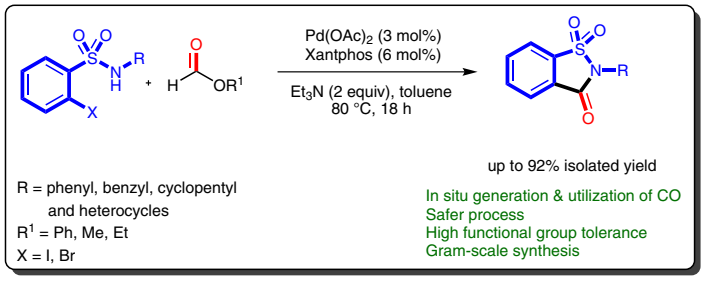
Synlett S. P. Chavan et al. Letter

In situ Generation and Utilization of CO: An Efficient Route towards N-Substituted Saccharin via Carbonylative Cyclization of 2-Iodosulfonamides

Sujit P. Chavan[a]
Adithyaraj K.[b]
Bhalchandra M. Bhanage*[a]

[a] Department of Chemistry, Institute of Chemical Technology, N. Parekh Marg, Matunga, Mumbai-400019, India
bm.bhanage@gmail.com
bm.bhanage@ictmumbai.edu.in
[b] Integrated Science Education & Research Centre (ISERC), Visva Bharati University, Santiniketan 731235, West Bengal, India



Received: 25.02.2017
Accepted after revision: 20.04.2017
Published online: 18.05.2017
DOI: 10.1055/s-0036-1588422; Art ID: st-2017-d0143-l

Abstract The present protocol demonstrates the synthesis of N-substituted saccharines via carbonylative cyclization of 2-iodosulfonamides using a $Pd(OAc)_2$/Xantphos catalyst system and phenyl formate as a CO source. A variety of saccharin derivatives is synthesized under milder reaction conditions.

Key words carbonylative cyclization, palladium catalysis, CO surrogate, phenyl formate, N-substituted saccharin.

The saccharin framework is a key structural motif in several biologically active compounds such as ipsapirone, CU-CPD103, supidimide, and repinotan (Figure 1).[1] Saccharin derivatives serves as inhibitors of serine proteases,[2] analgesics,[3] aldehyde dehydrogenase inhibitors,[4] human mast cell tryptase inhibitors,[5] human leukocyte elastase (HLE) inhibitors,[6] and 5-HT1a antagonists.[7] A number of synthetic pathways for the production of N-substituted saccharin derivatives has been well documented in the literature.[8]

Oxidative cyclization of N-substituted *o*-methylarenesulfonamides using different catalyst systems such as H_5IO_6-CrO_3, $PhI(OAc)_2/I_2$, W lamp or $PhI(OAc)_2/I_2$, Hg lamp have been reported for the synthesis of N-substituted saccharins.[9] Dolenc and co-workers extended the methodology to access amino acid derivatives of saccharin using the H_5IO_6-CrO_3 catalytic system.[10] In addition, the synthesis of N-substituted saccharins has been explored by direct *ortho* lithiation of arylsulfonamides.[11] Functionalization of saccharin using phenylboronic acid or triarylbismuth as arylating agents with stoichiometric amounts of copper catalyst has been reported.[12] Recently, the synthesis of N-substituted saccharines via intermolecular oxidative C–H imidation of arenes with saccharin using hypervalent iodine(III) as an oxidant under transition-metal-free conditions has been reported.[13] Transition-metal-catalyzed carbonylation is an effective way to synthesize a large range of carbonyl compounds using carbon monoxide.[14] The carbonylative C–H activation of 4-methyl-*N*-(perfluorophenyl)benzenesulfonamide for the synthesis of the corresponding saccharin using $Pd(OAc)_2$ as catalyst and two equivalent AgOAc as an additive under 1 atmosphere pressure of CO has been reported by Yu and co-workers.[15] However, the reaction was performed on a very small scale (0.125 mmol) and the general applicability of the reaction was not explored.

Although carbon monoxide is an inexpensive and commonly employed C1 source; its flammability and toxicity creates serious difficulties in handling. In recent years, several CO surrogates have been examined for various carbonylation processes.[16] The substoichiometric use of aryl formates for in situ generation and utilization CO is reliable and has shown its efficacy for carbonylative cyclizations.[17]

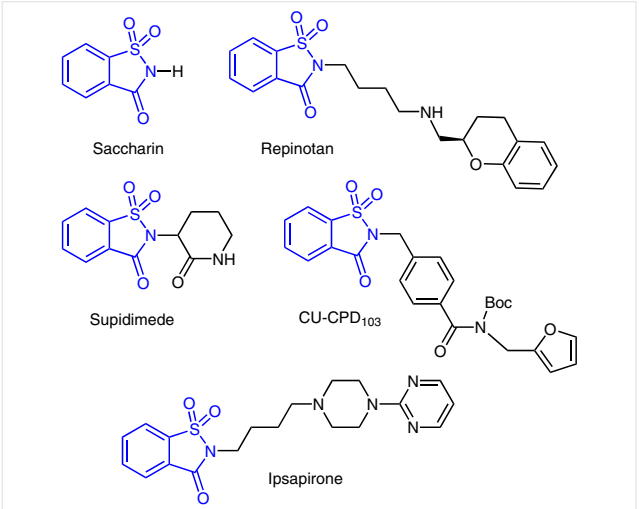
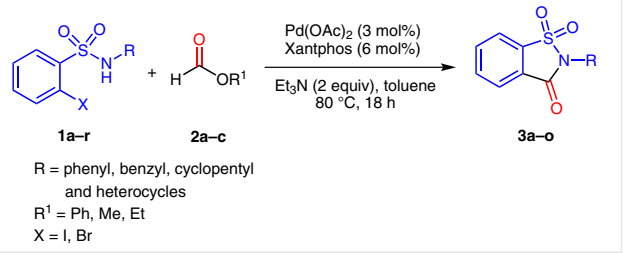


Figure 1 Bioactive saccharine derivatives

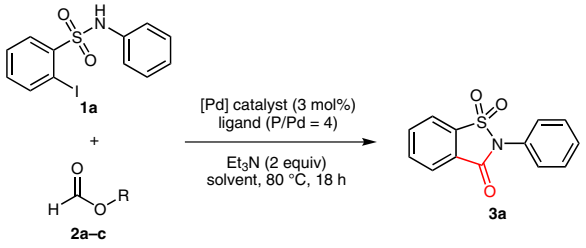
Recently, we have demonstrated the efficacy of phenyl formate as a CO source in palladium-catalyzed carbonylative cyclization of N-substituted 2-iodobenzamides and 2-iodoanilides for the synthesis of phthalimides and benzoxazinones, respectively.[18] In the present work, the $Pd(OAc)_2$/Xantphos-catalyzed carbonylation of 2-iodobenzenesulfonamides for the synthesis of saccharin derivatives is presented (Scheme 1). To the best of our knowledge, the carbonylative synthesis of saccharine derivatives using a CO surrogate has been not reported.



Scheme 1 General reaction scheme for saccharine synthesis

Initially, we investigated the $Pd(OAc)_2/Ph_3P$-catalyzed carbonylative cyclization of *N*-phenylbenzenesulfonamide **1a** to produce *N*-phenylsaccharin **3a** (2-phenylbenzo[*d*]isothiazol-3(2*H*)-one 1,1-dioxide) using different CO surrogates and Et_3N as a base at 80 °C for 18 hours (Table 1 entries 1–3). Phenyl formate was found to be a better CO source than alkyl formates presumably because of the higher decomposition energies of alkyl formates compare to aryl formates.[19] Using phenyl formate as the CO source, we next studied the effect of different phosphine ligands on the cyclization of **1a**. Use of $P(tBu)_3{\cdot}HBF_4$ gave a 60% yield of **3a**, while bidentate ligands such as 1,3-bis(diphenylphosphino)propane (dppp), 1,1-bis(diphenylphosphino)ferrocene (dppf) provided **3a** in 65% and 70% yields, respectively (Table 1, entries 4–6). 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos) proved to be the best ligand for this transformation and provided a 94% yield of **3a** (Table 1, entry 7). Reaction in the absence of ligand resulted in a poor yield (Table 1, entry 8). It has been observed that the catalyst precursor has a vital role in coupling reactions.[20] Hence, we screened various palladium precursors such as $PdCl_2(PhCN)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2$, and $Pd(dba)_2$ (Table 1, entries 9–12). To investigate the role of solvent, experiments were carried out using polar and nonpolar solvents, wherein it was observed that nonpolar solvents are most effective (Table 1, entries 13–16). Reacting at higher temperatures led to a drop in yield, and a small amount of dehalogenated material was detected by GC–MS (Table 1, entry 17).

Table 1 Screening of Reaction Parameters[a]

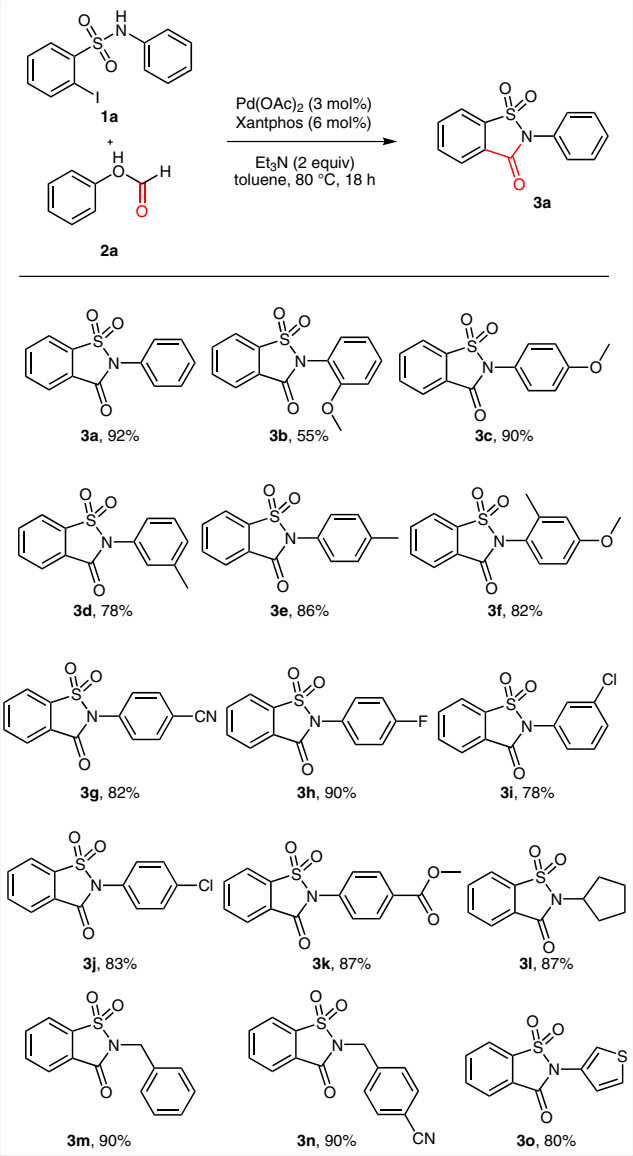


Entry	Formate	Catalyst	Ligand	Solvent	Yield (%)[b]
1	HCO_2Me	$Pd(OAc)_2$	Ph_3P	toluene	34
2	HCO_2Et	$Pd(OAc)_2$	Ph_3P	toluene	30
3	HCO_2Ph	$Pd(OAc)_2$	Ph_3P	toluene	67
4	HCO_2Ph	$Pd(OAc)_2$	$P(tBu)_3{\cdot}HBF_4$	toluene	60
5	HCO_2Ph	$Pd(OAc)_2$	dppp	toluene	65
6	HCO_2Ph	$Pd(OAc)_2$	dppf	toluene	70
7	HCO_2Ph	$Pd(OAc)_2$	Xantphos	toluene	94
8	HCO_2Ph	$Pd(OAc)_2$	–	toluene	10
9	HCO_2Ph	$PdCl_2(PhCN)_2$	Xantphos	toluene	72
10	HCO_2Ph	$PdCl_2(PPh_3)_2$	Xantphos	toluene	86
11	HCO_2Ph	$PdCl_2$	Xantphos	toluene	64
12	HCO_2Ph	$Pd(dba)_2$	Xantphos	toluene	84
13	HCO_2Ph	$Pd(OAc)_2$	Xantphos	mesitylene	90
14	HCO_2Ph	$Pd(OAc)_2$	Xantphos	benzene	80
15	HCO_2Ph	$Pd(OAc)_2$	Xantphos	DMF	68
16	HCO_2Ph	$Pd(OAc)_2$	Xantphos	THF	56
17[c]	HCO_2Ph	$Pd(OAc)_2$	Xantphos	toluene	82

[a] Reaction conditions: **1a** (1.0 mmol), **2** (1.5 mmol), catalyst (3 mol %), ligand (6 mol %) and Et_3N (3 mmol) in solvent (1 mL), 18 h, 80 °C.
[b] GC yields.
[c] At 100 °C.

With the optimized reaction conditions in hand, a range of 2-iodosulfonamides was subjected to carbonylative cyclization to generate the corresponding saccharins in good to excellent yields (Scheme 2).[21] Using 2-iodosulfonamides bearing various substituents on the *N*-aryl group revealed that the steric and electronic properties of the substituents had little effect on reaction resulting in the formation of **3b–k** in very good yield. 2-Iodobenzenesulfonamides bearing *N*-cyclopentyl, *N*-benzyl, and *N*-benzyl substituents led to the corresponding N-substituted saccharine derivatives being formed in good to moderate yields (**3l–n**). Finally, the *N*-3-thiophenyl substrate furnished **3o** in good yield.

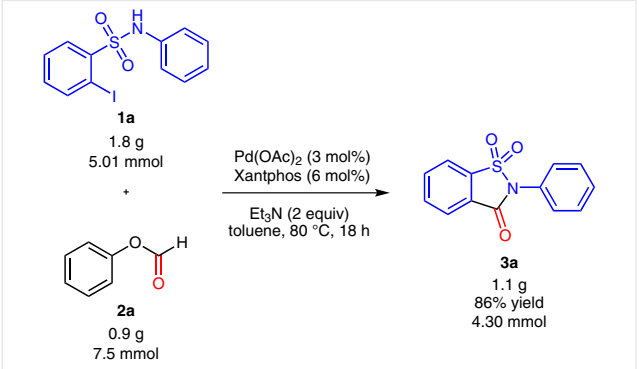
To illustrate the practical utility of the protocol, a gram-scale reaction was performed. Thus, cyclization of **1a** (1.5 g) provided **3a** in 86% isolated yield (Scheme 3). Efforts were



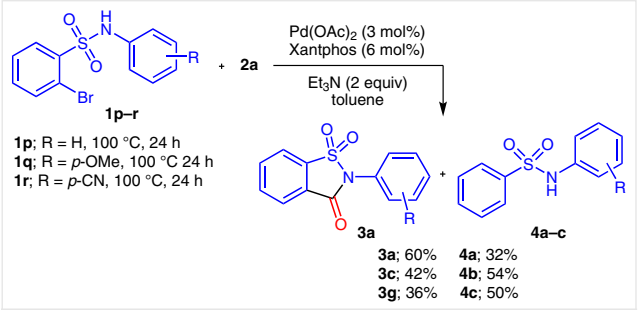
Scheme 2 Substrate scope for the synthesis of *N*-substituted saccharines. [a] *Reagents and conditions*: **1a–o** (1 mmol), **2a** (1.5 mmol), $Pd(OAc)_2$ (3 mol%), Xantphos (6 mol%), Et_3N (3 mmol) in toluene (1 mL), 18 h, 80 °C.

also made to utilize more challenging 2-bromo-*N*-phenylbenzenesulfonamide as staring material, but this resulted in poor to moderate yields of the desired products along with dehalogenated products (Scheme 4).

In conclusion, the use of phenyl formate for in situ generation of CO proved to be an effective and safe alternative to high-pressure carbonylation for the synthesis of N-substituted saccharin derivatives via carbonylative cyclization of 2-iodobenzenesulfonamides. The methodology tolerates a variety of functional groups and gives N-substituted saccharin derivatives in good to excellent yields.



Scheme 3 Gram-scale synthesis of *N*-phenyl saccharine



Scheme 4 Carbonylative cyclization of 2-bromosulfonamide

Acknowledgment

S.P.C. is grateful to the CSIR, New Delhi for providing a Senior Research Fellowship.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588422.

References and Notes

(1) (a) Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199. (b) Soler, L.; Cerrada, V.; Matia, M. P.; Novella, J. L.; Alvarez-Builla, J. *ARKIVOC* **2007**, *(iv)*, 312. (c) Fiorino, F.; Caliendo, G.; Perissutti, E.; Severino, B.; Frecentese, F.; Preziosi, B.; Izzo, A. A.; Capasso, R.; Santagada, V. *Arch. Pharm.* **2005**, *338*, 548. (d) Lai, Z.; Gan, X.; Wie, L.; Alliston, K. R.; Yu, H.; Li, Y. H.; Groutas, W. C. *Arch. Biochem. Biophys.* **2004**, *429*, 191. (e) Caliendo, G.; Fiorino, F.; Perissutti, E.; Severino, B.; Scolaro, D.; Gessi, S.; Cattabriga, E.; Borea, P. A.; Santagada, V. *Eur. J. Pharm. Sci.* **2002**, *16*, 15. (f) Soubh, L.; Besch, A.; Otto, H. H. *Pharmazie* **2002**, *57*, 384. (g) De Monte, C.; Carradori, S.; Secci, D.; Dascenzio, M.; Vullo, D.; Ceruso, M.; Supuran, C. T. *Eur. J. Med. Chem.* **2014**, *84*, 240. (h) Csakai, A.; Smith, C.; Davis, E.; Martinko, A.; Coulup, S.; Yin, H. *J. Med. Chem.* **2014**, *57*, 5348.

(2) Martyn, D. C.; Moore, M. J. B.; Abell, A. D. *Curr. Pharm. Design* **1999**, *5*, 405.
(3) Gonzalez-Martin, G.; Lyndon, C.; Sunkel, C. *Eur. J. Pharm Biopharm.* **1998**, *46*, 293.
(4) Nagasawa, H. T.; Kawle, S. P.; Elberling, J. A.; DeMaster, E. G.; Fukuto, J. M. *J. Med. Chem.* **1995**, *38*, 1865.
(5) Combrink, K. D.; Gulgeze, H. B.; Meanwell, N. A.; Pearce, B. C.; Zulan, P.; Bissacci, G. S.; Roberts, D. G. M.; Stanley, P.; Seiler, S. M. *J. Med. Chem.* **1998**, *41*, 4854.
(6) (a) Groutas, W. C.; Huang, H.; Venkataraman, R.; Houser-Archield, N.; Epp, J. B. *Bioorg. Med. Chem.* **1993**, *1*, 273. (b) Hlasta, D. J.; Bell, M. R.; Boaz, N. W.; Court, J. J.; Desai, R. C.; Franke, C. A.; Mura, A. J.; Subramanyam, C.; Dunlap, R. P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1801. (c) Hlasta, D. J.; Bell, M. R.; Court, J. J.; Cundy, K. C.; Desai, R. C.; Ferguson, E. W.; Gordon, R. J.; Kumar, V.; Maycock, A. L.; Subramanyam, C. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 331.
(7) Romero, A. G.; Darlington, W. H.; Piercey, M. F.; Lahti, R. A. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1703.
(8) Jakopin, Z.; Dolenc, M. S. *Curr. Med. Chem.* **2010**, *17*, 651.
(9) (a) Xu, L.; Shu, H.; Liu, Y.; Zhang, S.; Trudell, M. L. *Tetrahedron* **2006**, *62*, 7902. (b) Gadanyi, S.; Kalai, T.; Jeko, J.; Berente, Z.; Hideg, K. *Synthesis* **2000**, 2039. (c) Kamogawa, H.; Yamamoto, S.; Nanasawa, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3824. (d) Katohgi, M.; Togo, H.; Yamaguchi, K.; Yokoyama, M. *Tetrahedron* **1999**, *55*, 14885.
(10) Jakopin, Z.; Dolenc, S. M. *Synth. Commun.* **2008**, *38*, 3422.
(11) (a) Desai, R. C.; Hlasta, D. J.; Monsour, G.; Saindane, M. T. *J. Org. Chem.* **1994**, *59*, 7161. (b) Hlasta, D. J.; Court, J. J.; Desai, R. C. *Tetrahedron Lett.* **1991**, *32*, 7179. (c) Lombardino, J. G. *J. Org. Chem.* **1971**, *36*, 1843. (d) Aliyenne, O. A.; Khiari, J. E.; Kraiem, J.; Kacem, Y.; Ben Hassine, B. *Tetrahedron Lett.* **2006**, *47*, 6405. (e) Proudfoot, J. R.; Patel, U. R.; Dyatkin, A. B. *J. Org. Chem.* **1997**, *62*, 1851.
(12) (a) Lam, P. Y. S.; Vincent, G.; Clark, C. G.; Deudon, S.; Jadhav, P. K. *Tetrahedron Lett.* **2001**, *42*, 3415. (b) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (c) Chan, D. M. T. *Tetrahedron Lett.* **1996**, *37*, 9013.
(13) (a) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382. (b) Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. (c) Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 5193.
(14) (a) Wu, X-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1. (b) Gabriele, B.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2012**, 6825. (c) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (e) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468. (f) Ali, B. E.; Alper, H. *Synlett* **2000**, 161. (g) Tamaru, Y.; Yoshida, Z. *J. Organomet. Chem.* **1987**, *334*, 213. (h) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571. (i) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414. (j) Mihovilovic, M. D.; Stanetty, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3612. (k) Mei, T-S.; Kou, L.; Ma, S.; Engle, K. M.; Yu, J-Q. *Synthesis* **2012**, *44*, 1778. (l) Wu, X-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986. (m) Gadge, S. T.; Bhanage, B. M. *RSC Adv.* **2014**, *4*, 10367. (n) Chavan, S. P.; Varadwaj, G. B. B.; Parida, K.; Bhanage, B. M. *ChemCatChem* **2016**, *8*, 2649. (o) Chavan, S. P.; Bhanage, B. M. *Asian J. Org. Chem.* **2016**, *5*, 1120.
(15) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.
(16) (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 5580. (b) Odell, L.; Russo, F.; Larhed, M. *Synlett* **2012**, *23*, 685. (c) Konishi, H.; Manabe, K. *Synlett* **2014**, *25*, 1971. (d) Wu, L.; Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6310. (e) Gautam, P.; Bhanage, B. M. *Catal. Sci. Technol.* **2015**, *5*, 4663.
(17) (a) Li, H.; Neumann, H.; Beller, M.; Wu, X. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 3183. (b) Hoshimoto, Y.; Ohata, T.; Sasaoka, Y.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2014**, *136*, 15877. (c) Konishi, H.; Nagase, H.; Manabe, K. *Chem. Commun.* **2015**, *51*, 1854. (d) Wang, H.; Dong, B.; Wang, Y.; Li, J.; Shi, Y. *Org. Lett.* **2014**, *16*, 186. (e) Zhang, Y.; Chen, J.-L.; Chen, Z-B.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem.* **2015**, *80*, 10643.
(18) Chavan, S. P.; Bhanage, B. M. *Eur. J. Org. Chem.* **2015**, 2405.
(19) Katafuchi, Y.; Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2011**, *353*, 475.
(20) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34*, 5497.
(21) **General Experimental Procedure for the Synthesis of N-Substituted Saccharins**

An oven-dried Schlenk tube was charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), Xantphos (34.7 mg, 0.06 mmol), 2-iodosulfonamide (1.0 mmol), phenyl formate (1.5 mmol), and Et_3N (3 mmol) under nitrogen, and the reaction mixture was stirred at 80 °C for 18 h. The reaction mixture was then diluted with EtOAc (10 mL) and aq $NaHCO_3$ (10 mL), and the aqueous phase was further extracted with EtOAc (3 × 20 mL). The combined organic layers washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (120–200 mesh) using EtOAc–PE as eluents to give the corresponding N-substituted saccharin **3a–o**.

Compound **3a**: isolated as white solid; 238 mg (92%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.6 Hz, 1 H), 8.02–7.98 (m, 1 H), 7.95–7.86 (m, 2 H), 7.59–7.52 (m, 5 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.3, 137.6, 135.0, 134.4, 130.1, 129.9, 128.7, 128.6. 127.1, 125.6, 121.2.

Compound **3h**: isolated as white solid; 249 mg (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 7.6 Hz, 1 H), 7.99 (d, *J* = 7.4 Hz, 1 H), 7.95–7.86 (m, 2 H), 7.54–7.49 (m, 1 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.30 (dt, *J* = 9.1, 2.2 Hz, 1 H), 7.24–7.20 (m, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.9, 161.9, 158.0, 137.4, 135.2, 134.6, 131.0, 130.9, 130.1, 130.0, 126.8, 125.7, 124.0, 124.0, 121.2, 117.2, 117.1, 116.0, 115.8.

Compound **3m**: isolated as white solid; 245 mg (90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.6 Hz, 1 H), 7.91 (d, *J* = 7.4 Hz, 1 H), 7.86–7.78 (m, 2 H), 7.50 (d, *J* = 7.3 Hz, 2 H), 7.37–7.29 (m, 3 H), 4.90 (s, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 158.8, 137.7, 134.7, 134.4, 134.3, 128.7, 128.6, 128.2, 127.2, 125.2, 121.0, 42.6.