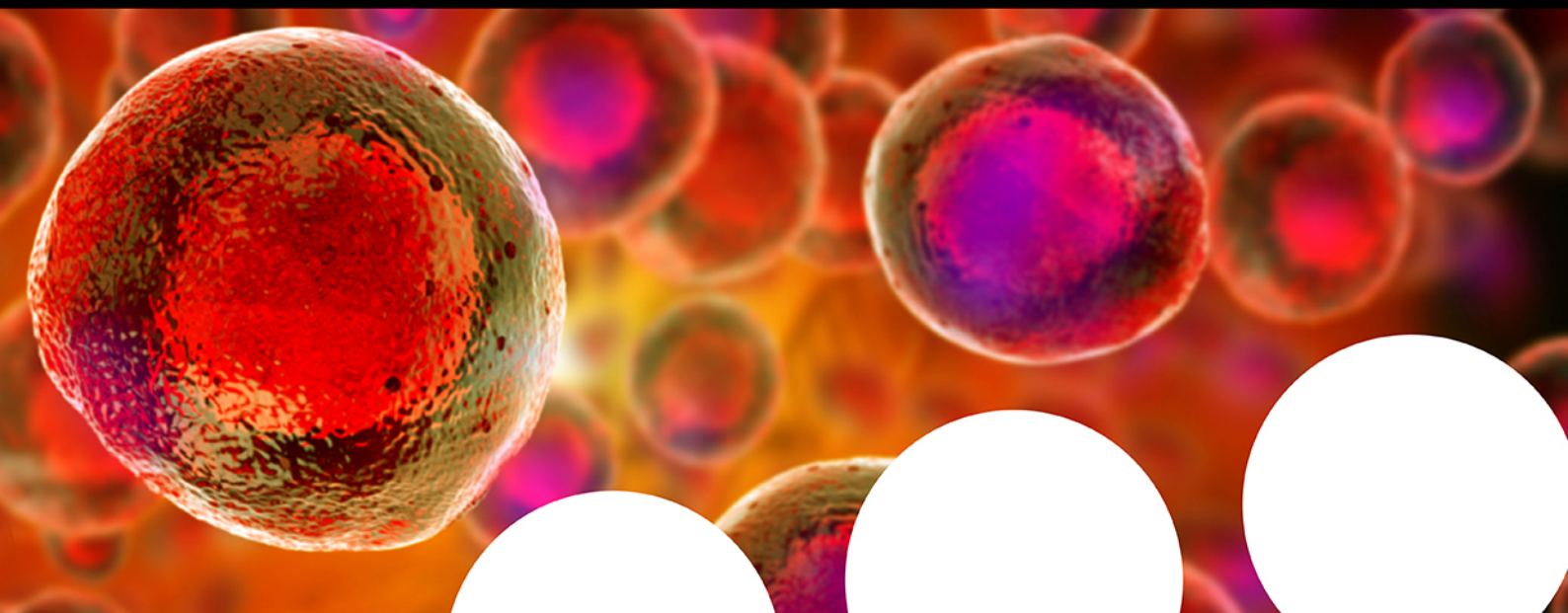


Your research is important and needs to be shared with the world



Benefit from the Chemistry Europe Open Access Advantage

- Articles published open access have higher readership
- Articles are cited more often than comparable subscription-based articles
- All articles freely available to read, download and share.

Submit your paper today.



www.chemistry-europe.org

Nickel-Catalyzed Cascade Cyclization-Negishi Coupling of Redox Active Esters for the Synthesis of Pyrrolidines

Juan Carlos Nieto-Carmona,^[a] Raúl San Román,^[a] Elena Buñuel,^[a] and Diego J. Cárdenas^{*[a]}

We have developed a Ni-catalyzed cascade cyclization/Negishi-coupling reaction for the formation of pyrrolidines and pyrrolidinones starting from *N*-protected allylamines and acrylamides which contain a redox active ester group. The reaction provides two C–C bonds in a single operation and takes place

with both alkylzinc and arylzinc bromides as nucleophiles. Activation of RAE by low valent Ni complexes involving a radical pathway followed by a fast cyclization of intermediate carbon radicals is proposed.

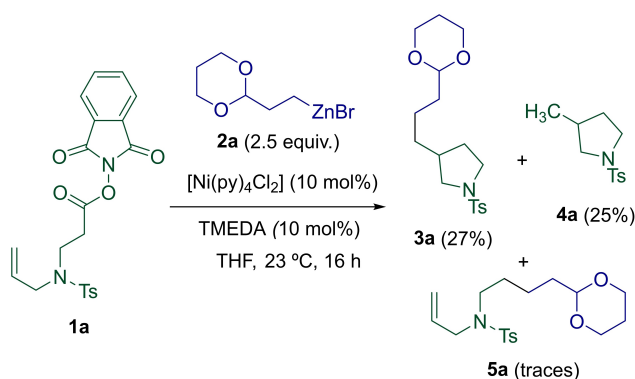
Introduction

The current developments of synthetically useful metal-catalyzed cross-coupling reactions are mainly related to first-row transition metal catalysis, especially with Ni derivatives,^[1] and the use of more convenient electrophiles compared the usual halides and pseudohalides.^[2] Regarding this point, carboxylic acid derivatives have become important substrates for the availability of the precursors and the occurrence of novel activation pathways, which allow different processes.^[3] Although the use of Pd in radical processes is being explored during the last years,^[4] the ability of Ni catalysts to activate electrophiles by radical pathways perfectly matches the reactivity of redox-active esters (RAEs) for their use in cross-coupling reactions involving alkyl radical intermediates.^[5] The novel activation pathways have allowed the development of methods for the formation of alkyl-alkyl bonds avoiding the problems associated to β -hydrogen elimination and the relatively difficult alkyl-alkyl reductive elimination. Some years ago, we developed novel methodology for the construction of two C(sp³)-C(sp³) bonds by a Ni-catalyzed cascade cyclization-coupling reaction.^[6] Both alkylzinc halides and alkyl Grignard reagents can be used as nucleophiles to give functionalized cyclic compounds following a non-trivial retrosynthetic disconnection. These reactions involve a radical mechanism initiated by Ni(I) catalytically active species formed upon reduction of the Ni(II) precatalyst with the organometallic reagent. We reasoned that the iodides previously used could be substituted by redox-

active esters, which have been successfully used in simple Ni-catalyzed cross-coupling reactions,^[7] and to take advantage of the presence of an alkene to realize a cyclization, prior to the coupling, which would allow the formation of two C–C bonds in a single operation. As we will see below, readily accessible β -alanine derivatives were convenient substrates for this transformation.

Results and Discussion

We first studied the Ni-catalyzed reaction of allylsulfonylamide **1a**, which contains a *N*-(acyloxy)phthalimide group, with alkylzinc bromide **2a** in the presence of Ni(py)₄Cl₂ and TMEDA (Scheme 1). The desired compound **3a** was obtained in 27% yield along with reduced cyclization derivative **4a** (25%) and traces of cross-coupling product **5a**. Optimization of the reaction conditions to obtain higher yields and selectivity started by screening different kinds of ligands instead of TMEDA (in the absence of added ligands yields were 24% for **3a** and 25% for **4a**). Thus, phenanthroline, bipyridine, di-Bu-(bipyridine), terpy, imidazolylpyridine, IMes, PCy₃, dppe, and xantphos did not allow to obtain the desired product over 30% yield (see Supporting Information for details). In contrast, pybox ligands afforded higher yields, providing (*S*)-sec-Bu(pybox) the



Scheme 1. Initial experiment with model substrate.

[a] J. C. Nieto-Carmona, R. San Román, E. Buñuel, D. J. Cárdenas
Department of Organic Chemistry, Facultad de Ciencias,
Universidad Autónoma de Madrid,
Institute for Advanced Research in Chemical Sciences (IAChem),
Avd. Francisco Tomás y Valiente 7, Campus de Cantoblanco, 28049, Madrid,
Spain
E-mail: diego.cardenas@uam.es

Supporting information for this article is available on the WWW under
<https://doi.org/10.1002/ejoc.202200992>

© 2022 The Authors. European Journal of Organic Chemistry published by
Wiley-VCH GmbH. This is an open access article under the terms of the
Creative Commons Attribution Non-Commercial NoDerivs License, which
permits use and distribution in any medium, provided the original work is
properly cited, the use is non-commercial and no modifications or adap-
tations are made.

best results in both yield and selectivity: 56% for **3a** and 19% for **4a**. Regarding the solvent, THF, toluene and xylene afforded similar results and were better than ethyl ether, acetonitrile, DME, dioxane and 1,2-dichloroethane. Coordinating solvents such as DMA, NMP, DMPU and DMSO provided low conversions. Other precatalysts such as NiCl_2 , $\text{Ni}(\text{acac})_2$, and $\text{Ni}(\text{cod})_2$ gave poorer results. Since cyclization may be competing with intermolecular reactions, we analyzed the effect of the substrate concentration on the reaction yield. No significant differences were observed between 0.013 and 0.1 M, and 0.05 M was chosen for subsequent study of the reaction scope. Reaction at 0°C afforded the same yield, but it decreased at 50°C (43%). The use of lower (1.5 or 2 equiv) or higher (3 equiv) amount of the organozinc reagent led to lower yields. Finally, different kinds of RAE derivatives were submitted to the optimized conditions. Results are shown in Table 1.

The best results were obtained with the phthalimido derivative, and therefore this kind of substrates was used for the study of the reaction scope. Unexpected formation of ester **6a** in low yields was observed for substrates **1b** and **1c**, probably by transesterification with Zn alkoxide. Scheme 2 summarizes the results obtained for a variety of substrates and organozinc reagents under the optimized reaction conditions.

Two different alkylzinc nucleophiles were reacted with substrates containing three kinds of *N*-protecting groups. When alkylzinc bromides were used as coupling partners (Scheme 2a) yields were moderate, but it is important to mention that two C–C bonds are formed in a single operation. Moreover, this method constitutes an interesting approach for the synthesis of 3-alkylpyrrolidines involving an unusual retrosynthetic disconnection and starting from carboxylic acids (Scheme 3). A related Ni-catalyzed dicarbofunctionalization for the preparation of

pyrrolidines, among other derivatives, has been recently reported.^[8]

Cyclization-reduction or simple coupling by-products were isolated in some cases in low yields (compounds **4** and **5**). The reaction was extended to arylzinc bromides providing the desired products in higher yields compared to the reactions with alkylzinc derivatives (Scheme 2b, **3 g–r**). Yields were higher with withdrawing cyano group compared to electron donating ones (OMe, Me). Reduction products were not detected in these cases, which suggests that the coupling process is faster with these nucleophiles. Anyhow, cyclization takes place before coupling and traces of simple cross-coupling non-cyclized derivatives were detected in only a few cases (**5 o–q**). In addition to the allyl derivatives, alkenylamides substituted with RAE moieties (**7–9**) were also suitable substrates and afforded the corresponding pyrrolidinones (**3 s–w**, Scheme 2b, bottom). The reaction of methyl-substituted compound **9** proceeded with high diastereoselectivity, whereas isomeric amide **8** afforded a mixture of diastereoisomers (6:4). We tried to extend the reaction for the formation of tetrahydrofurans and tetrahydrothiophenes. However, substrates similar to **1 a** in which the N tethering group was replaced with O or S afforded complex reaction mixtures. Other ineffective substrates can be found in the Supporting Information. This reaction faces several potential difficulties illustrated by the isolation or detection of different by-products. Thus, the formation of simple coupling compounds was observed in some cases which suggests that cyclization may not be as fast as necessary for the desired process to take place (compounds **6**, Scheme 2 and Table 1). The cyclized radical is often partially reduced to compounds **4**, probably by H abstraction from the solvent or even from the substrates (which would explain the moderate yields). In fact, when the reaction of **1 a** with *p*-cyanophenylzinc bromide was run in *d*₈-THF the reduction by-product **4 a** was hardly deuterated (*ca.* 6% deuteration, see Supporting Information). When the reaction of **1 a** was performed in the presence of 1.5 equiv. of BHT, the reaction yield was not affected, although the reaction was slower.^[9] This suggests a fast evolution and coordination of radicals to Ni. Instead, addition of 1.5 equiv of TEMPO had an effect and led to different results depending on the organozinc reagent which was reacted with **1 a** (Scheme 4). Thus, the use of *p*-cyanophenylzinc bromide (**2 f**) afforded a very low yield of the cyclization-coupling derivative **3 j** (8%, Scheme 4a). In contrast, the formal coupling product of TEMPO with the radical derived from **2 a** was obtained in 29% yield when using this alkylzinc reagent, and the desired product was not detected (Scheme 4b). These results point to the deactivation of the Ni catalyst by TEMPO.

The above-mentioned results shed some light into a possible reaction pathway. A proposal is shown in Scheme 5.

Thus, we propose the formation of catalytically active Ni(I) complex **A** (Scheme 4) by reduction of the Ni(II) precatalyst to Ni(0) followed by comproportionation with Ni(II). We have recently proposed the intimate mechanism for this process.^[10] Ni(I) is stabilized by the terdentate redox active pybox ligand, and it can activate the redox active ester in a single-electron transfer to form Ni(II) complex **B** and radical anion **C**. Homolytic

Table 1. Reaction yields (%) for different RAEs.

Reaction Scheme:

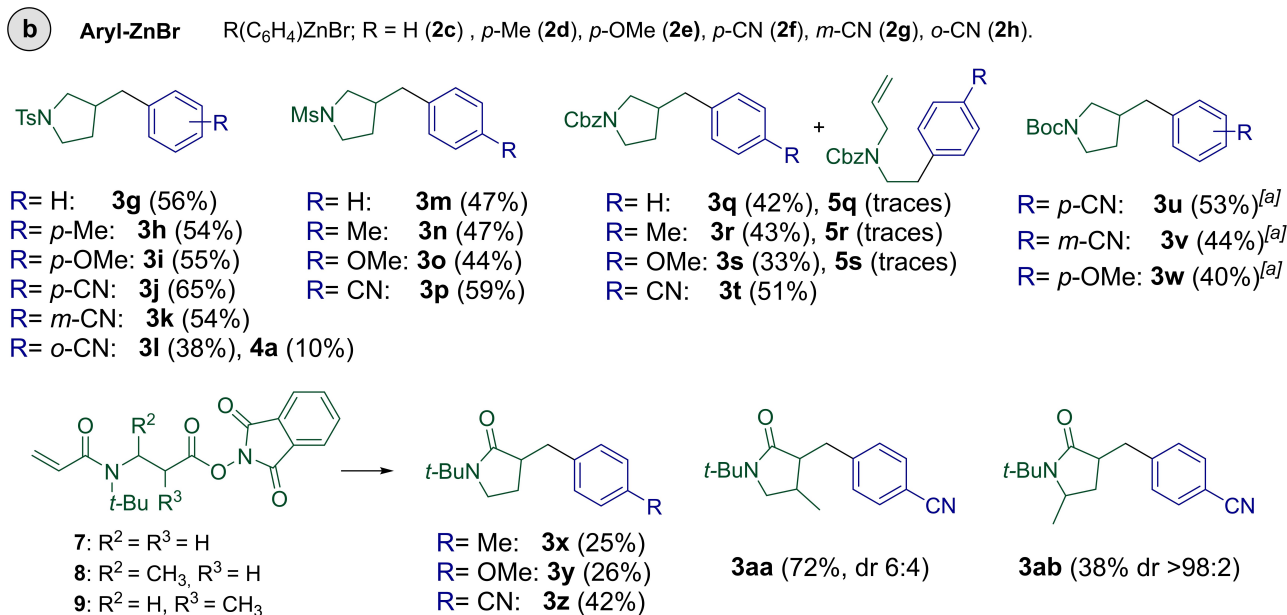
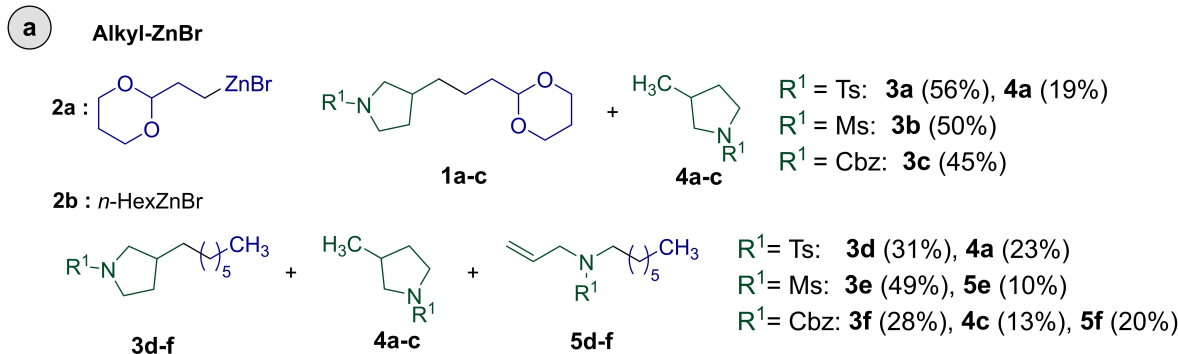
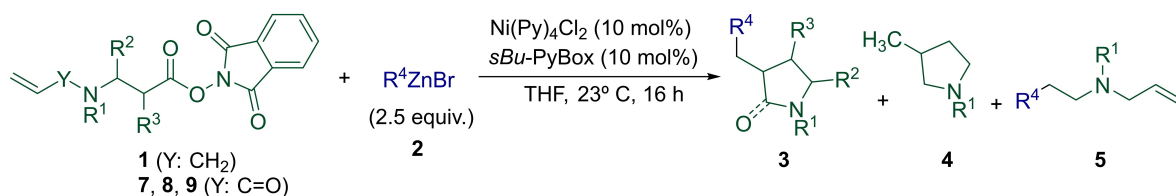
Substrate **1a-e** reacts with reagent **2a** (2.5 equiv.) in the presence of $\text{Ni}(\text{Py})_4\text{Cl}_2$ (10 mol%) and *s*Bu-PyBox (10 mol%) in THF at 23 °C for 16 h.

The reaction yields two products: **3a** (the major product) and **6a**.

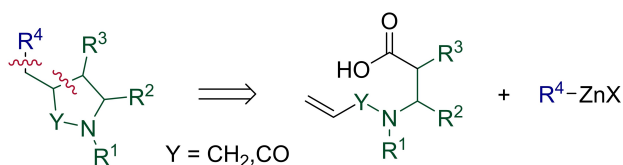
Structure Legend:

- 1a**: R = 1-phenylisoindolin-1-one
- 1b**: R = 1-(pyridin-2-yl)isothiazolidine-4-one
- 1c**: R = 1-pyrrolidinone
- 1d**: R = 1-(2,3,4,5-tetrachlorophenyl)isoindolin-1-one
- 1e**: R = 1-(1H-benzotriazol-1-yl)isoindolin-1-one

Entry	Substrate	3 a	4 a	6 a
1	1 a	56	19	-
2	1 b	-	-	21
3	1 c	-	-	9
4	1 d	31	26	-
5	1 e	16	8	-



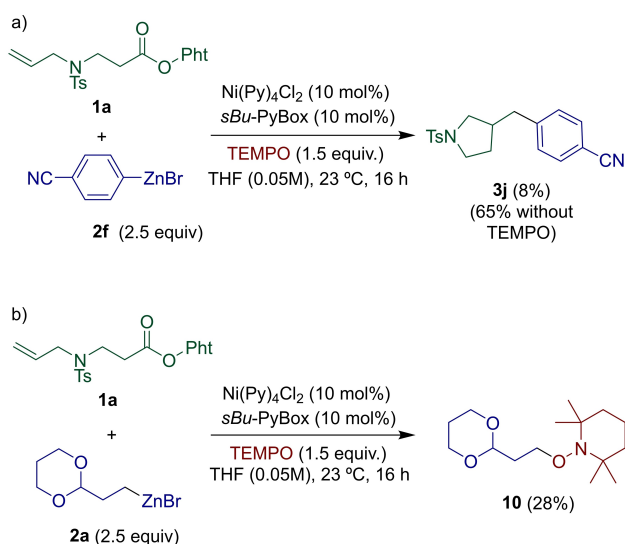
Scheme 2. Scope of the cyclization/cross-coupling reaction for alkyl-ZnBr (a) and aryl-ZnBr (b) reagents. ^[a] Yield was determined by ¹H-NMR using hexamethyldisilane as internal standard.



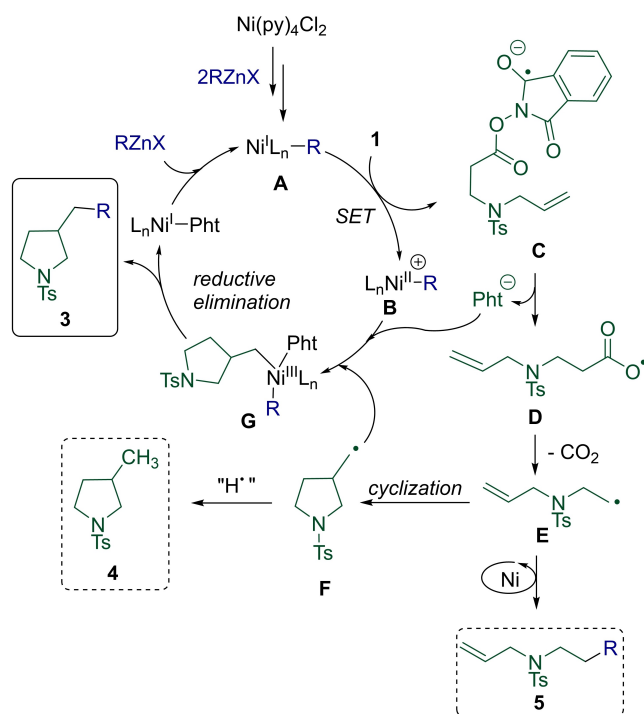
Scheme 3. Retrosynthetic analysis.

N–O cleavage would afford **D**, which would evolve to radical **E** by CO₂ elimination. Fast cyclization of **E** to **F** followed by coordination to Ni(II) intermediate **B** would give rise to

diorganonickel(III) complex **G**. Reductive elimination would lead to the desired products **3** and to a Ni(I) complex, which would experience a transmetalation reaction with the organozinc reagent to give the active alkylnickel(I) complex. Formation of the observed simple coupling compounds (**5**) is explained by a direct coordination of intermediate radical **E** to Ni(II) complex **B** prior to cyclization followed by reductive elimination. On the other hand, cyclized radicals **F** could also evolve by H abstraction from the solvent or from the substrate. It is important to mention that other mechanistic possibilities may take place. Thus coordination of radicals to Ni(I) instead to Ni(II)



Scheme 4. Reactions in the presence of TEMPO.



Scheme 5. Proposed reaction pathways.

species has been proposed in some cases, and we cannot discard this alternative.^[11]

Conclusion

We have developed a Ni-catalyzed cascade cyclization-coupling of allylamines and acrylamides containing redox active esters with alkyl and arylzinc bromides. Activation of the electrophiles probably takes place by single-electron transfer from Ni(I)

complexes. Subsequent decarboxylation leads to radical intermediates which experience a fast cyclization prior to the coordination to organo-Ni(II) intermediate complex, avoiding a simple Negishi coupling. The reaction implies the formation of two C–C bonds and affords substituted pyrrolidines or pyrrolidones from β -alanine derivatives in an unusual retrosynthetic approach.

Experimental Section

A vial was charged with the corresponding RAE (0.2 mmol, 1 equiv.), Ni(py)₄Cl₂ (10 mol%) and sBu-Pybox (10 mol%) under argon atmosphere. The vial was sealed and anhydrous and Ar-degassed THF (0.05 M) was added. After stirring for 3–4 min at room temperature, the resulting cloudy yellow-blue solution was treated in turn with the corresponding organozinc (0.5–0.2 M THF solution, 2.5 equiv). The solution turned dark brown, and the reaction mixture was stirred at room temperature overnight. Saturated aqueous NH₄Cl solution was added, and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over anhydrous MgSO₄ and the solvent was evaporated under vacuum. The products were purified by column chromatography in silica gel.

Acknowledgements

We thank the support by MICIU(CTQ2016-79826-R and PID2019-109088GB-I00) and for a FPI fellowship to J. C. N.-C.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Cross-coupling · Cyclization · Nickel · Pyrrolidines · Radical reactions

- [1] a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299–309; b) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670; c) F. Glorius, *Angew. Chem. Int. Ed.* **2008**, *47*, 8347–8349.
- [2] a) D. Yu, B. Li, Z. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486–1495; b) F. He, S. Ye, J. Wu, *ACS Catal.* **2019**, *9*, 8943–8960.
- [3] a) S. Murarka, *Adv. Synth. Catal.* **2018**, *360*, 1735–1753; b) S. K. Parida, T. Mandal, S. Das, S. K. Hota, S. De Sarkar, S. Murarka, *ACS Catal.* **2021**, *11*, 1640–1683.
- [4] a) X. Sun, X. Dong, H. Liu, Y. Liu, *Adv. Synth. Catal.* **2021**, *363*, 1527–1558; b) Q. Liu, X. Dong, J. Li, J. Xiao, Y. Dong, H. Liu, *ACS Catal.* **2015**, *5*, 6111–6137.
- [5] a) V. B. Phapale, M. Guisan-Ceinos, E. Buñuel, D. J. Cárdenas, *Chem. Eur. J.* **2009**, *15*, 12681–12688; b) R. Soler-Yanes, M. Guisan-Ceinos, E. Buñuel, D. J. Cárdenas, *Eur. J. Org. Chem.* **2014**, 6625–6629; c) R. Soler-Yanes, I. Arribas-Alvarez, M. Guisan-Ceinos, E. Buñuel, D. J. Cárdenas, *Chem. Eur. J.* **2017**, *23*, 1584–1590; d) P. Niu, J. Li, Y. Zhang, C. Huo, *Eur. J. Org. Chem.* **2020**, 5801–5814.

- [6] a) V. B. Phapale, E. Buñuel, M. García-Iglesias, D. J. Cárdenas, *Angew. Chem. Int. Ed.* **2007**, *46*, 8790–8795; b) M. Guisan-Ceinos, R. Soler-Yanes, D. Collado-Sanz, V. B. Phapale, E. Buñuel, D. J. Cárdenas, *Chem. Eur. J.* **2013**, *19*, 8405–8410.
- [7] a) J. Cornella, J. T. Edwards, T. Qin, S. Kawamura, J. Wang, C. Pan, R. Gianatassio, M. Schmidt, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 2174–2177; b) K. M. M. Huihui, J. A. Caputo, Z. Melchor, A. M. Olivares, A. M. Spiewak, K. A. Johnson, T. A. DiBenedetto, S. Kim, L. K. G. Ackerman, D. J. Weix, *J. Am. Chem. Soc.* **2016**, *138*, 5016–5019; c) T. Qin, J. Cornella, C. Li, L. R. Malins, J. T. Edwards, S. Kawamura, B. D. Maxwell, M. D. Eastgate, P. S. Baran, *Science* **2016**, *352*, 801–805; d) J. Xiao, Z. Li, J. Montgomery, *J. Am. Chem. Soc.* **2021**, *143*, 21234–21240; e) K. Kang, D. J. Weix, *Org. Lett.* **2022**, *15*, 2853–2857.
- [8] J.-B. Qiao, Y.-Q. Zhang, Q.-W. Yao, Z.-Z. Zhao, X. Peng, X.-Z. Shu, *J. Am. Chem. Soc.* **2021**, *143*, 12961–12967.
- [9] Reaction of radicals with BHT may be slow, and reaction inhibition may not be observed in these cases: E. Boess, C. Schmitz, M. A. Klusmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325.
- [10] M. T. Quirós, D. Collado-Sanz, E. Buñuel, D. J. Cárdenas, *Chem. Commun.* **2021**, *57*, 2424–2427.
- [11] J. Breitenfeld, J. Ruiz, M. D. Wodrich, X. Hu, *J. Am. Chem. Soc.* **2013**, *135*, 12004–12012. See also ref. 4c.

Revised manuscript received: October 18, 2022

Accepted manuscript online: October 19, 2022