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Electron-Donor–Acceptor Complex-Enabled Flow Methodology for the Hydrotrifluoromethylation of Unsaturated β-Keto Esters

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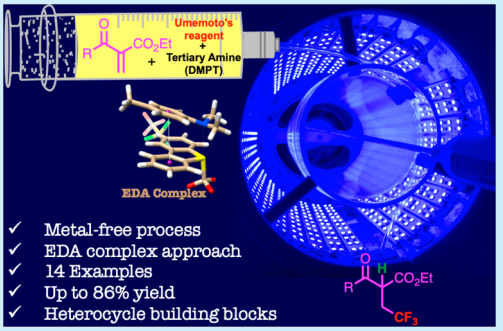
ABSTRACT: A novel electron-donor–acceptor (EDA) complex-enabled flow photochemical hydrotrifluoromethylation of unsaturated β-keto esters is described. The developed protocol has an easy experimental procedure and does not require the use of transition-metal-based photocatalysts, allowing the isolation of 14 new compounds in up to 86% yield. Control experiments and computational studies revealed that the reaction proceeds through a Michael-type 1,4-addition of a trifluoromethyl radical, followed by a proton transfer step. Furthermore, the reaction could be scaled up to 1 mmol, and the final product could be employed in the preparation of an isoxazolone and a pyrazolone as trifluoro-substituted heterocycles.

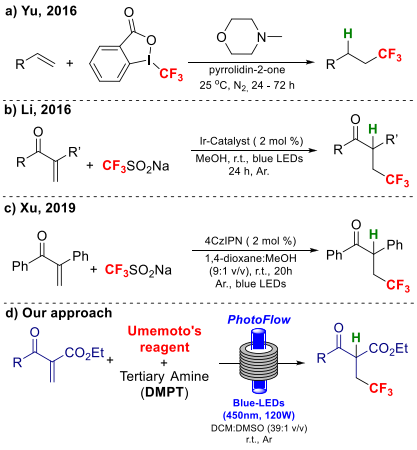


The formation of new carbon–carbon bonds is of great interest in organic synthesis and is usually involved in the construction of complex molecule backbones.[1] In this context, the development of new building blocks that can be further applied in the attainment of high-value compounds is essential.[2] Dicarbonyl derivatives have attracted the attention of the synthetic community and have been extensively used in the synthesis of bioactive heterocyclic scaffolds,[3j,k] such as pyrazolones,[3a−e] furans,[3f−i] pyrroles,[3f,j] lactams,[3k] and isoxazolones.[3l]

The hydrotrifluoromethylation of unsaturated β-keto esters still appears as a challenge in organic chemistry, and novel methodologies in this field are highly desirable to access novel trifluoro-containing molecules. The CF_3 group is known to increase the lipophilicity and metabolic stability of pharmaceuticals and enhance the biological activities.[4] Moreover, the development of new methodologies for hydrotrifluoromethylation is highly demanded, being a straightforward transformation for the formation of $C(sp^3)–CF_3$ bonds.[5] Photochemical methodologies appear as valuable alternatives to the traditional trifluoromethylation protocols, presenting several advantages.[6] Recently, important advances in the photochemical-enabled synthesis were described,[7] including strategies involving the formation of electron-donor–acceptor (EDA) complexes in photochemical transformations.[8]

The reported procedures for the hydrotrifluoromethylation of olefins using an EDA approach are mainly related to electron-rich olefins (Scheme 1a).[9] Thus, the use of conjugate Michael acceptors is still limited to either expensive iridium-based catalysts (Scheme 1b)[10] or organic photocatalysts (Scheme 1c).[11] Because of the lack of an EDA complex

Scheme 1. Previous Literature Reports and Our Proposal for Hydrotrifluoromethylation of Olefins



methodology for hydrotrifluoromethylation at the β carbonyl position, we envisioned that the use of an accessible tertiary amine as an electron-donor reagent together with an electron-acceptor CF_3 source would provide the corresponding multifunctional CF_3-containing derivatives through a photo-

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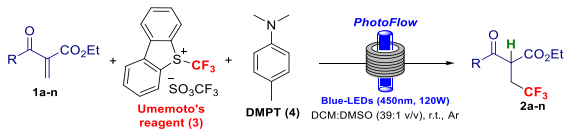
catalytic EDA complex protocol.[12] Moreover, it is important to highlight the advantages of this protocol, which was developed under continuous photoflow conditions, with shorter reaction times, great scalability, and better efficiency compared with batch photoreactors (Scheme 1d).

The dicarbonyl compound **1a** was prepared according to the literature protocol through oxidation of the corresponding Morita–Baylis–Hillman adduct.[13] Next, a series of optimization reactions were carried out under batch conditions (for full details, see the Supporting Information). Although initially we considered the use of diverse photocatalysts, such as the commercially available $[Ru(bpy)_3(PF_6)_2]$, the isolated yields were only low to moderate (up to 48%). To our delight, when the tertiary amine *N*,*N*-dimethyl-*p*-toluidine (DMPT, **4**) was added, the desired product **2a** was isolated in 47% yield. Remarkably, the ruthenium complex was no longer required for product formation, suggesting the formation of an EDA complex, presumably with Umemoto's reagent as the acceptor and the amine as the donor. Moreover, the reaction in the dark gave only a 9% yield, indicating that photoexcitation under blue-light irradiation is required.

Furthermore, during the batch optimization, a screening of the tertiary amine and its loading was carried out. When only 2 equiv of the tertiary amine was employed, the Umemoto reagent was not completely consumed, suggesting that after some reaction time no free tertiary amine was available to generate the corresponding EDA complex. On the other hand, the use of a higher amine loading (10 equiv) considerably decreased the yield. Thus, the best results were obtained with two consecutive additions (2 + 1 equiv) of DMPT, leading to product **2a** in 61% yield after 4.5 h under batch conditions.[14]

Considering that continuous flow photoreactors have more efficient irradiation and that the ratio of the tertiary amine to Umemoto's reagent is critical for the attainment of higher yields, we hypothesized that the transposition of this reaction to continuous conditions would greatly enhance the yield.[15] Therefore, a second optimization was conducted in a photoflow reactor (setup details are available in the Supporting Information), taking into account the flow rate and the amine loading (Table 1). As a result, the best reaction conditions are given in entry 4 of Table 1, with a flow rate of 1.0 mL min^{-1} and a residence time of 30 min. It is important to highlight that only 2 equiv of DMPT was employed with just 1.1 equiv of Umemoto's reagent (**3**), leading to the desired product **2a** in good yield (74%).

Table 1. Optimization of the Hydrotrifluoromethylation Reaction under Flow Conditions

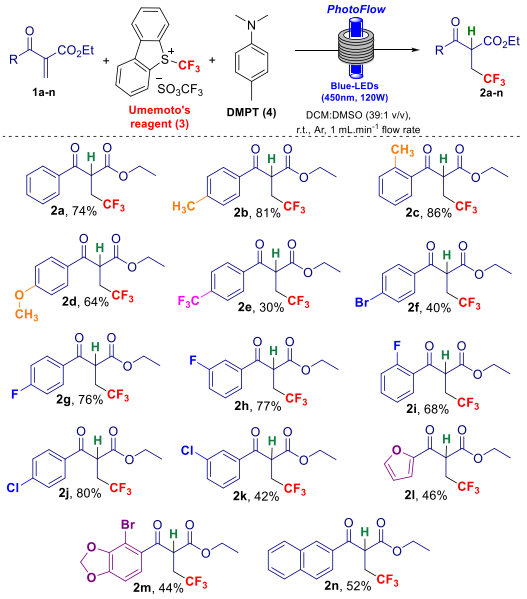


entry[a]	flow rate (mL min^{-1})	residence time (min)	DMPT loading (equiv)	yield (%)
1	3.0	10	2	66
2	2.0	15	2	72
3	0.5	60	2	72
4	1.0	30	2	74[b]
5	1.0	30	4	60

[a]All of the reactions were carried out in a 30 mL flow reactor with 120 W blue LEDs (λ_{max} = 450 nm) using 0.2 mmol of **1a**, 1.1 equiv (0.22 mmol) of Umemoto's reagent, DMPT, and DCM/DMSO (39:1) as the solvent (2 mL). [b]Average isolated yield (duplicates).

Having established the best flow reactor conditions, we turned our attention to the evaluation of the reaction scope (Scheme 2). Under the standard reaction conditions, several aryl-substituted derivatives were well-tolerated. For example, the presence of an electron-donating methyl group even at a sterically hindered *ortho* position led to the desired product **2c** in 86% yield. Despite the well-known bond dissociation energy related to halogenated adducts under photochemical reaction conditions, *para*-, *meta*-, and even *ortho*-halogenated products were synthesized in good yields (**2f–k**). Furthermore, a substrate with an electron-withdrawing *p*-trifluoromethyl group afforded **2e** in 30% yield. It is important to notice that although **2e** was synthesized in a lower yield (30%), this product contains two trifluoromethyl groups in its structure. Particularly, in this case, the starting material was not completely consumed. Finally, the use of heteroaryl substituents was also evaluated, affording products **2l** and **2m** in 46% and 44% yield, respectively. The use of a sterically hindered trisubstituted olefin (diethyl 2-benzylidenemalonate) was also evaluated under the optimized reaction conditions but failed to provide the desired product, suggesting that the use of terminal olefins might be crucial for this transformation.

Scheme 2. Scope of the Hydrotrifluoromethylation of Dicarbonyl Compounds under Flow Conditions



To experimentally confirm the formation of an EDA complex, UV–vis spectra of both Umemoto's reagent and DMPT in separate solutions and their corresponding mixtures were obtained. When the spectrum of the mixture is deconvoluted from the individual spectra, the EDA complex spectrum appears at λ_{max} = 400 nm (Scheme 3a). Besides, a titration of DMPT into a solution of Umemoto's reagent was also performed (Scheme 3b), and in agreement with the Le Châtelier's principle, a shift in the equilibrium toward the formation of the EDA complex occurs. Accordingly, it is possible to observe that the solution will possess an increased absorbance.

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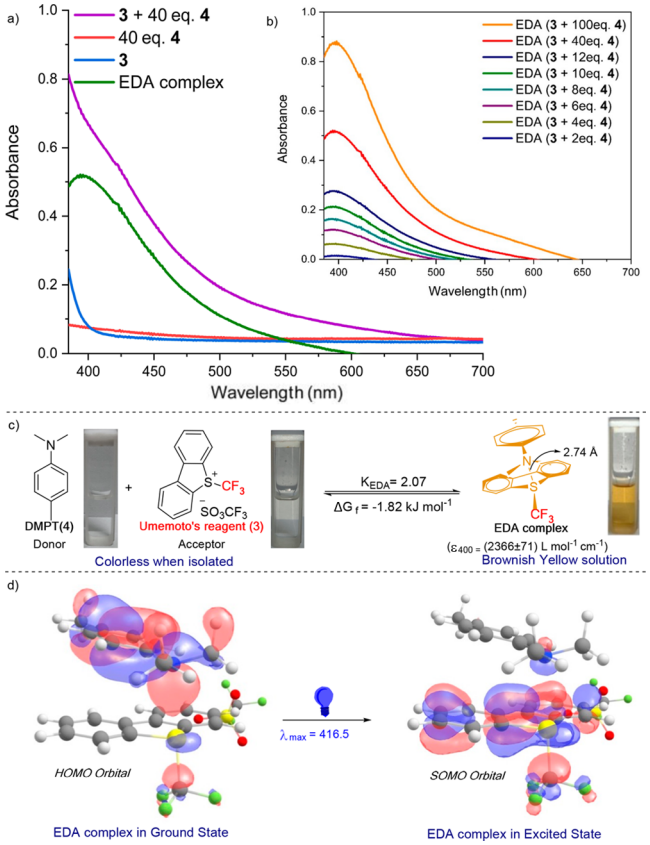
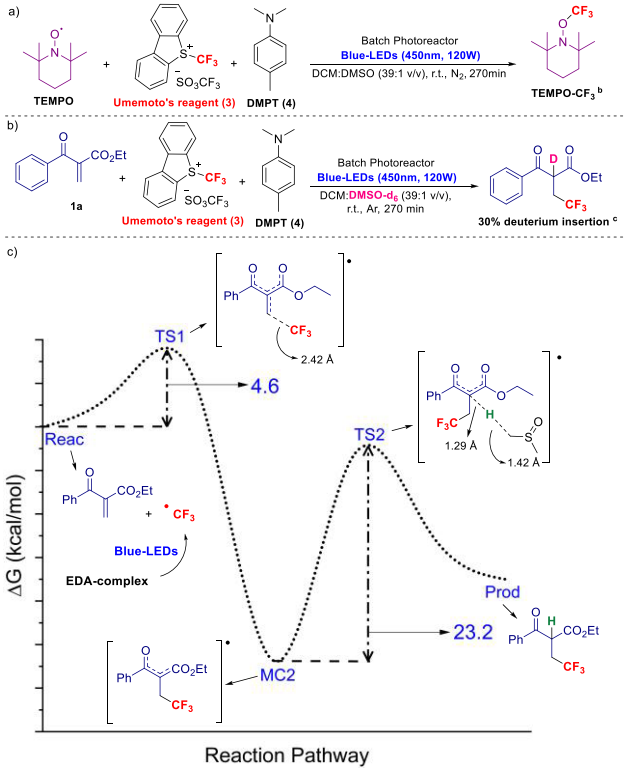
Scheme 3. (a) UV−Vis Spectra Demonstrating the Formation of an EDA Complex between Umemoto's Reagent (3) and DMPT (4); (b) UV−Vis Spectra of the EDA Obtained at Different Concentrations of DMPT; (c) EDA Complex Solution and DFT Data for the Formation of the EDA Complex; (d) Natural Transition Orbitals (NTOs) of the EDA Complex[a]



[a]All of the given structures, orbitals, and values were calculated at the B3LYP-D3/6-31G(d,p)//M06-2X-D3/6-31G(d) level of theory with insertion of solvent (DCM) using the SMD model.

Scheme 4. Studies Regarding the Mechanistic Proposal: (a) Reaction Employing TEMPO as a Radical Scavenger; (b) Reaction Employing DMSO-d_6; (c) Proposed Reaction Mechanism with ΔG along the Reaction Pathway[a]



[a]All of the given values were calculated at the B3LYP-D3/6-31G(d,p)//M06-2X-D3/6-31G(d) level of theory with insertion of solvent (DCM) using the SMD model. [b]Detected by ^{19}F NMR analysis of the crude reaction mixture using fluorobenzene as an internal standard. [c]Calculated from ^{1}H NMR analysis of the crude reaction mixture.

Next, DFT calculations were performed to confirm the EDA complex formation (Scheme 3c). The data allowed the calculation of ΔG_f (and consequently K_{EDA}), which enabled the theoretical determination of the concentration of EDA complex in solution. The combination of these data with the experimental absorbance determined during the titration UV−vis experiments allowed the prediction of the molar absorptivity of the EDA complex (ε_{400} = (2366 ± 71) L mol^{-1} cm^{-1}) (see the Supporting Information for full details).

Finally, the natural transition orbitals (NTOs) for the EDA complex ground state and its first singlet−singlet transition was simulated and indicated that the absorption at 400 nm corresponds to a charge transfer band (Scheme 3d).

We then turned our attention toward the hydrotrifluoromethylation reaction mechanism. Since a radical pathway was expected, attempts to trap CF_3 radical were carried out in the presence of TEMPO and led to the TEMPO−CF_3 product (detected through ^{19}F NMR analysis of the crude reaction mixture) (Scheme 4a).

To obtain further insight into the proton source in the final products, a control reaction employing DMSO-d_6 was also carried out and revealed 30% deuterium incorporation (Scheme 4b), suggesting proton transfer from the solvent.

The energy barriers involved in the proposed pathway were also determined through DFT calculations (Scheme 4c). Thus, on the basis of the experimental and computational evidence that the trifluoromethyl radical is formed independently from **2a**, the proposed reaction mechanism initiates through the Michael-type addition of the trifluoromethyl radical to the conjugated olefin. This step proceeds through a considerably low energy transition state (**TS1**) with a reaction barrier of only 4.6 kcal mol^{-1}. Moreover, this step is greatly thermodynamically favored (ΔG = −26.9 kcal mol^{-1}), probably related to the formation of a more stable α-dicarbonyl radical species (**CM2**). Finally, the reaction pathway then follows with the proton transfer (from DMSO), leading to the formation of the final product **2a**. This step is rate-limiting and proceeds through a second transition state (**TS2**) with a reaction barrier of 23.2 kcal mol^{-1}.

Finally, to highlight the synthetic applicability of product **2a**, a scale-up to 1 mmol was performed, affording the desired product without considerable loss of yield (68%). The preparation of two heterocycles employing product **2a** as the substrate was also demonstrated. First, **2a** was employed in the synthesis of trifluoromethyl-substituted isoxazolone derivative

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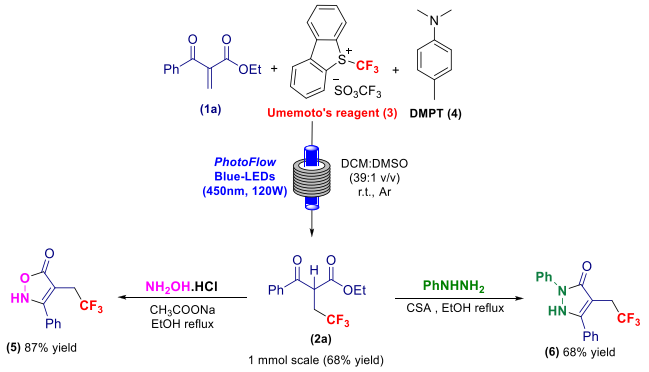
5 in 87% yield. Moreover, **2a** was also used in the preparation of highly functionalized pyrazolone **6** in 68% yield (Scheme 5).

Scheme 5. Reactions Employing 2a as a Building Block



In summary, a photochemical flow hydrotrifluoromethylation methodology for unsaturated β-keto esters is described herein. To the best of our knowledge, this constitutes the first photoflow protocol with an EDA approach to CF_3 radical conjugate additions into these dicarbonyl derivatives. The method does not require the use of any metal-based catalyst and proceeds through an EDA approach. Furthermore, under the optimized reaction conditions, a substrate scope of 14 derivatives was described in up to 86% yield. Control reactions and DFT calculations were performed and suggested a mechanism involving EDA formation followed by conjugate addition of trifluoromethyl radical and a proton transfer step. A scale-up to 1 mmol could be accomplished, leading to product **2a** in 68% yield. Finally, product **2a** could be successfully employed in the synthesis of two trifluoromethyl-substituted heterocycles that may serve as valuable bioactive molecules, opening up further synthetic transformations for these dicarbonyl trifluoro derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03187.

Experimental procedures, pictures of the reactor setup, copies of NMR spectra, computational data, and batch reaction conditions optimization study (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Choi, J.; Fu, G. C. *Science* **2017**, *356*, No. eaaf7230. (b) Lu, X.; Xiao, B.; Zhang, Z.; Gong, T.; Su, W.; Yi, J.; Fu, Y.; Liu, L. *Nat. Commun.* **2016**, *7*, 11129.

(2) (a) Goldberg, F. W.; Kettle, J. G.; Kogej, T.; Perry, M. W. D.; Tomkinson, N. P. *Drug Discovery Today* **2015**, *20*, 11. (b) Woerly, E. M.; Roy, J.; Burke, M. D. *Nat. Chem.* **2014**, *6*, 484. (c) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. *Nat. Chem.* **2018**, *10*, 383.

(3) (a) Dishington, A.; Feron, J. L.; Gill, K.; Graham, M. A.; Hollingsworth, I.; Pink, J. H.; Roberts, A.; Simpson, I.; Tatton, M. *Org. Lett.* **2014**, *16*, 6120. (b) Zhang, Y.; Benmohamed, R.; Huang, H.; Chen, T.; Voisine, C.; Morimoto, R. I.; Kirsch, D. R.; Silverman, R. B. *J. Med. Chem.* **2013**, *56*, 2665. (c) Ghosh, P. P.; Pal, G.; Paul, S.; Das, A. R. *Green Chem.* **2012**, *14*, 2691. (d) Pasceri, R.; Bartrum, H. E.; Hayes, C. J.; Moody, C. J. *Chem. Commun.* **2012**, *48*, 12077. (e) Hu, X.; Chen, F.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2018**, *20*, 6140. (f) White, A. R.; Kozlowski, R. A.; Tsai, S. C.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2017**, *56*, 10525. (g) He, C.; Guo, S.; Ke, J.; Hao, J.; Xu, H.; Chen, H.; Lei, A. *J. Am. Chem. Soc.* **2012**, *134*, 5766. (h) Lou, J.; Wang, Q.; Wu, K.; Wu, P.; Yu, Z. *Org. Lett.* **2017**, *19*, 3287. (i) Zhou, Y.; Zhu, F.; Liu, Z.; Zhou, X.; Hu, X. *Org. Lett.* **2016**, *18*, 2734. (j) Yang, J.; Mei, F.; Fu, S.; Gu, Y. *Green Chem.* **2018**, *20*, 1367. (k) Ma, J.; Zhong, L.; Peng, X.; Sun, R. *Green Chem.* **2016**, *18*, 1738. (l) De Castro, P. P.; Dos Santos, J. A.; De Siqueira, M. M.; Batista, G. M. F.; Dos Santos, H. F.; Amarante, G. W. *J. Org. Chem.* **2019**, *84*, 12573.

(4) (a) Levitre, G.; Dagousset, G.; Anselmi, E.; Tuccio, B.; Magnier, E.; Masson, G. *Org. Lett.* **2019**, *21*, 6005. (b) Chen, C.-T.; Chen, Y.-P.; Tsai, B.-Y.; Liao, Y.-Y.; Su, Y.-C.; Chen, T.-C.; Lu, C.-H.; Fujii, R.; Kawashima, K.; Mori, S. *ACS Catal.* **2020**, *10*, 3676. (c) Gelat, F.; Patra, A.; Pannecoucke, X.; Biju, A. T.; Poisson, T.; Besset, T. *Org. Lett.* **2018**, *20*, 3897.

(5) (a) Wu, X.; Chu, L.; Qing, F. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 2198. (b) Straathof, N. J. W.; Cramer, S. E.; Hessel, V.; Noël, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 15549.

(6) (a) Jacquet, J.; Blanchard, S.; Derat, E.; Desage-El Murr, M.; Fensterbank, L. *Chem. Sci.* **2016**, *7*, 2030. (b) Koike, T.; Akita, M. *Acc. Chem. Res.* **2016**, *49*, 1937. (c) Beatty, J. W.; Douglas, J. J.; Miller, R.; McAtee, R. C.; Cole, K. P.; Stephenson, C. R. J. *Chem.* **2016**, *1*, 456. (d) Zhu, M.; Zhou, K.; Zhang, X.; You, S. L. *Org. Lett.* **2018**, *20*, 4379.

(7) (a) Rehm, T. *Chem. - Eur. J.* **2020**, DOI: 10.1002/chem.202000381. (b) Williams, J. D.; Kappe, C. O. *Curr. Opin. Green Sust. Chem.* **2020**, *25*, 100351.

(8) (a) Tu, H. Y.; Zhu, S.; Qing, F. L.; Chu, L. *Chem. Commun.* **2018**, *54*, 12710. (b) Lima, C. G. S.; Lima, T. d. M.; Duarte, M.;

Jurberg, I. D.; Paixão, M. W. *ACS Catal.* **2016**, *6*, 1389. (c) Davies, J.; Booth, S. G.; Essafi, S.; Dryfe, R. A. W.; Leonori, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 14017. (d) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. *J. Am. Chem. Soc.* **2020**, *142*, 5461. (e) Cao, Z.-Y.; Ghosh, T.; Melchiorre, P. *Nat. Commun.* **2018**, *9*, 3274. (f) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2018**, *140*, 10700. (g) Li, Y.; Miao, T.; Li, P.; Wang, L. *Org. Lett.* **2018**, *20*, 1735. (h) Liu, B.; Lim, C. H.; Miyake, G. M. *J. Am. Chem. Soc.* **2018**, *140*, 12829.

(9) Cheng, Y.; Yu, S. *Org. Lett.* **2016**, *18*, 2962.

(10) Zhu, L.; Wang, L.-S.; Li, B.; Fu, B.; Zhang, C.-P.; Li, W. *Chem. Commun.* **2016**, *52*, 6371.

(11) Wang, H.; Zhang, J.; Shi, J.; Li, F.; Zhang, S.; Xu, K. *Org. Lett.* **2019**, *21*, 5116.

(12) Cheng, Y.; Yuan, X.; Ma, J.; Yu, S. *Chem. - Eur. J.* **2015**, *21*, 8355.

(13) Batista, G. M. F.; De Castro, P. P.; Carpanez, A. G.; Horta, B. A. C.; Amarante, G. W. *Chem. - Eur. J.* **2019**, *25*, 16555.

(14) Silva, R. C.; Villela, L. F.; Brocksom, T. J.; De Oliveira, K. T. *RSC Adv.* **2020**, *10*, 31115.

(15) (a) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796. (b) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. - Eur. J.* **2014**, *20*, 10562. (c) De Souza, J. M.; Brocksom, T. J.; McQuade, D. T.; De Oliveira, K. T. *J. Org. Chem.* **2018**, *83*, 7574. (d) De Souza, A. A. N.; Silva, N. S.; Müller, A. V.; Polo, A. S.; Brocksom, T. J.; De Oliveira, K. T. *J. Org. Chem.* **2018**, *83* (24), 15077.

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