Enantioselective Organocatalyzed Michael Additions of Nitroalkanes to 4-Arylidenedihydrofuran-2,3-diones and 4-Arylidenepyrrolidine-2,3-diones

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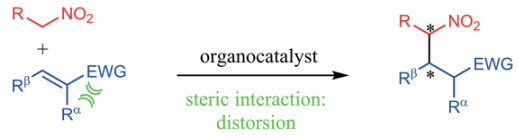
Abstract: Tremendous efforts have been devoted to the development of organocatalytic enantioselective Michael additions of nitroalkanes to α,β-unsaturated carbonyl compounds. However, using highly substituted electrophiles remain challenging, since the additional substituents decrease the electrophilicity. β-Arylidene-α-ketolactones and α-ketolactams are used as highly electrophilic Michael acceptors that afford the corresponding products in moderate to good yields, with high enantioselectivities. This success relies on their rigid structure that prevents deconjugation and the efficient recognition of the α-dicarbonyl motif by the hydrogen-bond donor catalyst.

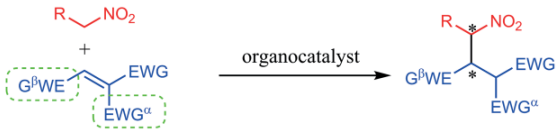
Michael additions are among the most versatile transformations in the toolbox of synthetic organic chemists.[1] The reaction course often implies the creation of one or several stereogenic centers, and a plethora of studies have been devoted to the control of their absolute configurations, with organocatalysis as the most successful method.[2] Among Michael additions, the reaction between nitroalkanes and α,β-unsaturated carbonyl compounds is especially appealing. This is due to the possibilities offered to the catalysts to create specific interactions to induce enantioselectivity and the polyfunctional nature of the products.[3,4] Indeed, the nitro and carbonyl functionalities can be chemoselectively proceeded to deliver valuable enantioenriched compounds such as pyrrolidines[5] or γ-amino alcohols.[6]

However, a limitation of this transformation is attained when highly substituted Michael acceptors are used. Indeed, additional substituents, especially at the α position, are deleterious to the reactivity because of unfavorable steric interactions that tend to hamper the conjugation between the olefin and the electron-withdrawing group (Scheme 1, Equation 1).[7] A first solution to tackle this problem is to add a second electron-withdrawing group either at the α or at the β position to increase the electrophilicity (Scheme 1, Equation 2).[8–10] It is also possible to tether the nucleophile to render the reaction intramolecular so that the favorable entropic factor overcomes the

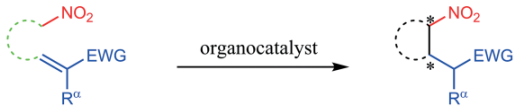
(Eq 1) α,β-disubstituted Michael acceptors are challenging substrates[7]



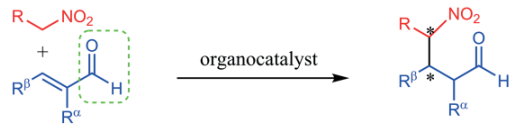
(Eq 2) Additional EWG at α- and/or β-position[8,9,10]



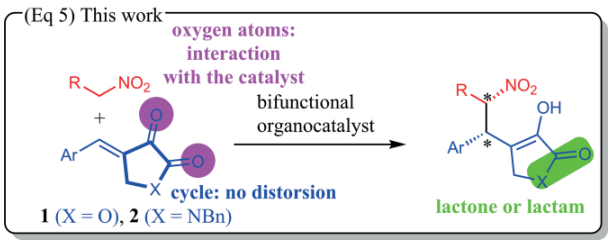
(Eq 3) Intramolecular reactions[11]



(Eq 4) Reactions with aldehydes[12]



(Eq 5) This work



[a] Dr. M. Fofana, Dr. Y. Dudognon, L. Bertrand, Prof. Dr. T. Constantieux, Prof. Dr. J. Rodriguez, Dr. D. Bonne, Dr. X. Bugaut
Aix Marseille Univ, CNRS, Centrale Marseille, ISM2,
Marseille, France
E-mail: damien.bonne@univ-amu.fr, xavier.bugaut@univ-amu.fr
https://ism2.univ-amu.fr/fr/annuaire/stereo/bonnedamien
https://ism2.univ-amu.fr/fr/annuaire/stereo/bugautxavier
[b] Dr. M. Fofana, Prof. Dr. I. Ndiaye
Département de Chimie, Faculté des Sciences et Techniques, Université Cheikh Anta Diop,

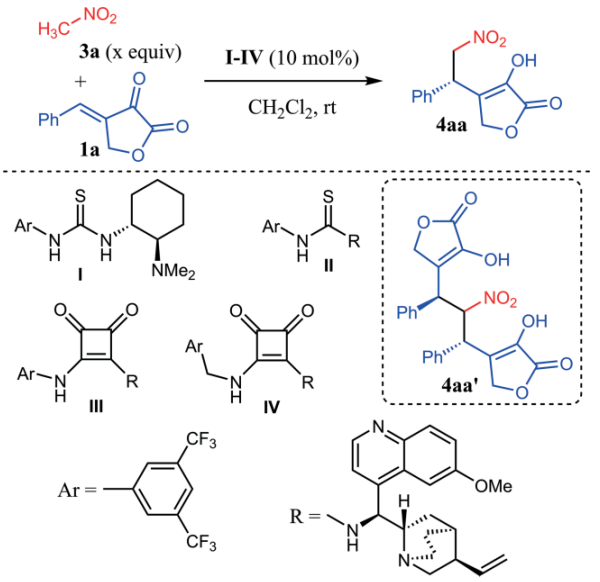
intrinsic low reactivity (Scheme 1, Equation 3).[11] In addition to this, there are also sporadic examples of the use of highly substituted aldehydes in the presence of a chiral secondary amine, where the very strong electron-withdrawing character of the intermediate iminium ion warrants reasonable reactivity (Scheme 1, Equation 4).[12]

These three strategies bring about isolated solutions but are inherently limited in terms of potential applications.[13] In this context, we made the hypothesis that bridging both α substituents could help to reduce the distortion that is responsible for the low reactivity (Scheme 1, Equation 5). Herein, we wish to disclose our results on the enantioselective Michael addition of nitroalkanes to β-arylidene-α-ketolactones **1**[14] and α-ketolactams **2**[15] catalyzed by bifunctional hydrogen-bonding catalysts.[4e,4g,4h] They appeared as especially interesting candidates for enantioselective organocatalyzed Michael additions with their rigid α-dicarbonyl structures that could be recognized by the hydrogen-bonding catalyst.[16] The resulting Michael adducts were obtained in moderate to good yields and diastereoselectivities, but with high enantioselectivities. It should be noted that a similar reaction with only ketolactams **2** has just been reported under Cu-catalysis.[17]

Our studies began with the reaction of β-phenylidene-α-ketolactone **1a** with 3 equivalents of nitromethane (**3a**) in the presence of Takemoto bifunctional (*R*,*R*)-thiourea **I** in CH_2Cl_2 at room temperature (Table 1, Entry 1).[4e] Michael adduct **4aa** was isolated as its enol form in encouraging yield (40 %) and enantiomeric excess (84 %). Quinine-derived thiourea **II**[4g] or squaramides **III** and **IV**[4h] all performed less efficiently (Entries 2–4). The next idea was to change the solvent ($CHCl_3$, toluene, EtOAc, Et_2O, CH_3CN) and the reaction temperature (–4 °C or –20 °C), but these modifications brought about no improvement of the reaction outcome.[18] At that point, we noticed that the expected product was accompanied by another compound **4aa′** resulting from the double Michael addition, and also extensive degradation.[19] To try to solve these issues, we naturally attempted to increase the amount of nitromethane (**3a**) to outcompete the undesired pathways. Pleasingly, a gradual increase to 10 and 20 equivalents of pronucleophile improved both the yield and the enantiomeric excess, with 10 equivalents standing as the best compromise (Entries 5–7). At that point of our studies, the re-evaluation of squaramide catalyst **III** at 0 °C further improved the enantiomeric excess (89 % *ee*) at the cost of a decrease of the yield (62 %). We kept these reaction conditions as the optimized ones to continue the study (Entry 8).

A study of the reaction scope and limitations was undertaken (Table 2). β-Arylidene-α-ketolactones **1b**–**d** bearing electron-withdrawing or slightly electron-donating substituents could be combined with nitromethane (**3a**) to deliver products **4ab**–**ad** in moderate yields but good enantiomeric excesses (Entries 1–3). However, it was not possible to evaluate Michael acceptors bearing more electron-donating substituents, heteroaromatics, or alkyl chains instead of the aromatic ring because they could not be prepared. On the opposite, adding substituents on the nitroalkane had a beneficial effect in the reaction outcome with **1a**, by increasing the stability of the resulting Michael adducts **4ba**–**ea** (Entries 4–7). Nitroethane (**3b**), phenylnitromethane (**3c**), bromonitromethane (**3d**), and ethyl nitroacetate (**3e**) all delivered the product with high yields. Diastereoselectivity was generally moderate, except for phenyl-substituted product **4ca** (Entry 5), but enantiomeric excesses reached 82 to 90 %.[20]

Table 1. Optimization of the reaction conditions.



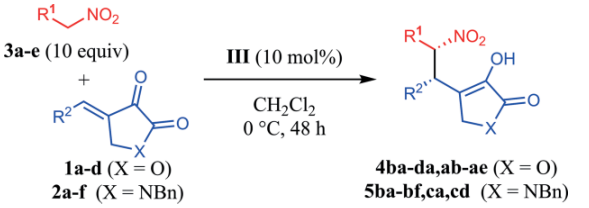
Entry	*x*	Catalyst	Time [h]	Yield [%][a]	*ee* [%][b]
1	3	**I**	72	40	84
2	3	**II**	72	30	80
3	3	**III**	72	28	84
4	3	**IV**	72	32	78
5	10	**I**	15	46	84
6[c]	10	**I**	15	70	79
7[c]	20	**I**	15	74	79
8[c]	10	**III**	48	62	89

[a] Yield of analytically pure product after flash chromatography. [b] *ee* determined by HPLC on chiral stationary phase. [c] Reaction run at 0 °C.

To try to expand the usefulness of the present transformation, we then turned our attention towards the corresponding β-arylidene-α-ketolactams, which seems easier to prepare and use.[15] Following the same reaction conditions, nitroalkanes **3b**–**c** were combined with β-arylidene-α-ketolactams **2a**–**f** (Entries 8–15). Products bearing diversified functional groups were obtained in moderate to good yields, and high enantiomeric excesses between 89 and 98 %. Diastereoselectivities were variable from nearly no selectivity to almost complete, with an improvement when R^1 is an aromatic substituent. Additionally, comparing the optical rotation value for compound **5ba** (–29.7, *c* = 1.02, $CHCl_3$) with the one obtained with the Cu-catalyzed variant (+31.7, *c* = 1.02, $CHCl_3$) allowed attributing the absolute and relative configurations for the products.[17] They are also in agreement with the stereoselection model discussed at the end of the article.

Moreover, 2-nitro-1-phenylethanone (**3f**) could be used as a more activated pronucleophile (Scheme 2). Pleasingly, a stoichiometric amount of this compound was sufficient to promote the Michael addition to **1a** and **2a**, followed by a *C*-to-*O*

Table 2. Scope of the Michael addition of nitroalkanes to β-arylidene-α-ketolactones and α-ketolactams.[a]

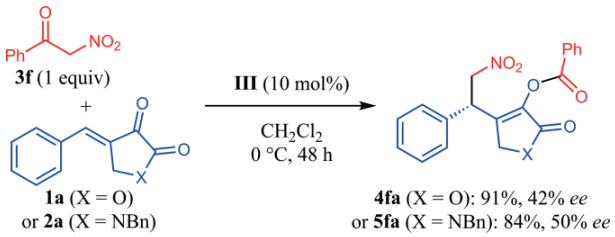


Entry	**3**: R^1	**1** or **2**: X, R^2	Product: yield [%],*dr*, *ee* [%][b]
1	**3a**: H	**1b**: O, 4-BrC_6H_4	**4ab**: 61, –, 88
2	**3a**: H	**1c**: O, 4-FC_6H_4	**4ac**: 54, –, 84
3	**3a**: H	**1d**: O, 4-MeC_6H_4	**4ad**: 61, –, 90
4	**3b**: Me	**1a**: O, Ph	**4ba**: 85, 7:1, 90
5	**3c**: Ph	**1a**: O, Ph	**4ca**: 90, 11:1, 88
6	**3d**: Br	**1a**: O, Ph	**4da**: 85, 2.5:1, 82 and 84
7	**3e**: CO_2Et	**1a**: O, Ph	**4ea**: 80, 1:1, 53 and 53
8	**3b**: Me	**2a**: NBn, Ph	**5ba**: 95, 6:1, 97
9	**3b**: Me	**2b**: NBn, 4-CNC_6H_4	**5bb**: 79, 1.2:1, 98
10	**3b**: Me	**2c**: NBn, 4-$NO_2C_6H_4$	**5bc**: 89, 1.6:1, 94
11	**3b**: Me	**2d**: NBn, 4-$MeOC_6H_4$	**5bd**: 85, 2.2:1, 95
12	**3b**: Me	**2e**: NBn, 2,4-$Cl_2C_6H_3$	**5be**: 95, 1.3:1, 91
13	**3b**: Me	**2f**: NBn, 3-thienyl	**5bf**: 78, 1.6:1, 93
14	**3c**: Ph	**2a**: NBn, Ph	**5ca**: 60, > 20:1, 89
15	**3c**: Ph	**2d**: NBn, 4-$MeOC_6H_4$	**5cd**: 42, 10:1, 90

[a] Reaction conditions: nitroalkanes **3a**–**e** (10 equiv.) and β-arylidene-α-ketolactones **1a**–**d** or α-ketolactams **2a**–**f** were stirred in the presence of catalyst **III** (10 mol-%) in CH_2Cl_2 at 0 °C for 48 hours. [b] Yield of analytically pure product after flash chromatography, *dr* determined by ^{1}H NMR and *ee* determined by HPLC on chiral stationary phase, for the major diastereomer, or for each of them when possible.[20]

benzoyl migration, to deliver products **4fa** and **5fa** in high yield. Despite moderate enantioselectivities (42 % and 50 % *ee* for **4fa** and **5fa**, respectively), this observation illustrates the concept of acyl group transfer as transient activation in organocatalysis.[21]

The observed reactivity and stereoselectivity provided by the quinine-derived squaramide catalyst could be rationalized



Scheme 2. Michael additions followed by *C*-to-*O* benzoyl migrations.

based on DFT studies present in the literature, notably for related additions of nitroalkanes to enones (Figure 1).[22] By taking inspiration directly from those precedents, we can assume that the nitroalkane interacts through double hydrogen bonding with the squaramide unit, which allows its easy deprotonation by the tertiary amine by stabilizing the nitronate ion. When an R^1 substituent is present on the pronucleophile, it is placed on the left side via an *anti-gauche* topology to escape from the steric hindrance of the quinuclidine bicyclic system. The resulting tertiary ammonium ion can now act as a hydrogen-bond donor to both the ketone and lactone/lactam of the electrophile to favor its approach by the lower face. The product is formed and the catalyst regenerated after C–C bond formation, followed by proton transfer from the catalyst to the intermediate enolate ion. The application of this model from the literature is in accordance with the observed enantio- and diastereoselectivities.

In conclusion, we have developed the first organocatalyzed addition of various nitroalkanes **3** to β-arylidene-α-ketolactones **1** and α-ketolactams **2**. The highly functionalized products **4** and **5** were obtained with moderate to good yields and diastereocontrol, but high enantioselectivities. Moreover, the present transformation is complementary to the Cu-catalyzed variant that has just been published.[17] Indeed, if those conditions generally allow attaining excellent diastereoselectivities,

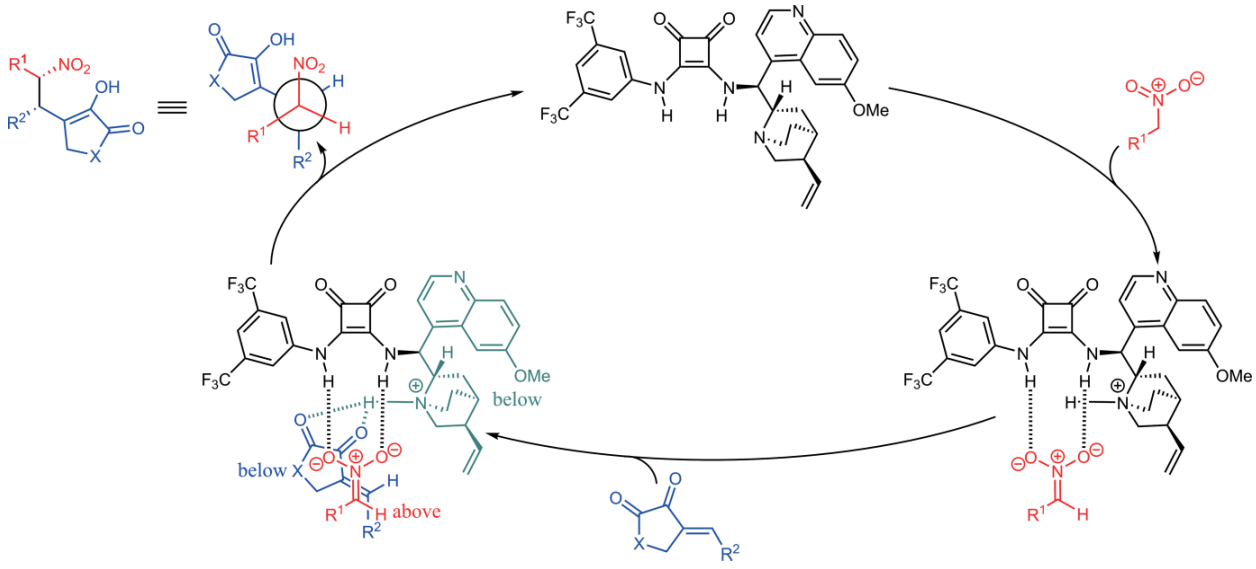


Figure 1. Reaction mechanism and rationalization of stereoselectivity.

the applicability has been demonstrated only for lactams and with non-functionalized nitroalkanes. Therefore, the present transformation brings elements of novelty by allowing the use of lactones in the electrophilic partner, and of pronucleophilic partners bearing a bromine atom, a phenyl ring, an ester function or a benzoyl group.

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Keywords: Enantioselectivity · Lactams · Lactones · Michael addition · Organocatalysis

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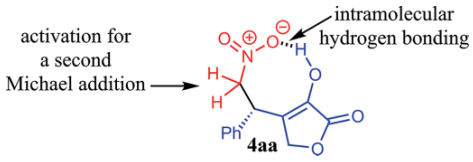
[15] a) For their preparation, see supporting information. A handful of catalytic enantioselective domino processes are known with those substrates. See: b) S. Zhang, Y.-C. Luo, X.-Q. Hu, Z.-Y. Wang, Y.-M. Liang, P.-F. Xu, *J. Org. Chem.* **2015**, *80*, 7288; c) Y. Lu, Y. Zhou, L. Lin, H. Zheng, K. Fu, X. Liu, X. Feng, *Chem. Commun.* **2016**, *52*, 8255; d) J.-L. Li, K.-C. Yang, Y. Li, Q. Li, H.-P. Zhu, B. Han, C. Peng, Y.-G. Zhi, X.-J. Gou, *Chem. Commun.* **2016**, *52*, 10617; e) C. Wang, H. Jia, C. Zhang, Z. Gao, L. Zhou, C. Yuan, Y. Xiao, H. Guo, *J. Org. Chem.* **2017**, *82*, 633; f) J.-L. Li, L. Fu, J. Wu, K.-C. Yang, Q.-Z. Li, X.-J. Gou, C. Peng, B. Han, X.-D. Shen, *Chem. Commun.* **2017**, *53*, 6875; g) Q. Li, L. Zhou, X.-D. Shen, K.-C. Yang, X. Zhang, Q.-S. Dai, H.-J. Leng, Q.-Z. Li, J.-L. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 1913; *Angew. Chem.* **2018**, *130*, 1931; h) Q.-Z. Li, Y. Liu, H.-J. Leng, J.-L. Li, *Synlett* **2018**, *29*, 2601; i) Y. Wang, Y. Chen, X. Li, Y. Mao, W. Chen, R. Zhan, H. Huang, *Org. Biomol. Chem.* **2019**, *17*, 3945; j) X. Lu, Y. Zhang, Y. Wang, Y. Chen, W. Chen, R. Zhan, J. C. G. Zhao, H. Huang, *Adv. Synth. Catal.* **2019**, *361*, 3234; k) X. Zhao, J. Xiong, J. An, J. Yu, L. Zhu, X. Feng, X. Jiang, *Org. Chem. Front.* **2019**, *6*, 1989.

[16] For the use of α-dicarbonyl compounds as pronucleophiles in organocatalysis, see: a) O. Baslé, W. Raimondi, M. M. Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246; b) W. Raimondi, D. Bonne, J. Rodriguez, *Angew. Chem. Int. Ed.* **2012**, *51*, 40; *Angew. Chem.* **2012**, *124*, 40; c) W. Raimondi, O. Baslé, T. Constantieux, D. Bonne, J. Rodriguez, *Adv. Synth. Catal.* **2012**, *354*, 563; d) W. Raimondi, D. Bonne, J. Rodriguez, *Chem. Commun.* **2012**, *48*, 6763.

[17] a) The complementary Cu-catalyzed alternative conditions were reported during the preparation of our manuscript: Y. Huang, Z. Zha, Z. Wang, *Org. Lett.* **2020**, DOI: https://doi.org/10.1021/acs.orglett.0c00030; for other metal-catalyzed transformations on the same substrates, see:; b) X. Hu, Y. Zhou, Y. Lu, S. Zou, L. Lin, X. Liu, X. Feng, *J. Org. Chem.* **2018**, *83*, 8679; c) Y. Huang, Y. Li, J. Sun, J. Li, Z. Zha, Z. Wang, *J. Org. Chem.* **2018**, *83*, 8464.

[18] See supporting information for further details.

[19] Even though no experimental proof could be collected, it is likely that the product **4aa** exhibits intramolecular hydrogen-bonding between the enol function and the nitro group. This intramolecular activation could explain why the double addition product **4aa'** is observed even in the presence of a large excess of nitromethane:



[20] For the examples where the enantiomeric excesses were determined for both diastereomers, values are very similar (Table 2, Entries 6 and 7). This observation points towards an epimerization at the position α to the nitro group in the basic reaction conditions.

[21] a) For a review, see: J. Rodriguez, A. Quintard, *Synthesis* **2019**, *51*, 1923; for recent related example, see: b) K. Mondal, S. C. Pan, *J. Org. Chem.* **2018**, *83*, 5301; c) Y.-X. Song, D.-M. Du, *Adv. Synth. Catal.* **2019**, *361*, 5042.

[22] a) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631; b) M. N. Grayson, *J. Org. Chem.* **2017**, *82*, 4396.