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Direct C3 Carbamoylation of 2*H*-Indazoles

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We developed a novel method for direct C3 carbamoylation of 2*H*-indazoles using oxamic acids as carbamoyl radical sources. In the presence of ammonium persulfate, carbamoyl radicals were generated from oxamic acids, then used for further reactions with 2*H*-indazoles to afford the desired products. The reaction proceeds under metal- and catalyst-free conditions. This simple process allows for the efficient synthesis of C3 carbamoylated 2*H*-indazoles, which are important scaffolds in organic synthesis.

Indazoles, nitrogen-containing heterocycles, are important scaffolds in organic synthesis and have been found in many biologically active compounds.[1] 2*H*-Indazoles are of particular interest, as they have recently been confirmed to exhibit many significant biological activities, including antitumor and anti-inflammatory properties (Figure 1).[2] While there have been no shortage of attempts to synthesize indazole scaffolds, many studies on the synthesis of 2*H*-indazoles have some limitations due to their thermodynamically less favored properties.[3] Direct functionalization of 2*H*-indazoles at the C3 position has been particularly challenging because of low reactivity at that site.[4]

Nevertheless, direct C3 functionalization of 2*H*-indazoles remains a target worth pursuing, as it would provide an efficient route for the synthesis of various 2*H*-indazole derivatives. Very recently, some remarkable breakthroughs concerning C3 functionalization of 2*H*-indazoles through acylation,[4c,5] arylation,[4d,6] alkylation,[5b] alkenylation,[7] trifluoromethylation,[8] selenylation,[9] and phosphorylation,[10] have been achieved using pioneering approaches, including visible-light-mediated reactions (Scheme 1, I).[11,12] While a number of different approaches to the synthesis of C3 functionalization of 2*H*-indazoles have been developed, successful direct C3 carbamoylation of 2*H*-indazoles is comparatively rarely reported (Scheme 1, II). Carbamoylation is one of the most efficient methods to introduce an amide motif into a molecule.[13] Carbamoylation reactions provide rapid C–H carbamoylated heterocycles that would typically otherwise be synthesized from conventional amide-coupling reactions, which require the use of prefunctionalized starting compounds and wasteful coupling reagents.[14] Amide motifs have been found in many natural products, pharmaceuticals, and specialized materials,

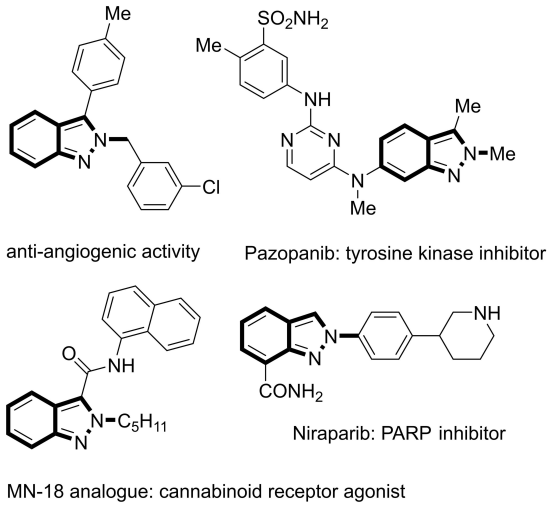
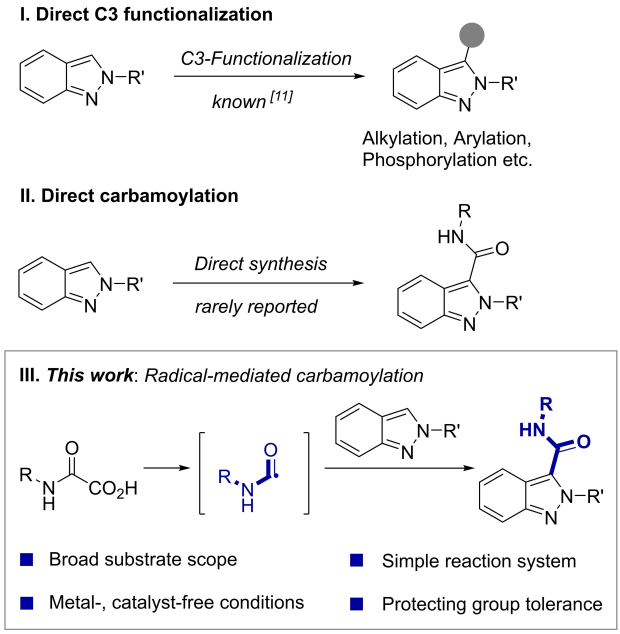


Figure 1. Bioactive compounds containing the 2*H*-indazole moiety.



Scheme 1. Synthesis of C3 carbamoylated 2*H*-indazoles.

and amide-functionalized *N*-heterocycles are important scaffolds in medicinal chemistry. 2*H*-indazoles containing amide motifs also demonstrate biological properties (Figure 1).

With this in mind, the development of a direct and efficient method for the carbamoylation of 2*H*-indazoles that relies on simple processes would be significant. We envisioned that direct C3 carbamoylation of 2*H*-indazoles might be possible

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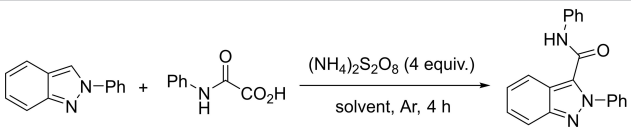
using in situ-generated carbamoyl radicals.[15] Herein, we report an efficient direct carbamoylation of 2*H*-indazoles using oxamic acids as carbamoyl radical sources (Scheme 1, III). Notably, the reaction proceeds without using any catalysts or metal reagents.

Our initial studies of C3 carbamoylation of 2*H*-indazoles involved a reaction between 2-phenyl-2*H*-indazole (**1a**) and oxanilic acid (**2a**) in the presence ammonium persulfate. We assumed that carbamoyl radicals would be generated by ammonium persulfate under proper reaction conditions. Accordingly, we examined various reaction conditions, and selected examples of the optimization studies are summarized in Table 1. Solvent screening revealed that the desired reaction did not take place in DCM, CH_3CN, and DMF (Table 1, entries 1–3). However, the desired products were obtained when the reactions were performed in DMSO (entries 4–13 and entries 15–16). Notably, improved yield was observed when the reaction was carried out in DMSO at 60 °C for four hours (entry 4, 71%). Higher temperatures did not improve the reaction yield (entries 5 and 6). In contrast, lower yields were observed as the reaction temperature decreased (entries 7 and 8, 50 °C: 56% and 23 °C 20% yields respectively). A slightly diminished reaction yield was observed as reaction time was shortened (entry 9, 3 h: 67%), although a longer reaction time did not improve the reaction yield (entry 10, 5 h: 70%). Varying the amount of ammonium sulfate did not improve the reaction yields (entries 11–14). As we were curious about the role of water in this reaction, we employed a molecular sieve, ultimately observing no improvement in reaction yield (entry 15). Then, we tested the role of oxidants. Importantly, no reaction was observed when the reaction was carried out in the absence of $(NH_4)_2S_2O_8$ (entry 16). Therefore, we concluded that the presence of an oxidant is necessary to this transformation. We speculated that the decomposition of persulfate would be important to the generation of the carbamoyl radicals under the reaction conditions.[16] The reaction yield was diminished when $K_2S_2O_8$ was used instead of $(NH_4)_2S_2O_8$ (entry 17). The reaction still occurred under air atmosphere, though we noted a slightly decreased yield (entry 18).

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

Entry	Solvent	Temp. [°C]	Reaction time [h]	Yield [%][b]
1	DCM	60	4	Trace
2	CH_3CN	60	4	Trace
3	DMF	60	4	Trace
4	**DMSO**	**60**	**4**	**71**
5	DMSO	70	4	70
6	DMSO	80	4	69
7	DMSO	50	4	56
8	DMSO	23	4	20
9	DMSO	60	3	67
10	DMSO	60	5	70
11[c]	DMSO	60	4	65
12[d]	DMSO	60	4	63
13[e]	DMSO	60	4	42
14[f]	DMSO	60	4	69
15[g]	DMSO	60	4	69
16[h]	DMSO	60	4	0
17[i]	DMSO	60	4	21
18[j]	DMSO	60	4	58

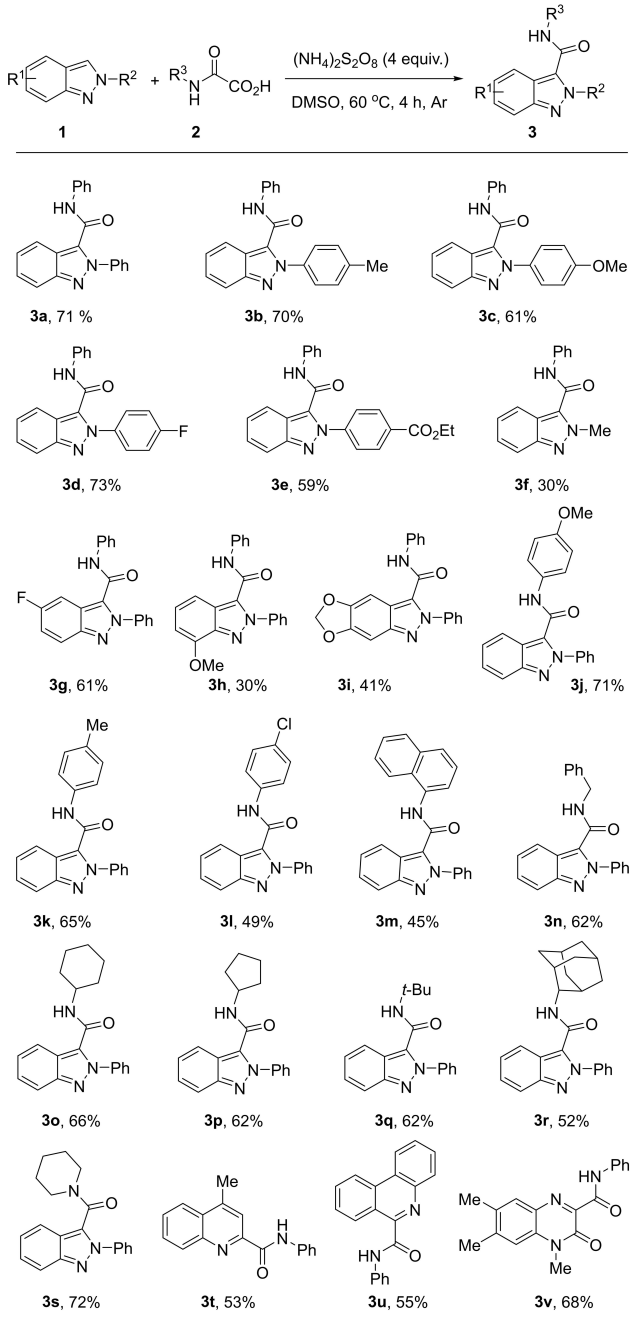
[a] Conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (4.0 equiv.), $(NH_4)_2S_2O_8$ (4.0 equiv.), solvent (0.25 M) under Ar. [b] Isolated yield after column chromatography. [c] 3.0 equiv. of $(NH_4)_2S_2O_8$ was added. [d] 3.0 equiv. of $(NH_4)_2S_2O_8$ and 3.0 equiv. of **2a** were added. [e] 2.0 equiv. of $(NH_4)_2S_2O_8$ and 2.0 equiv. of **2a** were added. [f] 5.0 equiv. of $(NH_4)_2S_2O_8$ was added. [g] 4 Å molecular sieve (50 mg) was added. [h] The reaction performed in the absence of $(NH_4)_2S_2O_8$. [i] $K_2S_2O_8$ was used instead of $(NH_4)_2S_2O_8$. [j] Under air atmosphere.

With the optimized reaction conditions identified, we explored the substrate scope of the synthesis of C3 carbamoylated 2*H*-indazoles. The reaction proved to be tolerant to various 2*H*-indazoles and oxamic acids (Table 2). First, we examined various aryl substituents at N2 of the 2*H*-indazoles (**3a**–**3e**). Aryl substituents with either electron-donating (**3b** and **3c**) or electron-withdrawing (**3d** and **3e**) groups afforded the target products in moderate to good yields (59–73% yields). Notably, an alkyl-substituted 2*H*-indazole also proved to be a suitable substrate in this reaction even though the reaction yield was relatively low (**3f**, 30%). We then determined the electronic effect of the 2*H*-indazole structures. The electronic effect on the arene structure of 2*H*-indazole seems to be crucial; 7-methoxy-2-phenyl-2*H*-indazole provided the product with a diminished yield compared with 5-fluoro-2-phenyl-2*H*-indazole (**3g**: 61% *vs.* **3h**: 30%). Next, various oxamic acids were employed in this transformation (**3j**–**3s**). *N*-Aryl oxamic acids with either electron-donating (**3j** and **3k**) or electron-withdrawing (**3l**) groups provided the desired products in 49–71% yields. A diminished yield was observed with electron-withdrawing substituent at the para-position of the oxamic acid (**3l**, 49%). The use of *N*-naphthyl oxamic acid **2m** gave the desired product **3m** in 45% yield. The decrease in the yield of **3m** might be due to the substituent's steric effect. Furthermore, the products starting from *N*-alkyl oxamic acids were obtained in 52–72% yields (**3n**–**3s**). Various alkyl groups, including benzyl (**3n**, 62%), cyclohexyl (**3o**, 66%), cyclopentyl (**3p**, 62%), and *tert*-butyl (**3q**, 62%) groups, provided the desired products in good yields even though a slightly diminished reaction yield was observed with sterically hindered 2-adamantan-2-yl-amino-2-oxoacetic acid (**3r**, 52% yield). In addition, the reaction using 2-oxo-2-(piperidin-1-yl) acetic acid **2s** successfully provided the desired product **3s** in 72% yield. Moreover, other heterocyclic compounds such as quinoline (**3t**), phenanthridine (**3u**), and quinoxalin-2(1*H*)-one (**3v**) also provided the desired products in this transformation.

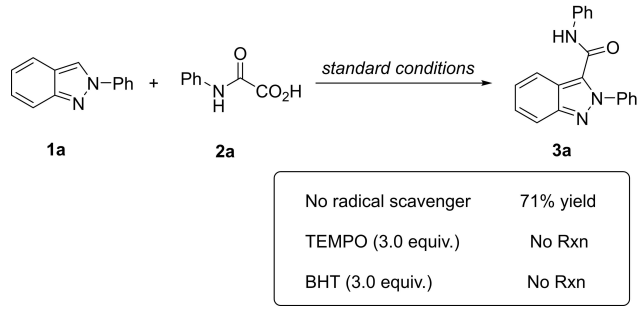
To gain mechanistic insight into this transformation, we performed control experiments (Scheme 2). We employed TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and BHT (butylated hydroxytoluene) as radical inhibitors.[17] These conditions did not provide the desired products, suggesting that this transformation primarily involved a radical pathway.

On the basis of previous reports and our results, a plausible reaction pathway is shown in Scheme 3.[4c,10a,16,18] The reaction begins with the decomposition of persulfate $S_2O_8^{2-}$ in DMSO to

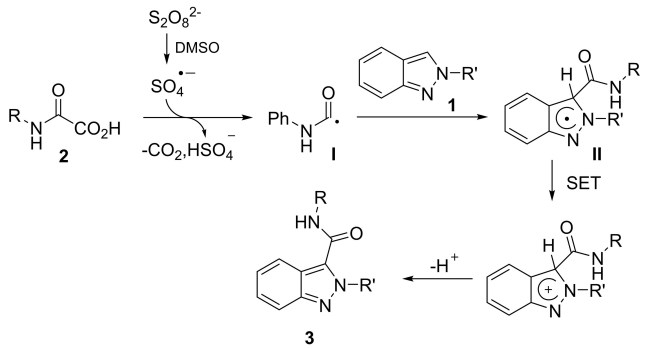
Table 2. Substrate scope.[a]



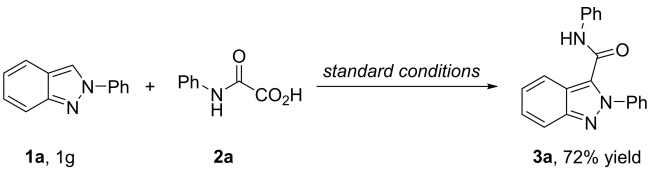
[a] Conditions: **1a** (0.5 mmol, 1.0 equiv.), **2a** (4.0 equiv.), $(NH_4)_2S_2O_8$ (4.0 equiv.) in DMSO (0.25 M) at 60 °C for 4 h under Ar. Isolated yield after column chromatography.



Scheme 2. Control experiments.



Scheme 3. Proposed reaction pathway.



Scheme 4. Gram-scale synthesis.

generate the sulfate radical anion $SO_4^{\bullet-}$. The subsequent CO_2 emission and hydrogen atom transfer from oxamic acid by the sulfate radical anion $SO_4^{\bullet-}$ provides the carbamoyl radical **I**. Then, a Minisci-type radical addition to 2*H*-indazole **1** affords intermediate **II**.[19] Single electron transfer (SET) and deprotonation finally furnish desired product **3**.

To show the utility of this transformation, we performed a gram-scale reaction with model substrates **1a** and **2a** under reaction conditions (Scheme 4). A good yield of the desired product **3a** was obtained without loss.

In summary, we have developed an efficient and direct means of C3 carbamoylation of 2*H*-indazoles. We also confirmed that this process can be applied to gram-scale reactions. Notably, this transformation did not require any metal reagents or catalysts. This simple process would provide a facile access to C3 carbamoylated 2*H*-indazoles, which are important scaffolds of various bioactive compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbamoylation · 2*H*-Indazoles · Minisci reaction · Radical reaction · Synthetic methods

[1] A. Schmidt, A. Beutler, B. Snovydovych, *Eur. J. Org. Chem.* **2008**, *2008*, 4073–4095.
[2] a) M. De Angelis, F. Stossi, K. A. Carlson, B. S. Katzenellenbogen, J. A. Katzenellenbogen, *J. Med. Chem.* **2005**, *48*, 1132–1144; b) L.-J. Huang, M.-L. Shih, H.-S. Chen, S.-L. Pan, C.-M. Teng, F.-Y. Lee, S.-C. Kuo, *Bioorg. Med. Chem.* **2006**, *14*, 528–536; c) M. Minu, A. Thangadurai, S. R. Wakode, S. S. Agrawal, B. Narasimhan, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2960–2964; d) W. Aman, J. Lee, M. Kim, S. Yang, H. Jung, J.-M. Hah, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1188–1192; e) J. Pérez-Villanueva, L. Yépez-Mulia, I. González-Sánchez, J. F. Palacios-Espinosa, O. Soria-Arteche, T. D. R. Sainz-Espuñes, M. A. Cerbón, K. Rodríguez-Villar, A. K. Rodríguez-Vicente, M. Cortés-Gines, Z. Custodio-Galván, D. B. Estrada-Castro, *Molecules* **2017**, *22*, 1864; f) J. Liu, C. Qian, Y. Zhu, J. Cai, Y. He, J. Li, T. Wang, H. Zhu, Z. Li, W. Li, L. Hu, *Bioorg. Med. Chem.* **2018**, *26*, 747–757.
[3] S.-G. Zhang, C.-G. Liang, W.-H. Zhang, *Molecules* **2018**, *23*, 2783.
[4] a) E. J. Brnardic, R. M. Garbaccio, M. E. Fraley, E. S. Tasber, J. T. Steen, K. L. Arrington, V. Y. Dudkin, G. D. Hartman, S. M. Stirdivant, B. A. Drakas, K. Rickert, E. S. Walsh, K. Hamilton, C. A. Buser, J. Hardwick, W. Tao, S. C. Beck, X. Mao, R. B. Lobell, L. Sepp-Lorenzino, Y. Yan, M. Ikuta, S. K. Munshi, L. C. Kuo, C. Kreatsoulas, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5989–5994; b) M. Ye, A. J. F. Edmunds, J. A. Morris, D. Sale, Y. Zhang, J.-Q. Yu, *Chem. Sci.* **2013**, *4*, 2374–2379; c) G. Bogonda, H. Y. Kim, K. Oh, *Org. Lett.* **2018**, *20*, 2711–2715; d) S. Vidyacharan, B. T. Ramanjaneyulu, S. Jang, D.-P. Kim, *ChemSusChem* **2019**, *12*, 2581–2586.
[5] a) Y.-L. Liu, Y.-L. Pan, G.-J. Li, H.-F. Xu, J.-Z. Chen, *Org. Biomol. Chem.* **2019**, *17*, 8749–8755; b) L. Liu, P. Jiang, Y. Liu, H. Du, J. Tan, *Org. Chem. Front.* **2020**, *7*, 2278–2283.
[6] S. A. Ohnmacht, A. J. Culshaw, M. F. Greaney, *Org. Lett.* **2010**, *12*, 224–226.
[7] a) M. Naas, S. El Kazzouli, E. M. Essassi, M. Bousmina, G. Guillaumet, *Org. Lett.* **2015**, *17*, 4320–4323; b) S. Vidyacharan, A. Murugan, D. S. Sharada, *J. Org. Chem.* **2016**, *81*, 2837–2848.
[8] a) P. Ghosh, S. Mondal, A. Hajra, *J. Org. Chem.* **2018**, *83*, 13618–13623; b) A. Murugan, V. N. Babu, A. Polu, N. Sabarinathan, M. Bakthadoss, D. S. Sharada, *J. Org. Chem.* **2019**, *84*, 7796–7803.
[9] A. Dey, A. Hajra, *J. Org. Chem.* **2019**, *84*, 14904–14910.
[10] a) M. Singsardar, A. Dey, R. Sarkar, A. Hajra, *J. Org. Chem.* **2018**, *83*, 12694–12701; b) P. Ghosh, S. Mondal, A. Hajra, *ACS Omega* **2019**, *4*, 9049–9055.
[11] For a review of direct functionalization of indazole derivatives, see: S. Ghosh, S. Mondal, A. Hajra, *Adv. Synth. Catal.* **2020**, *362*, 3768–3794.
[12] For selected reviews on photoredox catalysis, see: a) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102–113; b) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687–7697; c) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617–1622; d) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; e) D. M. Schultz, T. P. Yoon, *Science* **2014**, *343*, 1239176; f) S. Afewerki, A. Córdova, *Chem. Rev.* **2016**, *116*, 13512–13570; g) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; h) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035–10074; i) B. König, *Eur. J. Org. Chem.* **2017**, *2017*, 1979–1981; j) C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Chem. Rev.* **2018**, *118*, 7532–7585.
[13] a) D. Zhang, J. Liu, A. Córdova, W.-W. Liao, *ACS Catal.* **2017**, *7*, 7051–7063; b) M. Jouffroy, J. Kong, *Chem. Eur. J.* **2019**, *25*, 2217–2221; c) X. Chu, Y. Wu, H. Lu, B. Yang, C. Ma, *Eur. J. Org. Chem.* **2020**, *2020*, 1141–1144.
[14] a) R. M. de Figueiredo, J.-S. Suppo, J.-M. Campagne, *Chem. Rev.* **2016**, *116*, 12029–12122; b) E. Massolo, M. Pirola, M. Benaglia, *Eur. J. Org. Chem.* **2020**, *2020*, 4641–4651.
[15] a) F. Minisci, F. Fontana, F. Coppa, Y. M. Yan, *J. Org. Chem.* **1995**, *60*, 5430–5433; b) M. Betou, L. Male, J. W. Steed, R. S. Grainger, *Chem. Eur. J.* **2014**, *20*, 6505–6517; c) W. F. Petersen, R. J. K. Taylor, J. R. Donald, *Org. Lett.* **2017**, *19*, 874–877; d) Q.-F. Bai, C. Jin, J.-Y. He, G. Feng, *Org. Lett.* **2018**, *20*, 2172–2175.
[16] M. T. Westwood, C. J. C. Lamb, D. R. Sutherland, A.-L. Lee, *Org. Lett.* **2019**, *21*, 7119–7123.
[17] E. T. Denisov, I. V. Khudyakov, *Chem. Rev.* **1987**, *87*, 1313–1357.
[18] a) K. C. C. Aganda, J. Kim, A. Lee, *Org. Biomol. Chem.* **2019**, *17*, 9698–9702; b) M. Singsardar, S. Laru, S. Mondal, A. Hajra, *J. Org. Chem.* **2019**, *84*, 4543–4550; c) K. Mahanty, D. Maiti, S. De Sarkar, *J. Org. Chem.* **2020**, *85*, 3699–3708; d) S. Neogi, A. K. Ghosh, K. Majhi, S. Samanta, G. Kibriya, A. Hajra, *Org. Lett.* **2020**, *22*, 5605–5609.
[19] R. S. J. Proctor, R. J. Phipps, *Angew. Chem. Int. Ed.* **2019**, *58*, 13666–13699; *Angew. Chem.* **2019**, *131*, 13802–13837.

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