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Letter

Organocatalytic Michael Addition of Unactivated α-Branched Nitroalkanes to Afford Optically Active Tertiary Nitrocompounds

Beñat Lorea, Ane García-Urricelqui, José M. Odriozola, Jesús Razkin, Maialen Espinal-Viguri, Mikel Oiarbide,* Antonia Mielgo,* Jesús M. García,* and Claudio Palomo*

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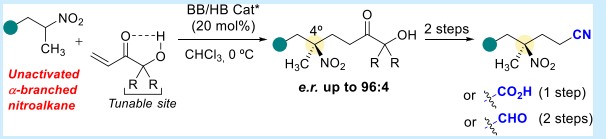
ABSTRACT: The direct, asymmetric conjugate addition of unactivated α-branched nitroalkanes is developed based on the combined use of chiral amine/ureidoaminal bifunctional catalysts and a tunable acrylate template to provide tertiary nitrocompounds in 55−80% isolated yields and high enantioselectivity (*e.r.* up to 96:4). Elaboration of the ketol moiety in thus obtained adducts allows a fast entry to not only carboxylic and aldehyde derivatives but also nitrile compounds and enantioenriched 5,5-disubstituted γ-lactams.



Stereoselective methods for the preparation of α-stereogenic nitrocompounds are highly appealing owing to the synthetic versatility of the nitro group.[1] For example, reduction would lead to the corresponding α-stereogenic amines, which are widespread substructures within natural products and bioactive compounds.[2] In addition, natural products that contain the nitro group are known to exhibit a wide range of biological activities.[3] However, the number of nitro-containing molecules under development within drug discovery programs is marginal, in part because the nitro functionality is classified as a "structural alert",[4] a situation that may result in missed opportunities.[1b] Another problem is that current enantioselective methodologies to prepare α-stereogenic nitrocompounds are not general.[5] In particular, the catalytic, asymmetric α-functionalization of secondary (α-branched) nitroalkanes progresses slowly (Figure 1). Catalytic methodologies have been described for accessing optically active tertiary nitrocompounds bearing no α-stereocenter (two identical R^1 substituents)[6,7] or an activating α-substituent Z, with Z = COR, CO_2R, CN, or similar.[8] The success of these latter methods is strongly bound to the presence of an electron-withdrawing substituent, which can ease formation of the transient nitronate anion while providing an additional handle for catalyst binding. In sharp contrast, methods for direct, highly enantioselective α-functionalization of α-aryl and α-alkyl nitroalkanes remain underdeveloped. Steric constraints toward electrophiles dictated by the R^1/R^2 substituents in the transient nitronate **A** (Figure 1) may account for the low reactivity observed, while discrimination across the two enantiotopic faces in **A** becomes increasingly challenging as the similarity in size and electronic nature of R^1 vs R^2 increases.

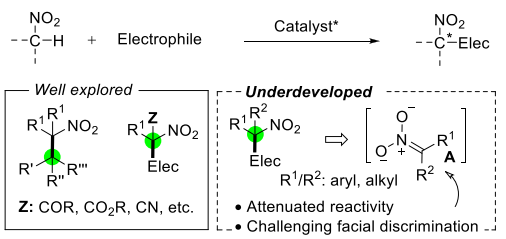


Figure 1. Asymmetric C_α-functionalization of α-branched nitroalkanes leading to tertiary nitrocompounds.

Efforts toward overcoming these issues are rare in the literature (Scheme 1). Yamaguchi described an organocatalytic conjugate addition of α-branched nitroalkanes to enones using 5−10 mol % of L-proline and 4-silyloxy L-proline rubidium salts (Scheme 1a),[9] although no data regarding the nitronate facial selectivity were reported. A couple of reports involving transition metal catalysis and chiral *P,N*-ligands are known. Kanai and Shibasaki[10] reported the palladium-catalyzed allylic alkylations of secondary nitroalkanes with the assistance of 10 mol % of base, typically DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), but attempts to get asymmetric induction at the α-position of the nitro functionality resulted in suboptimality (≤49% enantioselectivity obtained, Scheme 1b). More recently, Trost[11] described the palladium-catalyzed decarboxylative allylic alkylation of nitroesters affording α-aryl, α-allylic nitroalkanes with high enantioselectivities (Scheme 1c). Finally, Hyster reported an innovative enzymatic photoredox α-alkylation of nitroalkanes (Scheme 1d) which, however, shows strong substrate dependence.[12] With the existing limitations in mind and the apparent lack of any successful

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Scheme 1. Efforts on Catalytic Asymmetric α-Functionalization of α-Branched Alkyl/Aryl Nitroalkanes

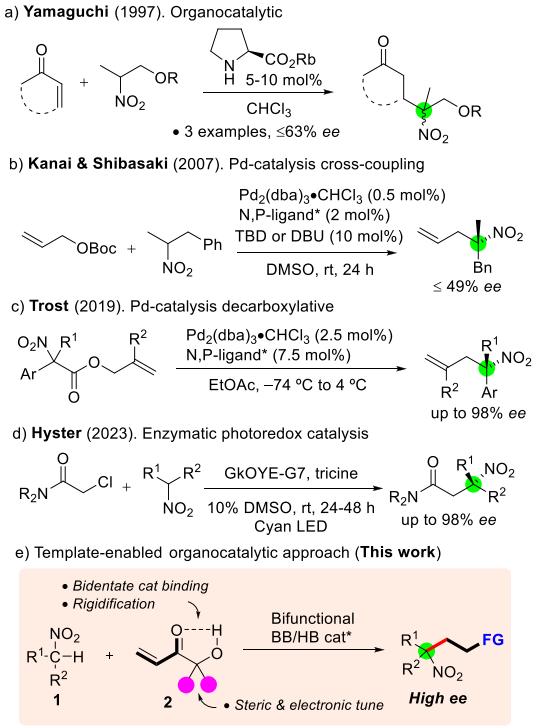
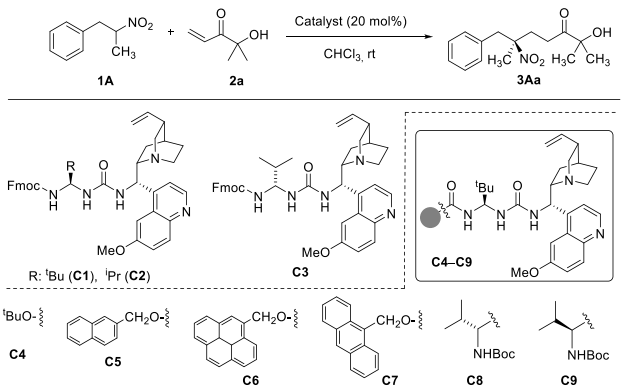


Table 1. Catalyst Screening for the Reaction of 1A with 2a[a]



entry	cat.	t (h)[b]	yield (%)[c]	e.r.[d]
1	**C1**	20	nd	78:22
2	**C2**	23	81	75:25
3	**C3**	26	68	62:38
4	**C4**	48	nd	65:35
5	**C5**	36	nd	75:25
6	**C6**	20	70	89:11
7	**C7**	14	74	90:10
8	**C8**	22	76	72:28
9	**C9**	43	80	65:35

[a]Reactions conducted on a 0.2 mmol scale in 0.6 mL of $CHCl_3$ (mol ratio **1A**/**2a**/catalyst 5:1:0.2). nd: Not determined. [b]Time for full conversion. [c]Yield of the isolated product. [d]Determined by chiral HPLC.

asymmetric organocatalytic approach toward α-stereogenic α-aryl/alkyl and α-alkyl/alkyl tertiary nitrocompounds, we set out to investigate the Brønsted base-catalyzed additions of unactivated α-branched nitroalkanes to well suited Michael acceptors. Here, our preliminary results along these lines are presented which demonstrate the feasibility of such a realization upon proper combination of chiral amine/ureidoaminal bifunctional catalysts and α′-hydroxy enones **2** as an acrylic ester/aldehyde surrogate with a tunable *gem*-disubstitution (Scheme 1e).

Previous research from these laboratories has shown that acrylic ester/aldehyde surrogates **2** fit well in Michael addition reactions that proceed through either H-bonding or metal-chelation mediated activation mechanisms.[13] The ability of the ketol moiety to act as a bidentate H-bond donor/acceptor and thus tightly bind to the bifunctional organocatalyst was believed to be crucial in these developments. In addition, intramolecular H-bonding in **2** should also increase enone innate electrophilicity while favoring transition state rigidification. In this context, we envisioned that these features might counterbalance the alleged low reactivity of α-disubstituted nitronates **A** and eventually induce threshold enantioface discrimination. For the initial assessment, we commenced by studying the reaction of 1-phenyl-2-nitropropane **1A** with α′-hydroxy enone **2a** in the presence of various chiral bifunctional organobases. The reactions using 20 mol % of the popularized thiourea and squaramide-type catalysts or related ones[14,15] proceeded smoothly at room temperature in chloroform to afford adduct **3Aa**. Although enantioselectivities were marginal in these cases, these experiments proved the organocatalytic approach was indeed feasible.[16] Then, we turned our attention to urea-aminal type catalysts, which have the capability for multiple H-bonding interactions[17] (Table 1) and might facilitate better stereocontrol. The reaction with catalyst **C1** reached complete conversion after 20 h at room temperature and led to a product of 78:22 *e.r.* (entry 1). With this promising result in hand, a series of related catalysts with varying substituents at the aminal carbon (R group) and the acyl termination were evaluated next. The change from R = ^{t}Bu (**C1**) to R = ^{i}Pr (**C2**) led to a small decrease in the enantioselectivity (entry 1 vs 2). However, the configuration of the aminal carbon in the catalyst should be preserved (*S*), as changing it to (*R*), cat **C3**, decreased both the yield and the enantioselectivity (compare entries 2 and 3). Modifying the aminal *N*-acyl side chain had a substantial impact. Thus, compared with the Fmoc carbamate **C1**, *tert*-butyl carbamate **C4** resulted in inferiority, but the naphthylmethyl carbamate **C5** led to a similar 75:25 *e.r.* (entries 1 and 4 vs 5). Gratifyingly, the larger arylmethyl carbamates **C6** and **C7**, derived from 4-pyrenylmethanol and 9-anthracenylmethanol, respectively, accomplished even better results, leading to product **3Aa** in good isolated yields (70% and 74%) and about 90:10 *e.r.* (entries 6 and 7). Finally, catalysts with an additional α-amino acid residue attached, such as **C8** and **C9**, did not improve the reaction outcome (entries 8 and 9).[18]

With 20 mol % **C7** in $CHCl_3$ at rt set as the best standard conditions, the influence of the nature of the two geminal R groups on template **2** in the reaction outcome was next investigated. Initial experiments showed that increasing the size of the R alkyl groups (*n*Pr, *i*Bu) caused a decrease in selectivity (see Supporting Information Table on page S27). The screening of acceptors **2** was then expanded to other alkyl- and aryl-substituted congeners.[16] Interestingly, the aryl-substituted hydroxy enones were also competent acceptors (Table 2, entries 3, 4, and 6). The fluorinated derivatives **2c**

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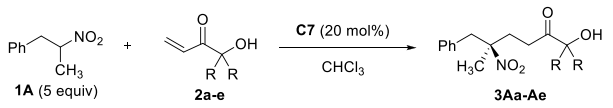
Table 2. Influence of the R Groups of Enone Template 2[a]



a R: Me; **b** R: Ph; **c** R: 3,5-$(CF_3)_2C_6H_3$ [Ar^F]; **d** R: C_6F_5; **e** R,R: $-(CH_2)_5-$

entry	R, R	T (°C)	t (h)	prod.	yield (%)[b]	e.r.[d]
1	Me	rt	14	**3Aa**	74	90:10
2	Me	0	96	**3Aa**	55[c]	91:9
3	Ph	rt	24	**3Ab**	70	84:16
4	Ar^F	rt	16	**3Ac**	72	90:10
5	Ar^F	0	93	**3Ac**	70	96:4
6	C_6F_5	rt	15	**3Ad**	64	84:16
7	C_6F_5	0	93	**3Ad**	67	91:9
8	$-(CH_2)_5-$	rt	39	**3Ae**	66	89:11

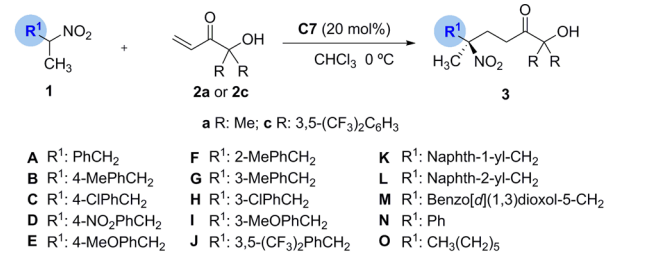
[a]Reactions run at 0.2 mmol scale in 0.6 mL of $CHCl_3$ (mol ratio **1A**/**2**/**C7** 5:1:0.2). [b]Yield for full conversion. [c]Conversion. [d]Determined by HPLC.

and **2d** were found to be more reactive than **2b**, allowing one to carry out the reaction at 0 °C (entries 5 and 7), and among them, **2c** provided the same selectivity as **2a** at room temperature (entries 1 and 4); however, at 0 °C, it afforded the highest enantioselectivity (entry 5, 96:4 *e.r.*). On the other hand, enone **2e** featuring a cyclohexyl moiety was also efficient in terms of selectivity at rt, but it was much less reactive (entry 8, 39 h reaction). From these experiments, it seems that for this reaction the 3,5-bis(trifluoromethyl)phenyl substituents exhibit the best compromise between electronic and steric effects.

Under the above optimized conditions (catalyst **C7** in $CHCl_3$ at 0 °C), the reaction scope was investigated (Table 3). Gratifyingly, various nitroethanes **1** with a *m*- or *p*-substituted phenylmethyl branch reacted with **2c** satisfactorily to afford the corresponding addition products **3Ac**−**3Ec** and **3Gc**−**3Ic** in good yields and with enantiomeric ratios ranging from the lowest 90:10 to the highest 96:4. Nitroethane **1F**, bearing an *o*-tolylmethyl substituent, and **1J**, bearing a *m*-disubstituted phenylmethyl group, led to products **3Fc** and **3Jc** with slightly eroded selectivities (89:11 and 87:13 *e.r.*). Bicyclic arylmethyl systems such as 1- and 2-naphthylmethyl nitroethanes **1K** and **1L** and guaiacol-derived nitroethane **1M** were also competent providing products **3Kc**, **3Lc**, and **3Mc** in 93:7, 95:5, and 94:6 *e.r.*, respectively. Even nitroalkane **1O**, with two simple alkyl groups at Cα, provided the product **3Oc** with an acceptable 81:19 *e.r.*, constituting a rare example of nonenzymatic enantioselective access to this kind of tertiary nitrocompound. On the other hand, the present method appears less suitable for α-aryl branched nitroalkanes, as shown in the moderate enantioselectivity (62:38 *e.r.*) with which product **3Nc** is obtained from nitroethane **1N**. Finally, obtention of products **3Ea**, **3Fa**, **3Ja**, **3Na**, and **3Oa** in decent to good enantioselectivities proved the method can be applied using the parent α'-hydroxy enone **2a**, a template easier to prepare in large quantity than **2c**.

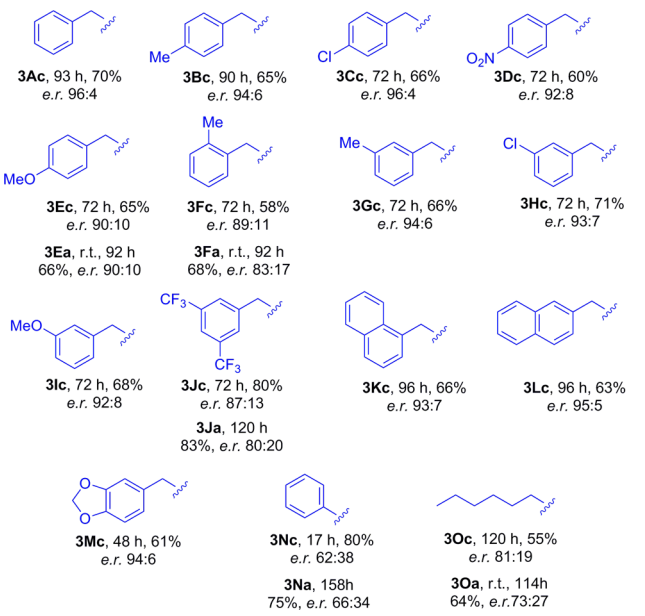
Both the nitro and the ketol groups in the thus obtained adducts could be transformed conveniently. For instance, as shown in Scheme 2, oxidation of **3Ac**, **3Cc**, **3Gc**, and **3Lc** with periodic acid afforded carboxylic acids **4** in 75−80% isolated yields. Alternatively, reduction of **3Lc** with borane and subsequent 1,2-diol oxidation afforded aldehyde **5** in a good yield. In these transformations, 3,3′,5,5′-tetrakis-

Table 3. Substrate Scope for the Reaction of 1 with 2a/c[a]



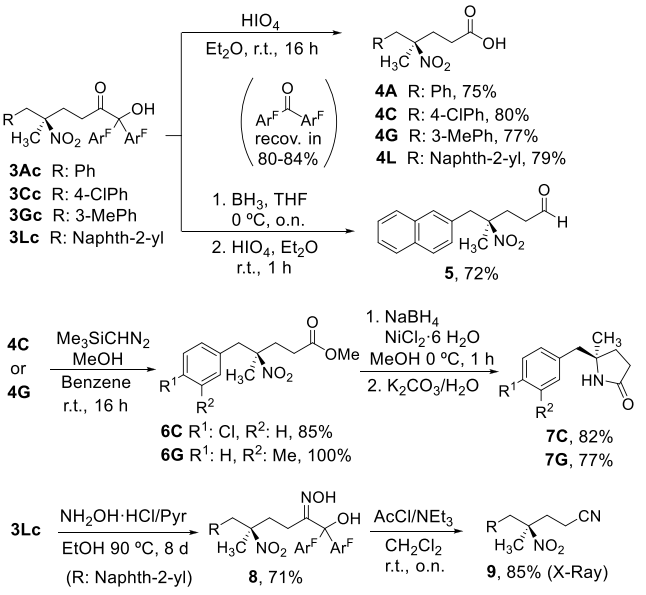
a R: Me; **c** R: 3,5-$(CF_3)_2C_6H_3$

A R^1: $PhCH_2$ **F** R^1: 2-$MePhCH_2$ **K** R^1: Naphth-1-yl-CH_2
B R^1: 4-$MePhCH_2$ **G** R^1: 3-$MePhCH_2$ **L** R^1: Naphth-2-yl-CH_2
C R^1: 4-$ClPhCH_2$ **H** R^1: 3-$ClPhCH_2$ **M** R^1: Benzo[*d*](1,3)dioxol-5-CH_2
D R^1: 4-NO_2PhCH_2 **I** R^1: 3-$MeOPhCH_2$ **N** R^1: Ph
E R^1: 4-$MeOPhCH_2$ **J** R^1: 3,5-$(CF_3)_2PhCH_2$ **O** R^1: $CH_3(CH_2)_5$



[a]Reactions run at 0.2 mmol scale in 0.6 mL of $CHCl_3$ (mol ratio **1**/**2a** or **2c**/**C7** 5:1:0.2). Yields of isolated products. *e.r.* determined by chiral HPLC.

Scheme 2. Chemical Elaboration of Adducts



(trifluoromethyl)benzophenone was obtained in 80−84% yields which could be recycled for the preparation of **2c**.[16] The γ-nitro carboxylic acids **4** could then be converted into 5,5-disubstituted γ-lactams.[19] Thus, esterification of acids **4C**

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and **4G**, ulterior reduction of the nitro group in nitro esters **6C** and **6G** with $NaBH_4/NiCl_2$, and subsequent treatment with an aqueous solution of K_2CO_3 gave the γ-lactams **7C** and **7G** in high overall yield.[20] The synthetic utility of this methodology was further illustrated with a successful two-step conversion of the ketol moiety into the corresponding nitrile. Thus, condensation of **3Lc** with hydroxylamine in hot ethanol produced oxime **8** in 71% yield. Subsequent acetylation of **8** in the presence of triethylamine was accompanied by spontaneous fragmentation giving rise to nitrile **9** in 85% isolated yield.[21] In this process, the diaryl ketone byproduct was, again, recovered in 80% yield. The absolute configuration of compound **9** was determined by single crystal X-ray analysis which served to establish that of the remaining adducts.

The superior performance of ureidoaminal-based catalysts, i.e., **C7**, as compared with (thio)urea- and squaramide-based catalysts in these reactions might be ascribed to the capacity of the former to lead to highly ordered transition states (TSs) involving at least one additional hydrogen-bonding interaction. Figure 2 shows two plausible TS structures for the key C−C

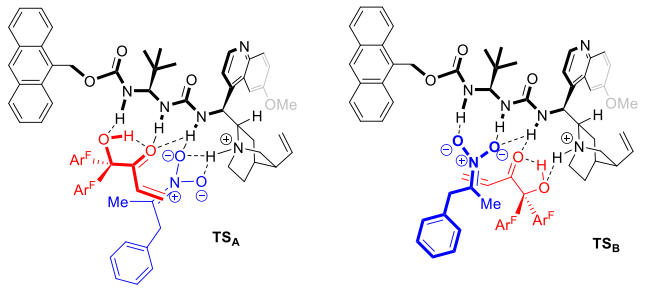

Figure 2. Plausible TS's for the key C−C bond formation.

bond forming step in which the nitronate *Re*-face approaches the enone *Si*-face in concordance with the experimentally observed main product isomer. While the simultaneous coordination of the Nuc/Elec pair of reactants to the protonated catalyst obeys the Takemoto-type geometry in TS_A, in TS_B the opposite, Pápai-type geometry would operate.[22,23] As depicted in both models, the ketol hydroxy and carbonyl groups would probably be hydrogen-bonded internally, contributing to substrate activation and TS conformational rigidification. However, the nonchelated situation with both hydroxy and carbonyl groups hydrogen-bonded to the catalyst exclusively cannot be discarded.

In summary, a new approach to enantioenriched α-tertiary nitrocompounds via unprecedented organocatalytic Michael addition of unactivated α-branched nitroalkanes is reported. The method is based on: (i) key advantages as acceptors of newly developed α'-hydroxy enones which serve as surrogates of acrylic acid/ester,[24] aldehyde, and nitrile functionalities equally and (ii) the combined use of cinchona alkaloid-derived ureidoaminal catalysts. This methodology provides alternative routes to access relevant compound families in optically active form, inter alia 5,5-disubstituted γ-lactams bearing a quaternary stereocenter, whose enantioselective synthesis is still a challenge.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03340.

Experimental procedures, spectroscopic data of products, ^1H NMR and ^{13}C NMR spectra, HPLC charts, and crystallographic data (PDF)

Accession Codes

CCDC 2300164 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Mikel Oiarbide − *Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU, 20018 San Sebastián, Spain;* orcid.org/0000-0003-0362-0136; Email: mikel.oiarbide@ehu.eus

Antonia Mielgo − *Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU, 20018 San Sebastián, Spain;* orcid.org/0000-0001-8197-017X; Email: antonia.mielgo@ehu.eus

Jesús M. García − *Departamento de Ciencias, Institute for Advanced Materials and Mathematics (InaMat²), Universidad Pública de Navarra (UPNA), 31006 Pamplona, Spain;* orcid.org/0000-0001-6632-097X; Email: jmgdqaso@unavarra.es

Claudio Palomo − *Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU, 20018 San Sebastián, Spain;* orcid.org/0000-0001-9809-2799; Email: claudio.palomo@ehu.eus

Authors

Beñat Lorea − *Departamento de Ciencias, Institute for Advanced Materials and Mathematics (InaMat²), Universidad Pública de Navarra (UPNA), 31006 Pamplona, Spain*

Ane García-Urricelqui − *Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU, 20018 San Sebastián, Spain*

José M. Odriozola − *Departamento de Ciencias, Institute for Advanced Materials and Mathematics (InaMat²), Universidad Pública de Navarra (UPNA), 31006 Pamplona, Spain*

Jesús Razkin − *Departamento de Ciencias, Institute for Advanced Materials and Mathematics (InaMat²), Universidad Pública de Navarra (UPNA), 31006 Pamplona, Spain*

Maialen Espinal-Viguri − *Departamento de Ciencias, Institute for Advanced Materials and Mathematics (InaMat²), Universidad Pública de Navarra (UPNA), 31006 Pamplona, Spain*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c03340

Notes

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