Chiral Trifluoromethylated Enamides: Synthesis and Applicability

Alexandru Postole,[a] Pablo Martínez-Pardo, [a] Víctor García-Vázquez, [a] and Belén Martín-Matute [a]*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden.

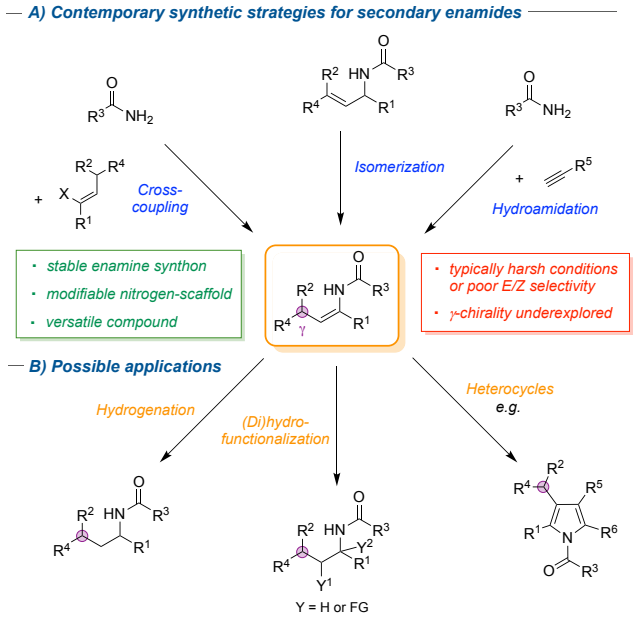
Supporting Information Placeholder

ABSTRACT: Enamides are valuable building blocks in organic synthesis that give access to complex nitrogen-containing compounds. However, despite their high interest, synthetic strategies to access enamides with carbon-centered chirality are scarce. Herein, we report a mild and robust synthetic method towards novel γ–chiral, trifluoromethylated enamides from easily accessible α–chiral allylic amines through efficient chirality transfer (up to 99.5%) with excellent yields, diastereo- and enantioselectivities. A broad and diverse scope is presented that tolerates various substituents and functional groups. Additionally, multiple organic transformations were performed to access new chiral complex scaffolds. Among them, a novel protocol for the *E/Z* isomerization of enamides is presented.

Enamides are stable and masked enamine surrogates, which are of utmost interest in synthetic organic chemistry.[1] The ambiphilic character of the double bond allows for manifold synthetic transformations, while simultaneously being tempered/protected by the electron-withdrawing functionality upon the nitrogen center.[2,3] The unique structural properties of this potent functional group offers a balanced compromise between stability and reactivity.[4] As a result, a growing interest in its reactivity has been sparked over the last years to exploit its potential in various organic transformations. Besides being important pharmacophores in natural products and active drugs with various anticancer, antifungal and cytotoxic properties,[5–8] enamides have recently emerged as versatile building blocks in a direct entry to complex nitrogen-containing molecules.[9–13] Apart from asymmetric hydrogenation as a well-studied and powerful approach to yield chiral amines and amino acids,[14] recent reports include hydrofunctionalization[15–18] and difunctionalization[19–22] of the double bond, C–H activation,[23–26] asymmetric C–C bond formation,[27,28] [4+2] and [2+2] cycloadditions,[29,30] rearrangements[31,32] and synthesis of heterocycles (Scheme 1B).[33–36] As a result, new methodologies to obtain these versatile compounds, especially with unprecedented derivatization patterns, are highly desirable.

Classical approaches for the synthesis of enamides include acid-catalyzed condensation of ketones/aldehydes and amides,[37,38] Curtius rearrangement of α,β-unsaturated acyl azides,[39] Peterson olefination[40] and Horner-Wadsworth-Emmons reactions.[41]

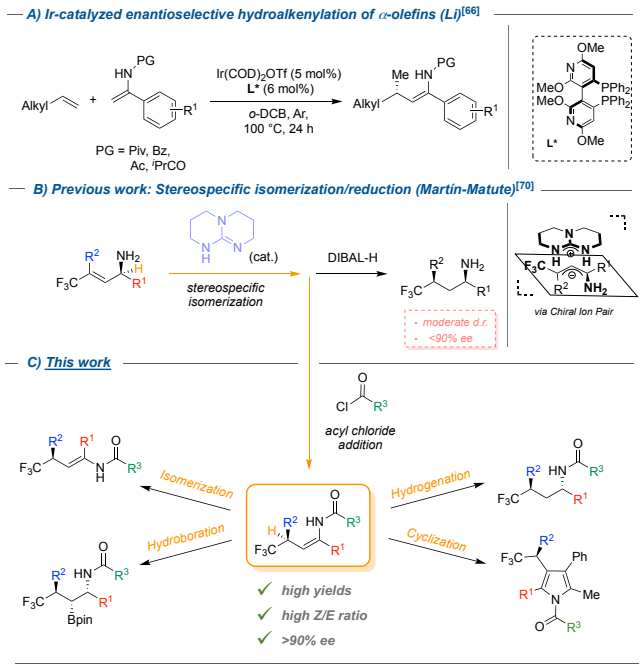
Scheme 1. A) Modern Synthetic Methodologies for Secondary Enamides and B) Examples of Possible Organic Transformations



However, these methods typically suffer from harsh conditions, low yields and are unable to control the *E/Z* olefin stereoselectivity. The most commonly employed method is the metal-catalyzed cross-coupling between an amide and alkenyl halide or triflate.[5,6,42–46] Other important transition metal-catalyzed strategies encompass the hydroamidation of terminal alkynes with primary amides[47–49] and the isomerization of *N*-allyl amides (Scheme 1A).[50–53] Therein, Trost and co-workers reported a highly efficient Ru-catalyzed isomerization to obtain geometrically defined and highly substituted enamides.[54] Recently, the groups of Maulide, Jiao and Xu presented a more direct approach by *N*-dehydrogenation of amides, which either requires strong oxidative conditions or superstoichiometric amounts of reagents and is limited to tertiary enamides.[55–57] Currently, synthetic strategies to access enamides with a stereogenic center, especially at the more challenging Cγ-position, are scarce and the field is underexplored. Nevertheless, such compounds seem to be of interest as demonstrated by recent examples for the syntheses of axially chiral enamides.[58–60] Additionally, the construction of CF_3-substituted chiral sp^3-carbon centers remains a difficult synthetic task despite the high potential of fluorinated motifs in medicinal chemistry.[61,62] Thus, efficient asymmetric methodologies to access such

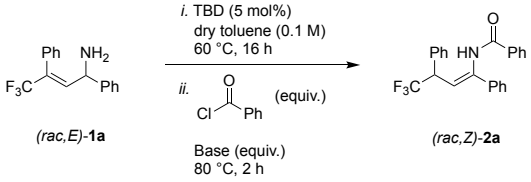
moieties, particularly without the usage of oxidative/corrosive trifluoromethyl sources (Togni, Umemoto reagents, etc.), are still underdeveloped.[63–65] There is only one example for the synthesis of γ-chiral enamides, described by the group of Li through an elegant Ir-catalyzed hydroalkenylation strategy of unactivated α-olefins promoted by a chiral ligand (Scheme 2A).[66] This method involves pre-protected substrates and the scope is limited to aliphatic alkenes. According to our previous interest,[67–69] we recently developed a one-pot stereoselective isomerization method of α-chiral allylic amines catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a simple organocatalyst followed by a diastereoselective reduction of the imine-tautomer with DIBAL-H to obtain α,γ-chiral aliphatic amines (Scheme 2B).[70]

Scheme 2. Enantioselective Strategies for the Synthesis of γ–Chiral Enamides



In the first key step, the chirality of the α-chiral allylic amine is transferred from Cα- to Cγ-position by the TBD organocatalyst in a stepwise manner, through the formation of a tight-ion-pair intermediate with induced non-covalent chirality. A mixture of imine and enamine intermediates were formed, which upon reduction afforded α,γ-chiral trifluoromethylated amines, however only moderate diastereoselectivity was obtained. Herein, we report the selective trapping the enamine-tautomer after the stereospecific isomerization through subsequent acid chloride addition in a one-pot two steps procedure to synthesize γ-chiral, trifluoromethylated secondary enamides, which can be further transformed into various chiral complex scaffolds (Scheme 2C).

Table 1. Optimization of the One–Pot Synthesis of *(rac,Z)*–2a.[a]



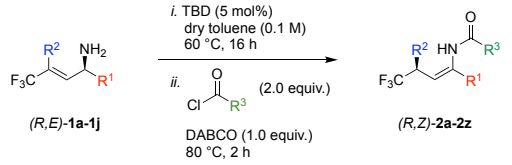
Entry	Base (equiv.)	BzCl (equiv.)	Yield [%][b]
1	Et_3N (2.2)	1.0	65
2	Et_3N (2.2)	2.0	79
3	Et_3N (2.2)	2.5	78
4	Et_3N (2.8)	2.0	83
5	Et_3N (2.8)	2.0	46[c]
6	DMAP (1.0)	2.0	31
7	TBD (1.0)	2.0	30
8	DABCO (1.0)	2.0	>95
9	DABCO (0.5)	2.0	64

[a] Reaction conditions: *(rac,E)*-**1a** (0.15 mmol). [b] Yields determined by ^{1}H-NMR integration relative to 1,3,5-trimethoxybenzene (TMB) as internal standard. [c] At 20 °C. [d] Reaction time of 1 h.

As the optimal conditions for the stereospecific isomerization of α-chiral allylic amines have been previously established,[70] we started our investigation by optimizing the parameters for the one-pot two steps synthesis of the γ-chiral enamides by adding BzCl and Et_3N after the isomerization. Firstly, the amount of BzCl was examined and we observed that 2.0 equiv. of BzCl were necessary to obtain the desired product in high yields (Table 1, entry 1-3). Then, we optimized the equivalents of Et_3N (Table 1, entry 4). Lowering the temperature to 20 °C had drastic effect on the yield of the reaction (Table 1, entry 5). Further evaluation of other organic bases demonstrated that DABCO was the most efficient base for this step (Table 1, entry 6-8). Attempts to lower the amount of DABCO only led to a decreased in yield (Table 1, entry 9).

Next, we studied the scope of this two-step one-pot protocol towards γ-chiral enamides (Scheme 3). Firstly, the reaction could be successfully scaled up to 5 mmol (1.4 g) scale with the model substrate (**2a**), providing high yields and enantiomeric excess with excellent control over the *E/Z* stereoselectivity and transfer of the chirality (99.5%). The opposite enantiomer ((***S***)-**2a**) could also be successfully synthesized. Various substituents at the R^1-position on the α-chiral allylic amine (Cα) could be tolerated including trifluoromethyl- (**2b**), bromide- (**2c**) and *m*-methoxy-groups (**2d**). The bulky naphthyl-substituent (**2e**)

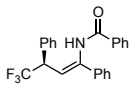
Scheme 3. Scope of α–Chiral Allylic Amines and Acyl Chlorides



(*R,E*)-**1a-1j** → (*R,Z*)-**2a-2z**

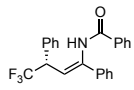
*R*¹ - Allylic amines

gram scale

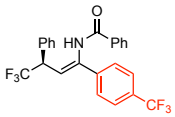


2a, 86%,[a] 94% *ee*
Z/E = 98:2
99.5% *c.t.*
(from **1a**: 94% *ee*, *E/Z* = 99.5:0.5)

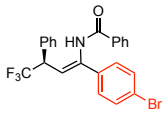
(*S*)-enantiomer



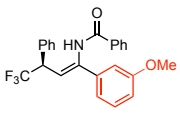
(***S***)-**2a**, 81%, 87% *ee*
Z/E = 91:9
95% *c.t.*
(from (***S***)-**1a**: 92% *ee*, *E/Z* = 98:2)



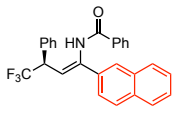
2b, 82%, 95% *ee*
Z/E = 96:4
97% *c.t.*
(from **1b**: 98% *ee*, *E/Z* = 99:1)



2c, 79%, 90% *ee*
Z/E = 96:4
95% *c.t.*
(from **1c**: 95% *ee*, *E/Z* = 99:1)

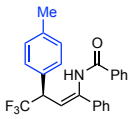


2d, 81%, 91% *ee*
Z/E = 93:7
95% *c.t.*
(from **1d**: 96% *ee*, *E/Z* = 98:2)

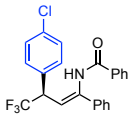


2e, 78%, 96% *ee*
Z/E = 99.5:0.5
99% *c.t.*
(from **1e**: 97% *ee*, *E/Z* = 99.5:0.5)

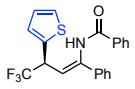
*R*² - Allylic amines



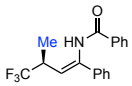
2f, 85%, 86% *ee*
Z/E = 94:6
94% *c.t.*
(from **1f**: 92% *ee*, *E/Z* = 97:3)



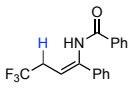
2g, 79%, 88% *ee*
Z/E = 95:5
95% *c.t.*
(from **1g**: 93% *ee*, *E/Z* = 99:1)



2h, 62%, 92% *ee*
Z/E = 92:8
98% *c.t.*
(from **1h**: 93% *ee*, *Z/E* = 100:0)



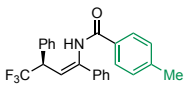
2i, 41%,[b] 74% *ee*
Z/E = 77:23
91% *c.t.*
(from **1i**: 81% *ee*, *E/Z* = 87:13)



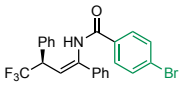
2j, 64%, *Z/E* = 90:10
(from **1j**: *E/Z* = 91:9)

*R*³ - Acyl chlorides

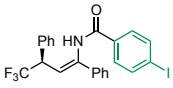
from **1a**: 94% *ee*, *E/Z* = 99.5:0.5



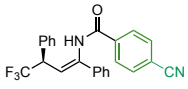
2k, 84%, 92% *ee*
Z/E = 98:2
98% *c.t.*



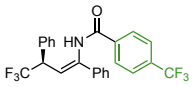
2l, 83%, 92% *ee*
Z/E = 93:7
98% *c.t.*



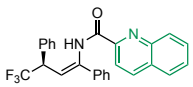
2m, 69%, 92% *ee*
Z/E = 95:5
98% *c.t.*



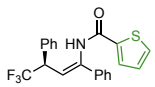
2n, 92%, 92% *ee*
Z/E = 96:4
98% *c.t.*



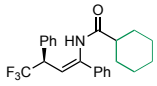
2o, 93%, 93% *ee*
Z/E = 98:2
99% *c.t.*



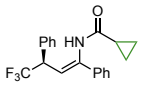
2p, 70%, 92% *ee*
Z/E = 98:2
98% *c.t.*



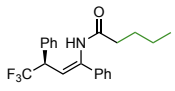
2q, 83%, 92% *ee*
Z/E = 98:2
98% *c.t.*



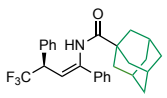
2r, 69%, 92% *ee*
Z/E = 83:17
98% *c.t.*



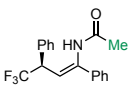
2s, 83%, 92% *ee*
Z/E = 89:11
98% *c.t.*



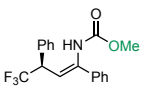
2t, 69%, 92% *ee*
Z/E = 95:5
98% *c.t.*



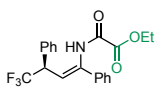
2u, 45%, 92% *ee*
Z/E = 81:19
98% *c.t.*



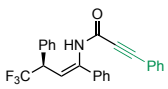
2v, 82%, 91% *ee*
Z/E = 81:19
97% *c.t.*



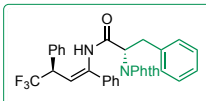
2w, 68%, 91% *ee*
Z/E = 89:11
97% *c.t.*



2x, 77%, 93% *ee*
Z/E = 89:11
99% *c.t.*



2y, 52%, 93% *ee*
Z/E = 86:14
99% *c.t.*



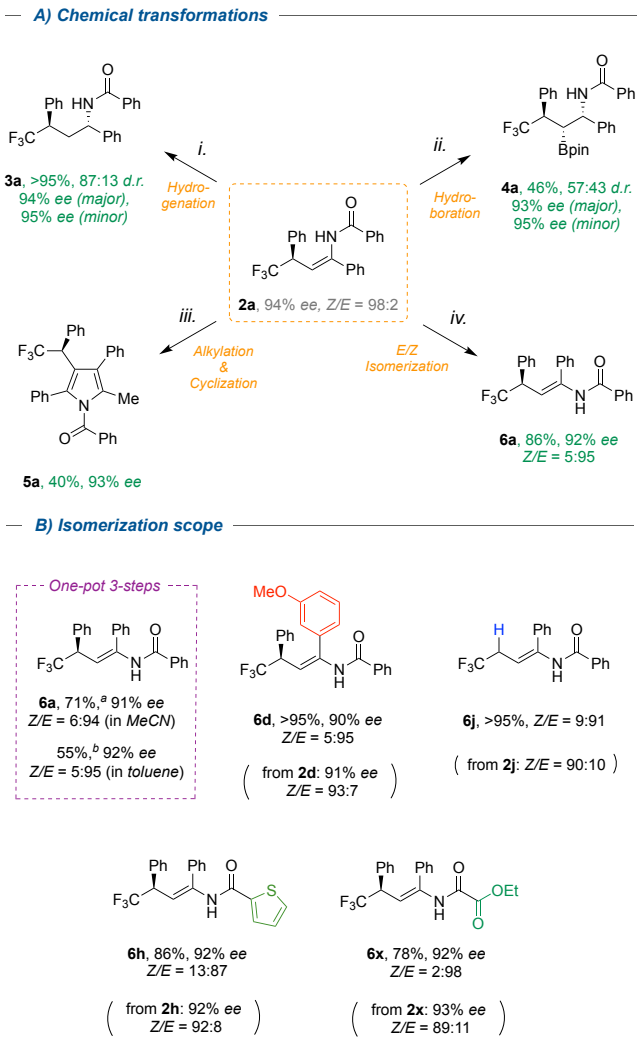
2z, 89%, 92% *ee*
61:39 *d.r.*
98% *c.t.*
from *L*-Phenylalanin

Reaction conditions: *i. (R,E)*-**1a-1y** (0.25 mmol, 1 equiv.), TBD (0.013 mmol, 0.05 equiv.), dry toluene (2.5 mL, 0.1 M), 60 °C, 16 h. *ii.* Acyl chloride (0.5 mmol, 2.0 equiv.), DABCO (0.25 mmol, 1.0 equiv.), 80 °C, 2 h. Isolated yields are reported. *E/Z* ratio determined by ^{19}F NMR spectroscopy before purification. Chirality transfer (*c.t.*): ($ee_{product}/ee_{SM}$) x 100%. [a] Reaction performed on a 5.0 mmol (1.4 g) scale. [b] Isomerization at 100 °C.

afforded the desired compound with excellent stereoselectivity. Furthermore, the R^2-position of the α-chiral allylic amine (Cγ) was also varied by employing different substituents on the aryl group such as *p*-methyl (**2f**), *p*-chloride (**2g**), and even a thiophene heterocycle (**2h**) with good compatibility. The methyl-substituent (**2i**) proved to be more challenging probably due to increasing flexibility, and only moderate yields, *Z/E* ratios and *ee* was obtained. The achiral allylic amine **2j** was also successful. Limitations were highly electron-donating substituents such as *p*- and *o*-methoxy-substituents on the aryl at the R^1-position, and an electron-withdrawing *p*-trifluoromethyl-group at the R^2-position (see Supplementary Information). The R^3-position on the acyl chloride could also be varied with a diverse class of moieties. An electron-donating *p*-methyl- (**2k**), *p*-halides (**2l**, **2m**) and electron-withdrawing-groups (**2n**, **2o**) were all tolerated. Similarly, heterocycles such as quinoline (**2p**) and thiophene (**2q**) delivered the enamides in high yields, high enantiomeric excesses and *E/Z* ratio. Saturated cyclic (**2r**, **2s**) and acyclic (**2t**) side-chains were also compatible as well as a bulky adamantyl-group (**2u**), albeit with lower yield and decrease in *E/Z* ratio. Comparably, methyl- (**2v**) and methoxy-groups (**2w**) led to slight *E/Z* isomerization, but with good yields and enantiomeric excess. Furthermore, an ester- (**2x**) and alkyne-functional group (**2y**) was also tolerated. Interestingly, the acyl chloride of the natural amino acid *L*-Phenylalanin (**2z**) could be subjected to the reaction with excellent yields and enantiomeric excess, albeit with lower diastereoselectivity. Control reactions show that this originates from a racemization of the α-carbon stereocenter caused by deprotonation by DABCO. Some limitations include highly electron-donating group as in *p*-methoxy, cyclic amide, alkene and indole (see Supplementary Information).

To demonstrate the synthetic utility of our method, some organic transformations to access unprecedented scaffolds were carried out (Scheme 4A). For example, the model enamide **2a** was hydrogenated under simple Pd/C conditions at atmospheric pressure to obtain quantitative yields of **3a** with high diastereoselectivity. Importantly, this method provides the *anti*-diastereomer predominantly, in contrast with our previous approach.[70] Additionally, a Rh-catalyzed hydroboration protocol by Li and co-workers[71] with an achiral ligand can be applied to arrive to a boron-containing compound **4a** with three contiguous stereocenters. The pinacolborane moiety would provide another opportunity for other potential transformations. Next, alkylation to the respective tertiary enamide followed by a Au-catalyzed cyclization step, according to the conditions by Xu and co-workers,[72] furnished a pentasubstituted chiral pyrrole **5a** in 40% yield over two steps. With these results in hand, we wondered if it would be possible to invert the *E/Z* geometry of the double bond

Scheme 4. Chemical Transformations of γ–Chiral Enamides and Isomerization Scope



Reaction conditions: *i. Hydrogenation:* Pd/C (1 mol% Pd), 1 atm H_2, THF, 20 °C, 1.5 h; *ii. Hydroboration:* Rh(COD)SbF_6 (3.0 mol%), D*i*PrPF (3.6 mol%), HBpin (2.0 equiv.), dry THF, 30 °C, 16 h, N_2; *iii. Alkylation & Cyclization:* 3-Bromo-1-phenylpropyne (1.1 equiv.), NaH (1.2 equiv.), dry DMF, 0–20°C, 16 h, *then* [(JohnPhos)-AuCl] (5.0 mol%), HFIP, 20 °C, 16 h; *iv. Isomerization:* Ir[dF(CF_3)ppy]$_2$(dtbpy)PF_6 (1.0 mol%), white LEDs, dry MeCN, 60 °C, 16 h; [a] Reaction in dry MeCN after prior solvent evaporation. [b] Reaction in dry toluene without solvent evaporation.

to gain access to the opposite diastereoisomer. The only example for a general *E/Z* isomerization protocol of enamides has been reported by Gooßen and co-workers through addition of Et_3N at elevated temperatures to yield the thermodynamically favoured stereoisomer.[49] However, this approach did not yield any noticeable *E/Z* isomerization for our system. Correspondingly, we established a novel protocol for the *E/Z* photoisomerization of

enamides in the presence of an Ir-photocatalyst and white LED. Under these conditions, it is possible to carry out an isomerization of the double bond to obtain the opposite diastereoisomer **6a** with excellent inversion of the *E/Z* geometry. Control experiments prove that this reaction is indeed photocatalytic as both the photocatalyst and light are necessary. The *E/Z* isomerization could also be carried out in a one-pot three steps procedure starting directly from the α-chiral allylic amine **1a** with or without prior evaporation of the solvent (Scheme 4B). Furthermore, a small scope was synthesized with diverse substituents and functional groups in different positions. In all cases, excellent inversion of the *E/Z* geometry alongside with high yields were obtained. Limitations were discovered to be **2s** and **2y** (see Supplementary Information). Importantly, the previously introduced γ–chiral stereocenter is unaffected in all transformations.

In conclusion, an efficient method for the synthesis of novel chiral enamides scaffolds with a γ-stereogenic trifluoromethyl-group has been established in high yields, outstanding enantiomeric excesses and excellent control of the *E/Z* geometry. Furthermore, this method tolerates a wide variety of electronic substituents and functional groups as demonstrated by the broad and diverse scope. This method is also applicable on a gram-scale and access to both enantiomers is possible. Additionally, a wide variety of new chiral, complex scaffolds were synthesized and a novel protocol for the *E/Z* isomerization of enamides has been established.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, optimization of the reaction, characterization data of new compounds, separation of chiral products, and NMR spectra of new compounds (PDF).

AUTHOR INFORMATION

Corresponding Author

Belén Matín-Matute – ***Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;*** **orcid.org/0000-0002-7898-317X; Email: belen.martin.matute@su.se**

Authors

Alexandru Postole – ***Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;*** **orcid.org/0000-0002-8358-6961**

Pablo Martínez-Pardo – ***Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;*** **orcid.org/0000-0003-4819-0854**

Víctor García-Vázquez – ***Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden;*** **orcid.org/0000-0001-6123-8731**

Notes

The authors declare no competing financial interest.

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