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Visible-Light-Mediated Synthesis of Bicalutamide by Regioselective Hydroxysulfonylation of Acrylamides

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Synthesis of anticancer drug bicalutamide promoted by visible light in one step from the corresponding *N*-arylacrylamide is described. This approach involves a one-pot hydroxysulfonylation reaction through a photocatalytic redox process. The use of Na_2Eosin Y as photocatalyst and blue light allows the access to a broad range of α-hydroxysulfonylamides bearing a quaternary center in moderate to good yields with complete regioselectivity via radical process.

Introduction

The prostate cancer is the most common cancer in men over 65 years of age and ranks as the fourth most diagnosed cancer worldwide.[1] The drug bicalutamide (Figure 1), whose brand name is Casodex®, is a nonsteroidal antiandrogen prescribed for its treatment. Bicalutamide was discovered by Tucker and colleagues in 1980s[2,3] and commercialized by AstraZeneca from 1995 in a racemic mixture being both enantiomers metabolized in the liver.[4]

Bicalutamide synthesis has been previously reported using three different approaches (Scheme 1). *N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide is a commonly used intermediate in several published methods for synthesizing bicalutamide (Approach A, Scheme 1). This compound can be synthesized through nucleophilic aromatic substitution[5] or by reacting the corresponding aniline with methacryloyl chloride.[3] Subsequently, it can undergo a radical addition reaction with a sulfur radical under an oxygen atmosphere. This reaction generates a hydroperoxysulfide intermediate that can be oxidized by Oxone to produce bicalutamide after reductive work up with $NaBH_4$[6] or reduction of this intermediate with PPh_3 and oxidation with *m*CPBA.[7]

In these reports, several reaction steps are required. An epoxide is formed in the presence of an oxidant, then the sulfur moiety is introduced as thiol and subsequently the sulfone is obtained by an additional oxidation.[5] Alternatively, the epoxide

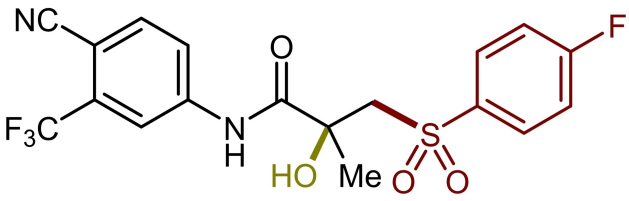
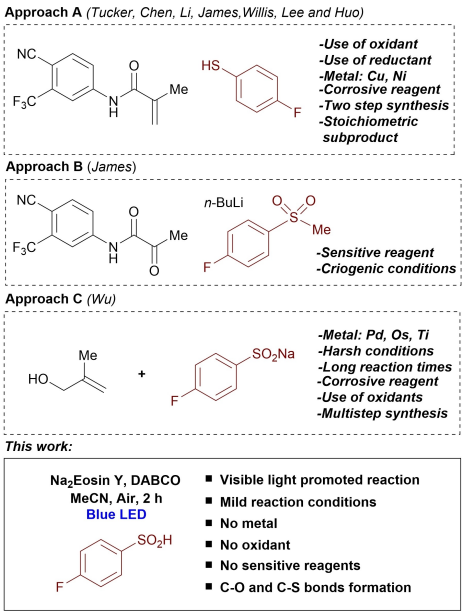


Figure 1. Structure of bicalutamide.



Scheme 1. Syntheses of bicalutamide.

can be opened with a sulfone intermediate previously synthesized using metal as copper[8] or nickel[9] at high temperatures. Hydroxysulfenylation of the *N*-acrylamide through an aerobic copper catalysis and oxidation with *m*CPBA to obtain bicalutamide has also been reported.[10]

In 2002, a second approach for synthesizing bicalutamide was described (Approach B, Scheme 1). This method involves a two-step synthesis starting from the costly material 4-cyano-3-trifluoromethyl aniline. The key step in this approach is a 1,2-addition of a methyl sulfone to a keto-amide using *n*-BuLi as

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base at −78 °C.[11,12] The same authors reported the syntheses of both pure enantiomers of bicalutamide starting with (*S*)- and (*R*)-citramalic acid.[13] Recently, the obtention of bicalutamide has been described through the direct substitution of an allylic alcohol with sodium arylsulfinate.[14] Although the synthetic route is very efficient, different metals such as palladium, titanium, and osmium, along with corrosive reagents as well as long reaction times are required (Approach C, Scheme 1).

Over the past few years, visible-light photoredox catalysis has emerged as a mild and eco-friendly methodology for constructing molecules via a radical pathway.[15] Specifically, visible-light mediated hydroxysulfonylation of alkenes enables the synthesis of β-hydroxysulfones in a single step. To achieve this, ruthenium or iridium catalysts and sulfonyl chlorides have been used on alkylidenecyclopropanes[16] and styrene derivatives.[17] β-Hydroxysulfones can also be synthesized using sodium sulfinates under aerobic oxidative conditions.[18] A recent study reported the sequential sulfonylation/hydroxylation of allylacetamides, resulting in the formation of β-*tert*-hydroxysulfones.[19] This is the only known example in the literature where sulfinic acids are used in conjunction with styrene derivatives under visible light.

To the best of our knowledge the visible-light mediated hydroxysulfonylation of acrylamides has not been reported to date.[20] Based on our previous work on chlorosulfonylation of acrylamides,[21] we envisioned the development of a methodology for the visible-light promoted hydroxysulfonylation of *N*-arylacrylamides. This methodology would allow to access one-pot to bicalutamide from the commercially available *N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide as well as a wide variety of α-hydroxy-β-sulfonylamides under mild conditions.

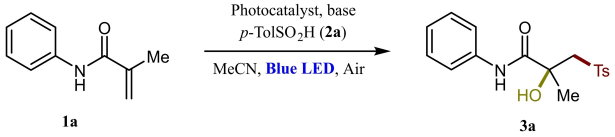
Results and Discussion

Our preliminary investigation centered on the reaction of *N*-phenylmethacrylamide as model substrate (**1a**), *fac*-Ir(ppy)$_3$ as the catalyst and sulfonyl chloride in acetonitrile under irradiation of 33 W blue LED strip lights under air.[22] Under these conditions only the formation of β-chlorosulfone was detected.

To prevent this outcome, we substituted the sulfonyl radical precursor with sulfinic acid and employed Eosin Y as the photoredox catalyst instead. Under these conditions, we observed the formation of β-hydroxysulfone **3**, albeit in low yield (entry 1, Table 1). Table 1 shows that when alternative bases, such as Cs_2CO_3 or DBU were used, traces of **3a** or no reaction was observed (entries 2–3). When using other photocatalysts such as Rose Bengal or *fac*-Ir(ppy)$_3$, **3a** was either not detected or formed in low yield (entries 4–5). However, using Na_2Eosin Y with DABCO led to a product isolated yield of 53% after 22 h (entry 6). Further increasing the equivalents of sulfinic acid resulted in a higher reaction yield (entries 7–8), with full conversion achieved in two hours and 70% yield obtained with 5 equivalents of *p*-tolylsulfinic acid (Entry 9).

After stablishing the optimal conditions, the scope of the transformation was investigated to demonstrate the versatility

Table 1. Optimization of the reaction conditions.



1a 3a

Entry	Photocatalyst	Base	**2a** (equiv.)	Yield[a]
1	Eosin Y	DABCO	2	18
2	Eosin Y	Cs_2CO_3	2	4
3	Eosin Y	DBU	2	N.R.
4	*fac*-Ir(ppy)$_3$	DABCO	2	27
5	Rose Bengal	DABCO	2	–
6	Na_2Eosin Y	DABCO	2	53[b]
7[c]	Na_2Eosin Y	DABCO	3	46[b]
8[c]	Na_2Eosin Y	DABCO	4	49[b]
9[c]	Na_2Eosin Y	DABCO	5	70[b]
10	Na_2Eosin Y	DABCO	5	70[b]

Reaction conditions: A solution of **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.2–0.5 mmol, 2.0–5.0 equiv.), base (0.2 mmol. 2.0 equiv.) and photocatalyst (3 mol%) in MeCN (0.1 M) was stirred at room temperature under irradiation with 33 W blue LED strip lights for 22 h. [a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield. [c] Reaction time 2 h.

of the protocol (Scheme 2). The reaction exhibited tolerance towards different functional groups. A range of *N*-arylacrylamides with different substituents on the aromatic ring on *ortho*-, *meta*- or *para* position containing electron-withdrawing groups (Br, CF_3) and electron-donating groups (Me, OMe, OEt) were used to afford hydroxysulfonylation products **3b**–**h** in moderate to good yields (36–64%).

Products **3i** and **3j** were obtained through the reaction between disubstituted arylacrylamides as *N*-(3,5-dimethylphenyl)methacrylamide and *N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide in yields of 59% and 35%, respectively. The use of heterocyclic acrylamide was also found to be compatible with the reaction conditions, resulting in the isolation of **3k** in moderate yield. However, the reaction with *N*-phenylacrylamide, which forms a tertiary center, only led to **3l** with 10% of isolated yield. Similar yields were obtained when dichloromethane was used as solvent for **1e**, **1h** and **1j**, but no product was detected in the case of **1k** and **1l**. Moreover, when two *N*-alkyl substituted acrylamides underwent the reaction conditions, they produced derivatives **3m** with a propyl substituent and **3n** with a phenethyl substituent in yields of 20% and 71%, respectively.

The transformation was then expanded to include various sulfinic acids (Scheme 3). Substituted benzenesulfinic acids with methoxy, bromo, fluor and nitro at different positions of the benzene ring were found to be suitable reagents, producing the corresponding products **3o**–**3t**. Disubstituted sulfinic acid was also used in the reaction, resulting in the desired product **3u** in 42% yield. Naphthalene-2-sulfinic acid and heterocyclic sulfinic acid were tolerated, and the derivatives **3v** and **3w** was isolated in 45 and 37% yield, respectively. However, aliphatic

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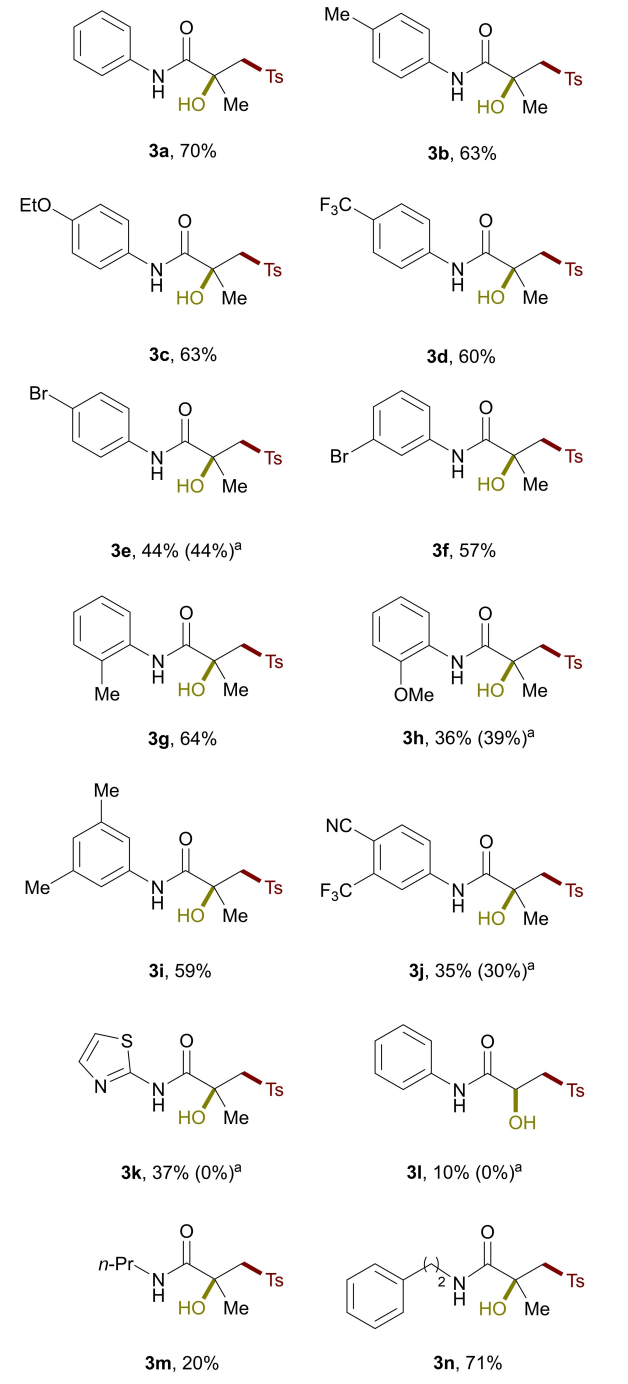
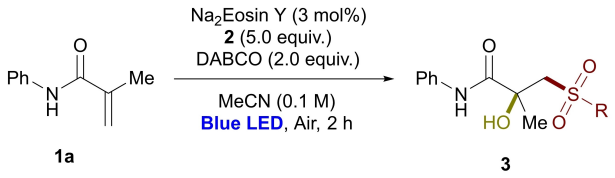
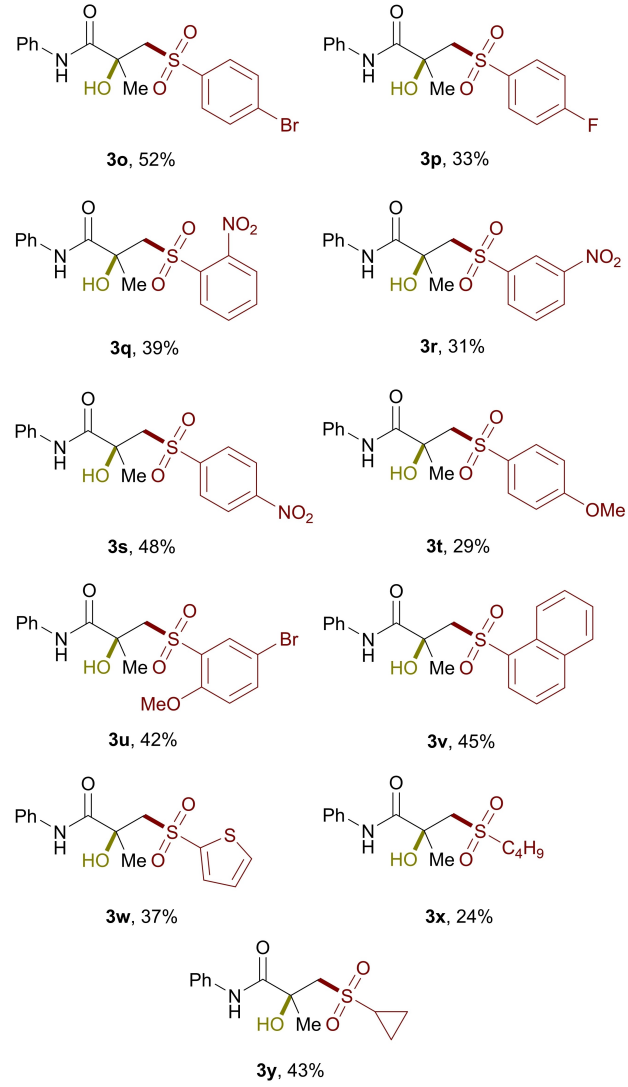


[a] Dichloromethane was used as solvent

Scheme 2. Scope of *N*-acrylamides.





Scheme 3. Scope of sulfinic acids.

sulfinic acid such as butane-1-sulfinic acid showed lower reactivity, only yielding 24% of **3x**. The product **3y**, synthesized from cyclopropanesulfinic acid, was isolated in 43% yield.

Finally, bicalutamide was obtained following the general procedure in 35% yield, which could be improved up to 52% when dichloromethane was used as solvent (Scheme 4). Unlike the previous reported methods for synthesizing bicalutamide, this approach does not require harsh conditions and can be completed in a single step from *N*-arylmethacrylamide **1j**.

It was demonstrated through control experiments that both the catalyst and light are essential in the hydroxysulfonylation reaction to obtain good yields (Scheme 5). In the presence of

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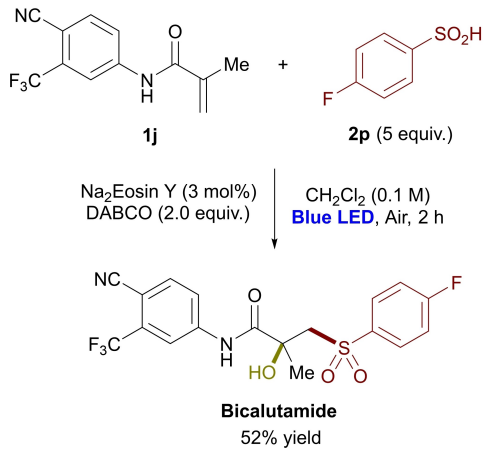
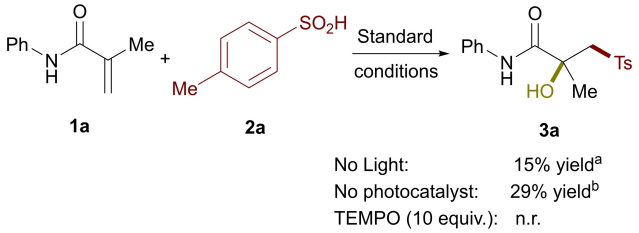


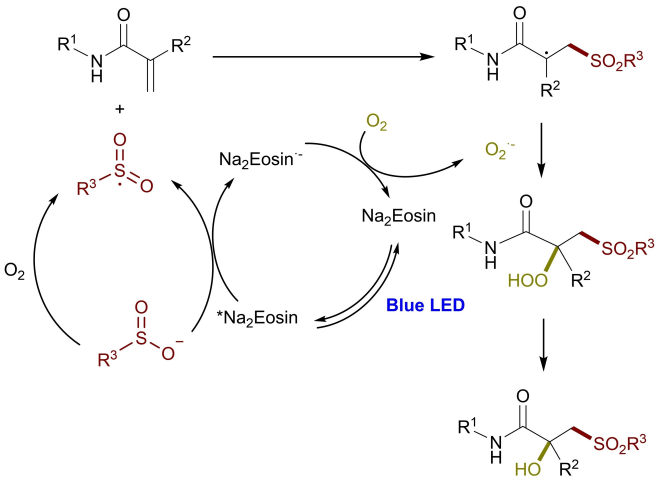
Scheme 4. Visible-light-promoted synthesis of bicalutamide.



Scheme 5. Control experiments. [a]Average of two experiments. [b]Average of three experiments.

2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), no reaction was observed, which points towards a radical mechanism.

A UV/Vis spectroscopic analysis allowed us to rule out the formation of an electron donor-acceptor complex (see Supporting Information for details). Lei et al. proposed the generation of a sulfonyl radical in the presence of oxygen during the aerobic oxysulfonylation of alkenes. This explanation accounts for the formation of **3a** even in the absence of light or a photocatalyst.[23] The mechanistic proposal is illustrated in Scheme 6. The catalytic cycle begins with the visible-light irradiation of photocatalyst. This leads to the generation of a sulfonyl radical through the oxidative SET of sulfinic salt. The sulfonyl radical is then added to the double bond of the acrylamide to afford a tertiary radical. The photocatalyst reduced oxygen to form superoxide, which subsequently complete the catalytic cycle. The tertiary radical reacts with this species and accepts a proton, resulting in the generation of a peroxide, which evolves into hydroxysulfonylamide through reduction by benzenesulfinate. The reduced photocatalyst is oxidated back to its fundamental state, while simultaneously reducing oxygen to form $O_2^{\bullet-}$. This species subsequently reacts with the tertiary radical, leading to the formation of a hydroperoxide, which is then reduced by benzenesulfinate anion or may undergo intermolecular redox, resulting in the formation of the hydroxysulfone derivative **3**.[24]



Scheme 6. Mechanistic proposal.

Conclusions

In summary, in this study a photocatalytic redox process was described for the one pot synthesis of bicalutamide from the commercially available *N*-(4-cyano-3-(trifluoromethyl)phenyl)methacrylamide. The use of Na_2Eosin Y as photocatalyst along with blue LED light, enabled the production of a diverse range of α-hydroxy-β-sulfonylamides that possess a quaternary center. The transformation was carried out via a radical mechanism with a complete regioselectivity, yielding moderate to good yields.

Experimental Section

General procedure of α-hydroxy-β-sulfonylation of acrylamides: To a Schlenk tube (10 ml size) equipped with a stirring bar was charged with the corresponding acrylamide (0.1 mmol, 1.0 equiv,), sulfinic acid (0.5 mmol, 5.0 equiv.), DABCO (0.2 mmol, 2.0 equiv.), Na_2Eosin Y (3.0 mol%) and MeCN (0.1 M). The resulting mixture was stirred at room temperature while being irradiated with 33 W blue LEDs, under an air atmosphere. After 2 h of reaction the solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel to give corresponding product.

Supporting Information

Additional references cited within the Supporting Information.[25–44]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: acrylamides · bicalutamide · difunctionalization of alkenes · hydrosysulfonylation · α-hydroxysulfones

[1] R. L. Siegel, MPH, K. D. Miller, H. E. Fuchs, A. Jemal, *CA: Cancer J. Clin.* **2022**, *72*, 1–93.
[2] B. J. Furr, B. Valcaccia, B. Curry, J. R. Woodburn, G. Chesterson, H. Tucker, *J. Endocrinol.* **1987**, *113*, R7–9.
[3] a) H. Tucker, J. W. Crook, G. J. Chesterson, *J. Med. Chem.* **1988**, *31*, 954–959; b) H. Tucker, (1982), Bicalutamide and its pharmaceutically acceptable salts and esters (Casodex (R)) (U. K. Patent No. 88769). European Patent Office.
[4] D. McKillop, G. W. Boyle, I. D. Cockshott, D. C. Jones, P. J. Phillips, R. A. Yates, *Xenobiotica* **1993**, *23*, 1241–1253.
[5] B. C. Chen, R. Zhao, S. Gove, B. Wang, J. E. Sundeen, M. E. Salvati, J. C. Barrish, *J. Org. Chem.* **2003**, *68*, 10181–10182.
[6] Y. Wang, W. Jiang, C. Huo, *J. Org. Chem.* **2017**, *82*, 10628–10634.
[7] C. Huo, Y. Wang, Y. Yuan, F. Chen, J. Tang, *Chem. Commun.* **2016**, *52*, 7233–7236.
[8] D.-K. Kim, H.-S. Um, H. Park, S. Kim, J. Choi, C. Lee, *Chem. Sci.* **2020**, *11*, 13071–13078.
[9] P. K. T. Lo, Y. Chen, M. C. Willis, *ACS Catal.* **2019**, *9*, 10668–10673.
[10] H. Xi, B. Deng, Z. Zong, S. Lu, Z. Li, *Org. Lett.* **2015**, *17*, 1180–1183.
[11] K. D. James, N. N. Ekwuribe, *Synthesis* **2002**, *7*, 850–853.
[12] E. E. Parent, C. S. Dence, C. Jenks, T. L. Sharp, M. J. Welch, J. A. Katzenellenbogen, *J. Med. Chem.* **2007**, *50*, 1028–1040.
[13] K. D. James, N. N. Ekwuribe, *Tetrahedron* **2002**, *58*, 5905–5908.
[14] Y.-J. Jhang, C.-Y. Chang, Y.-H. Lin, C.-C. Lee, Y.-K. Wu, *Tetrahedron Lett.* **2021**, *73*, 153060.
[15] a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; b) D. P. Hari, B. König, *Chem. Commun.* **2014**, *50*, 6688–6699; c) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166.
[16] C. Liu, Y.-J. Yang, J.-Y. Dong, M.-D. Zhou, L. Li, H. Wang, *Org. Chem. Front.* **2019**, *6*, 3944–3949.
[17] a) S. K. Pagire, S. Paria, O. Reiser, *Org. Lett.* **2016**, *18*, 2106–2109; b) M.-J. Bu, C. Cai, F. Gallou, B. H. Lipshutz, *Green Chem.* **2018**, *20*, 1233–1237; c) J. Wu, Y. Zhang, X. Gong, Y. Meng, C. Zhu, *Org. Biomol. Chem.* **2019**, *17*, 3507–3513; d) P.-J. Xia, F. Liu, S.-H. Li, J.-A. Xiao, *Org. Chem. Front.* **2022**, *9*, 709–714.
[18] a) A. Kariya, T. Yamaguchi, T. Nobuta, N. Tada, T. Miura, A. Itoh, *RSC Adv.* **2014**, *4*, 13191–13194; b) Y.-X. Chen, Z.-J. Wang, J.-A. Xiao, K. Chen, H.-Y. Xiang, H. Yang, *Org. Lett.* **2021**, *23*, 6558–6562.
[19] Z.-M. Qian, K.-L. Zuo, Z. Guan, Y.-H. He, *Tetrahedron* **2021**, *83*, 131999.
[20] Select examples of difunctionalization of acrylamides: a) W. Kong, M. Casimiro, N. Fuentes, E. Merino, C. Nevado, *Angew. Chem. Int. Ed.* **2013**, *52*,13086–13090; b) S. Tang, Y.-L. Deng, J. Li, W.-X. Wang, Y.-C. Wang, Z.-Z. Li, L. Yuan, S.-L. Chen, R.-L. Sheng, *Chem. Commun.* **2016**, *52*, 4470–4473; c) S. Zhi, H. Yao, W. Zhang, *Molecules* **2023**, *28*, 1145.
[21] M. Zurro, S. Torres-Oya, G. G. Otárola, J. J. Vaquero, E. Merino, *Synthesis* **2023**, *55*, 1783–1791.
[22] For complete optimization of the reaction conditions, detailed experimental procedures, and the characterization of starting materials and products, see the Supporting Information
[23] Q. Lu, J. Zhang, F. Wei, Y. Qi, H. Wang, Z. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 7156–7159.
[24] a) F. Recupero, C. Punta, *Chem. Rev.* **2007**, *107*, 3800–3842; b) H. Wang, Q. Lu, C. Qian, C. Liu, W. Liu, K. Chen, A. Lei, *Angew. Chem. Int. Ed.* **2016**, *55*, 1094–1097; c) J. Jung, J. Kim, G. Park, Y. You, E. J. Cho, *Adv. Synth. Catal.* **2016**, *358*, 74–80; d) Y. F. Liang, N. Jiao, *Acc. Chem. Res.* **2017**, *50*, 1640–1653.
[25] M. Zhang, X. Ding, A. Lu, J. Kang, Y. Gao, Z. Wang, H. Li, Q. Wang, *Org. Chem. Front.* **2021**, *8*, 961–967.
[26] Y. Liu, P. Xie, Z. Sun, X. Wo, C. Gao, W. Fu, T. P. Loh, *Org. Lett.* **2018**, *20*, 5353–5356.
[27] N. Münster, K. Harms, U. Koert, *Chem. Commun.* **2012**, *48*, 1866–1867.
[28] X. Yi, S. Lei, W. Liu, F. Che, C. Yu, X. Liu, Z. Wang, X. Zhou, Y. Zhang, *Org. Lett.* **2020**, *22*, 4583–4587.
[29] V. G. Correia, J. C. Abreu, C. A. E. Barata, L. H. Andrade, *Org. Lett.* **2017**, *19*, 1060–1063.
[30] B. Huang, Y. Zhao, C. Yang, Y. Gao, W. Xia, *Org. Lett.* **2017**, *19*, 3799–3802.
[31] L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278–3281.
[32] M. A. Hegazya, S. H. ElHamouly, M. M. Azabb, S. I. Beshirc, M. A. Zayedc, *Polym. Sci. Ser. B* **2014**, *56*, 182–190.
[33] R. J. Cvetovich, L. DiMichele, *Org. Process Res. Dev.* **2006**, *10*, 944–946.
[34] Y. Hannappel, L. Wiehemeier, M. Dirksen, T. Kottke, T. Hellweg, *Macromol. Chem. Phys.* **2021**, *222*, 2100067.
[35] G. S. Hamilton, in *Encyclopedia of Reagents for Organic Synthesis* (Ed.: L. A. Paquette) **1995**, *7*, 4939–4940.
[36] D. R. Gauthier Jr., N. Yoshikawa, *Org. Lett.* **2016**, *18*, 5994–5997.
[37] P. Bourbon, E. Appert, A. Martin-Mingot, B. Michelet, S. Thibaudeau, *Org. Lett.* **2021**, *23*, 4115–4120.
[38] M. Kawaguchi, T. Tani, R. Hombu, N. Ieda, H. Nakagawa, *Chem. Commun.* **2018**, *54*, 10371–10374.
[39] B. J. Linberg, *Acta Chem. Scand.* **1967**, *21*, 2215–2219.
[40] C. G. Overberger, J. J. Godfrey, *J. Polym. Sci.* **1959**, *40*, 179–201.
[41] M. Kinebuchi, et al., World Intellectual Property Organization, WO2020040104 A1 2020–02–27.
[42] S. Aoki, Y. Tomiyama, Y. Kageyama, Y. Yamada, M. Shiro, E. Kimura, *Chem. Asian J.* **2009**, *4*, 561–573.
[43] C. Lee, L. Field, *Synthesis* **1990**, 391–397.
[44] J. Goh, M. Maraswami, T.-P. Loh, *Org. Lett.* **2021**, *23*, 1060–1065.

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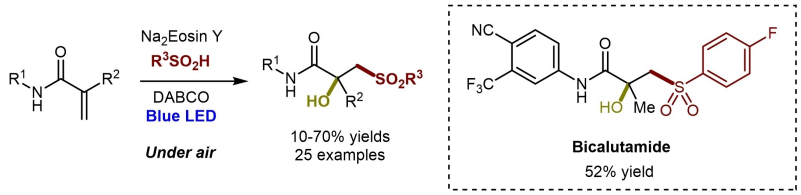

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