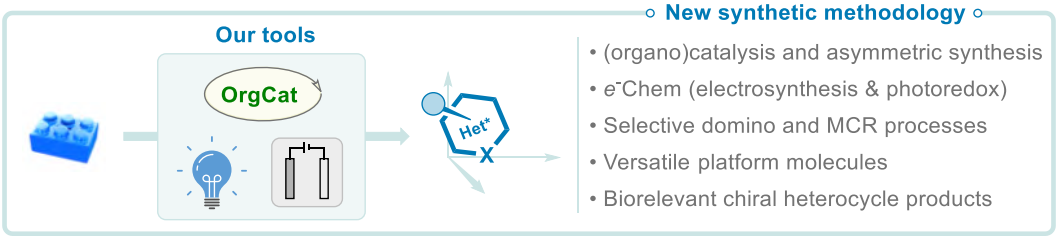
## SCIENTIFIC ACHIEVEMENTS

**Academic record (h-index: 23),** 77 publications, 7 book chapters, 5 patents, 31 invited lectures (academia & industry)

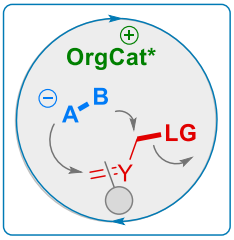
## *Organocatalytic synthesis of chiral bio-relevant heterocycles*

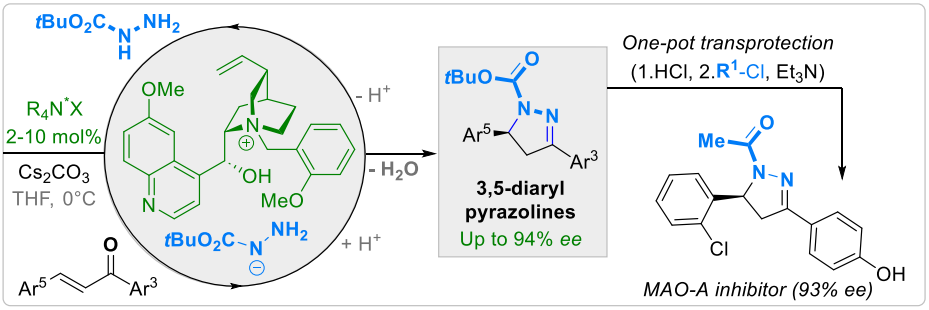
The development of *catalysts or catalytic systems*, able to accelerate the construction of molecular architectures, is at the heart of modern research in *sustainable* organic synthesis: seeking atom and energy *eco*nomy in order to minimize the environment imprint. Furthermore, the resurgence of organic synthesis assisted by technologies such as electrosynthesis and photochemistry, allowing straightforward electron or energy transfers *i.e. via* redox-chemistry "*e*$^-$Chem", affords novel "*eco*-efficient" opportunity. In quest of efficiency, our research endeavors deal with the achievement of catalytic and/or technology-driven domino and multicomponent synthetic methodologies capable to furnish original Csp$^3$-rich derivatives, with a focus on *chiral heterocycles*, known as valuable building blocks for the elaboration of medicinally relevant compounds while exploring the 3D chemical space.
*OUR SAVOIR-FAIRE* • Chiral bio-relevant heterocycles • Organocatalysis and asymmetric synthesis • Electrosynthesis and photo(redox) catalysis • Domino and MCR processes • Useful molecular platforms in synthesis (Meldrum's acid, triazine, isoxazolidin-5-ones as β-amino acid precursors).

*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) Segovia, C.; Nocquet, P.-A.; Levacher, V.; Brière, J.-F.; Oudeyer, S. Catalysts **2021**, 1249 (dearomatization). (h) Oudeyer, S.; Levacher, V.; Beucher, H.; Brière, J.-F. *Molecules* **2023**, 1071 (radical chemistry and dipoles).



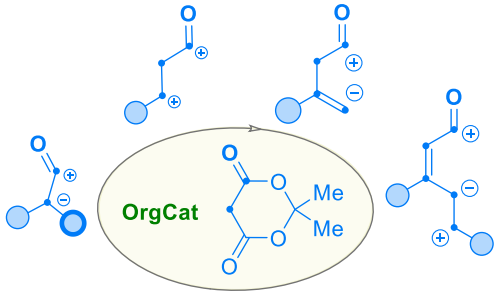

***I. Bisnucleophiles.*** Under catalytic phase-transfer (PTC) conditions the formation of an original chiral ion pair between quininium cation and hydrazine anion led to an enantioselective **domino aza-Michael-cyclocondensation reaction** to furnish enantioenriched **3,5-diaryl pyrazolines**. A convenient 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 (Racemic catalysis + TBD).



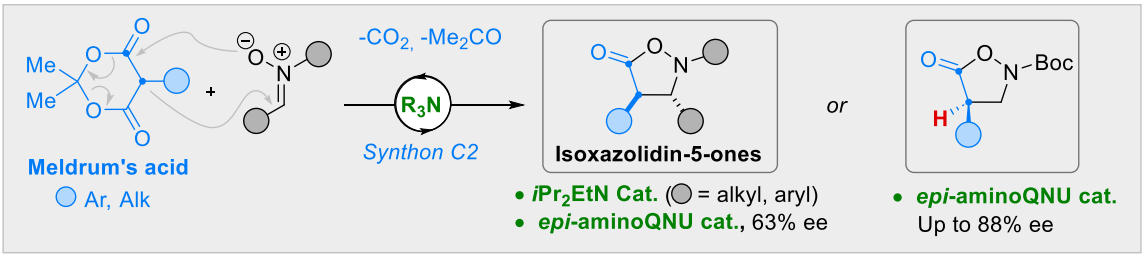



**See also:** *3,4-disubstituted pyrazolines from hydrazone as CB2 ligand* (a) Gembus, V.; Bonnet, J.-J.; Janin, F.; Bohn, P.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2010**, 3287. (b) Gembus, V.; Furman, C.; Millet, R.; Mansouri, R.; Chavatte, P.; Levacher, V.; Brière, J.-F. *Eur. J. Med. Chem.* **2012**, 396. ***Isoxazolines from N-Boc hydroxylamine bisbucleophile.*** Noël, R.; Gembus, V.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2014**, 1245.

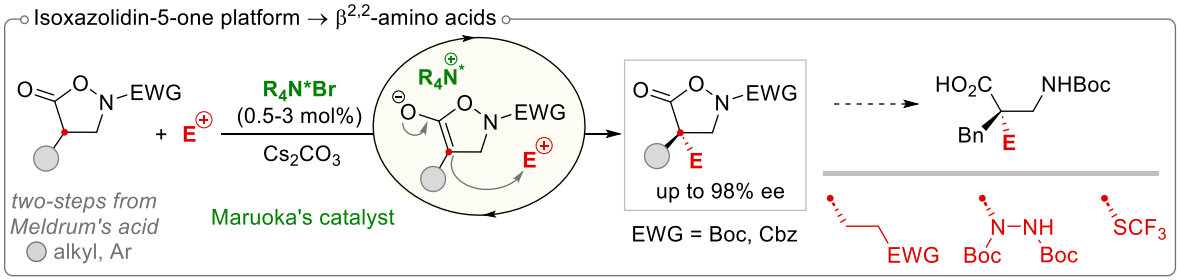
***II. The Meldrum's acid platform in organocatalysis.*** In search for new reactivities in organocatalysis, we have recently highlighted a unique behavior of **Meldrum's acid derivatives** with various nitrones leading to an unprecedented access to **isoxazolidin-5-ones**; useful precursors of β-amino acids. In the presence of a catalytic quantity of Brønsted base, Meldrum's acid derivatives, thanks to their high acidity (p$K_a$ = 4.8 in water), react as C2 to C5 synthons. The overall-mechanism was probed by the combined ESI-IMS-MS and DFT technics when reacting to nitrones (as C2-synthon) e*volving via* a **domino (3+2) cycloaddition-fragmentation-decarboxylation-protonation reaction**. (a) Postikova, S.; Tite, T.; Levacher, V.; Brière, J.-F. *Adv. Synth. Catal.* **2013**, 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**, 4086. (c) Tite, T.; Sabbah, M.; Levacher, V.; Brière, J.-F. *Chem. Commun.* **2013**, 11569 (protonation).



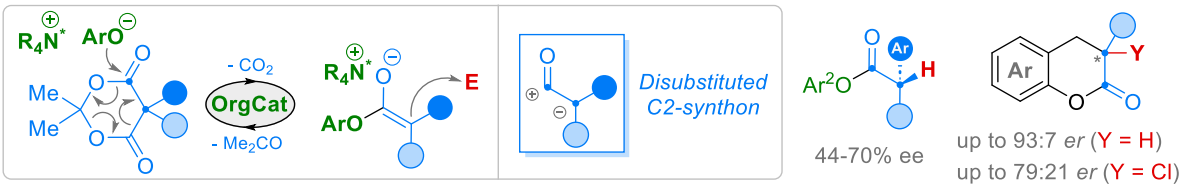
Acide de Meldrum => C2-C5 synthons



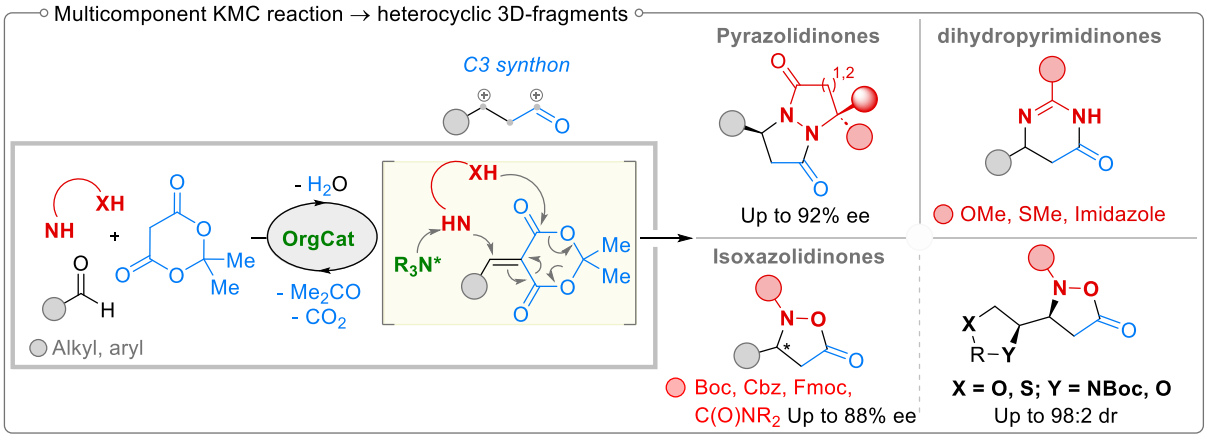

The readily available α-substituted *N*-alkoxycarbonyl isoxazolidin-5-ones allowed us to investigate the unprecedented catalytic α-functionalization reaction (C-S, C-N and C-C bonds) under PTC conditions. This isoxazolidinone proved to be an useful molecular platform to construct valuable $\beta^{2,2}$-amino acids. (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).



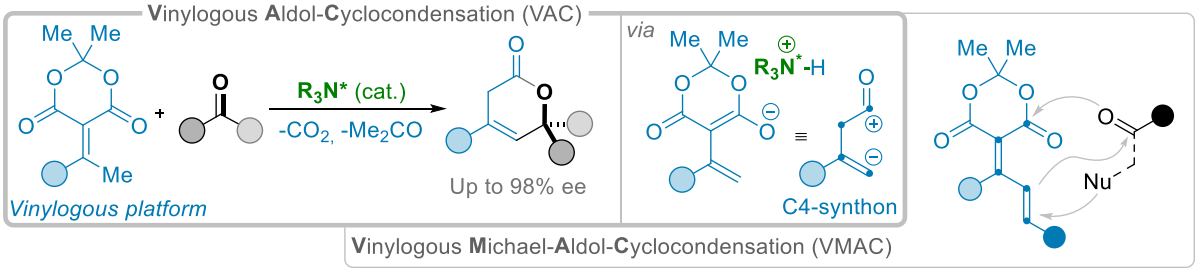
**In collaboration with Dr. Sylvain Oudeyer (Univ. Rouen Normandie).** Thanks to its electrophilic properties, the disubstituted Meldrum's acid platform reacts as a disubstituted C2-synthon under the organocatalytic addition of phenol derivatives. (a) Legros, F.; Martzel, T.; Brière, J.-F.; Oudeyer, 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.



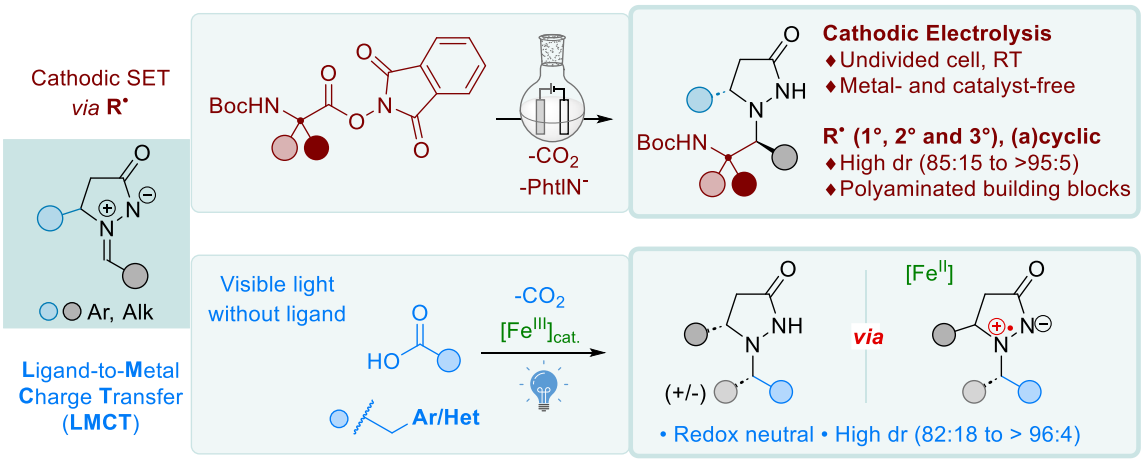

We discovered a novel stereoselective organocatalysed **multicomponent Knoevenagel-Michael-Cyclocondensation (KMC) reaction** allowing straightforward syntheses of 3D-heterocyclic fragments. This sequence exploits the high electrophilicity of alkylidene Meldrum's acid intermediates as 3C synthon. (a) 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. (e) Lebrêne, A.; Martzel, T.; Gouriou, L.; Sanselme, M.; Levacher, V.; Oudeyer, S.; Afonso, C.; Loutelier-Bourhis, C.;* Brière, J. F.* *J. Org. Chem.* 2021, *86*, 8600. (f) Annibaletto, J.; Martzel, T.; Levacher, V.; Oudeyer, S.; Brière, J.-F.* *Adv. Synth. Catal.* 2021, *363*, 4447 (enantioselective version). (d) Martzel, T.; Annibaletto, J.; Millet, P.; Pair, E.; Sanselme, M.; Oudeyer, S.; Levacher, V.; Brière, J.-F.* *Chem. Eur. J.* 2020, 8541.



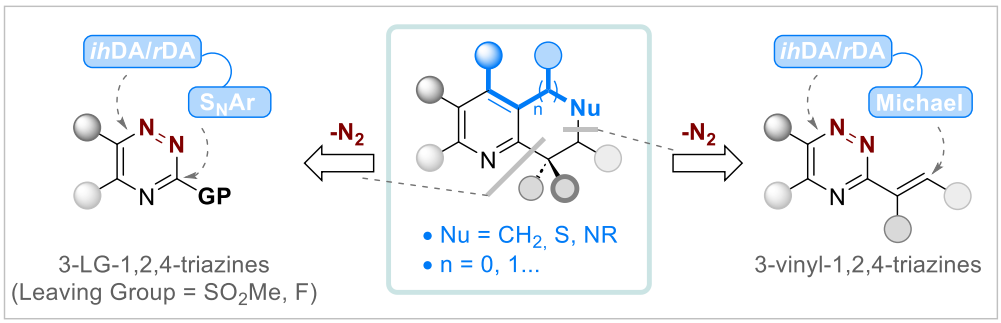

**In collaboration with Prof. Giang Vo-Thanh team (ICMMO, Univ. Paris-Saclay).** Alkylidene Meldrum's acid derived from ketones as a Novel Platform for the vinylogous series for the organocatalytic synthesis of dihydropyranones. Other developments towards a highly diastereoselective organocatalyzed domino sulfa- and aza-Vinylogous-Michael-Aldol-Cyclocondensation (VMAC) which highlights two vinylogous steps, an unprecedented hetero-1,6-conjugate addition and a diastereoselective aldol reaction triggering a formal (4+2) cycloaddition, which opens a new route to bio-relevant and original tricyclic heterocycle derivatives. (a) 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. (b) Milbeo, P.; Lebrêne, A.; Savchuk, M.; Vo-Thanh, G.; Oudeyer, S.; Beucher, H.; Brière, J.-F.* *Chem. Eur. J.* 2023, e202301311. (c) Savchuk, M.; Vo-Thanh, G.; Oudeyer, S.; Beucher, H.; Briere, J. F. *Org. Biomol. Chem.* 2024, 2948.




***III. e⁻Chem, electrosynthesis and LMCT photoredox catalysis.*** Highly stereoselective addition of radical species to chiral azomethine imines, thanks to electrosynthesis or iron-photoredox catalysis upon LMCT approach. Diastereoselective addition of redox active esters to azomethine imines by electrosynthesis. (a) Leleu, L.; Martzel, T.; Fall, A.; Sanselme, M.; Levacher, V.; Oudeyer, S.;* Brière, J.-F.* *Chem. Commun.* **2022**, *58*, 6100. (b) Fall, A.; Magdei, M.; Savchuk, M.; Oudeyer, S.; Beucher, H.; Brière, J. F. *Chem. Commun.* **2024**, *60*, 6316.




***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 or 3-LG-1,2,4-triazine molecular platforms was highlighted through Michael or $S_NAr$ type reactions followed by domino *inverse-electron-demand-hetero*-Diels–Alder (*ih*DA)/*retro*-Diels–Alder (*r*DA) reactions, thanks to organocatalytic activation in several instances, en route to new chemical space of valuable 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. (d) Buttard, F.; Berthonneau, C.; Hiebel, M.-A.; Brière, J.-F.*; Suzenet, F.* *J. Org. Chem.* **2019**, 3702. (e) Buttard, F.; Berthonneau, C.; Hiebel, M.-A.; BLapray, A.; Martzel, T.; Hiebel, M. A.; Oudeyer, S.; Suzenet,* F.; Brière, J. F.* *Adv. Synth. Catal.* **2024**, 316.



***V. Cooperative ion-pairs,*** **In collaboration with Stéphane Perrio (Univ. Caen Normandie)**. The catalytic formation of allylic sulfone anions is currently under investigation upon innovative sulfinate quaternary ammonium cooperative ion-pairs organocatalysis.


(a) Gembus, V.; Postikova, S.; Levacher, V.; Brière, J.-F.* *J. Org. Chem.* 2011, 4194. (b) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Adv. Synth. Catal.* 2016, 96. (c) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Eur. J. Org. Chem.* 2018, 5069. (d) Martzel, T.; Lohier, J.-F.; Gaumont, A.-C.; Brière, J.-F.; Perrio, S.* *Adv. Synth. Catal.* 2018, 2696.